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Recent Trends in Ocular Drug Delivery: Challenges and Approaches

Atharv Bhosale[1], Atish Dabade[1,*], Sarthak Khandekar[1], Rohan Upadhye[1]

Abstract

Drug topical regulation can be accessed most easily in the eye. When given topically as eye drops, medication ocular bioavailability is quite low. Drug entry into specific ocular locations is complicated by the complex anatomy and physiology of the human eye. Research has long been interested in the topical administration of successful treatments. Providing a suitable ocular penetration and extending the duration of drug residence is their challenging task. Many ocular barriers, including precorneal, corneal, and blood-corneal barriers, prevent drugs from being delivered to patients effectively. These cutting-edge methods highlight the advantages of using a variety of ocular drug delivery systems, such as gels, eye ointments, intravitreal injections, prodrugs, viscosity enhancers, penetration enhancers, liposomes, niosomes, microparticles, nanosuspensions, and microemulsions. Today, the ability of nanotechnology-based carriers to bind both lipophilic and hydrophilic pharmaceuticals, improve drug stability, prolong residence time, increase bioavailability, and boost ocular permeability is what makes them appealing. Determining how the created nanocarriers will behave requires using several in vitro, ex vivo, and in vivo characterization techniques. Definition of the eye anatomy, different ocular disorders, and delivery challenges to the eyes are the goals of this review. The benefits and downsides of various ocular dosage forms and methods of administration are investigated as well. Research on ocular drug delivery that aims to provide safe sustained release of drugs in the anterior and posterior portions of the eye can benefit from the accumulated data offered in this study as a valuable source of knowledge.

Keywords: Photoreceptor, permeability, mucopolysaccharides, vitreous humor, diabetic retinopathy, intraocular pressure, and mucoadhesive strength

INTRODUCTION

The anterior and posterior regions of the eye's intricate physiology make it a highly sensitive organ. The quality of life is significantly impacted by visual impairment resulting from a variety of disorders. About 40–60% of blind cases worldwide are caused by cataracts, which are the most common cause of blindness. Mutations in the genes related with the, β, and γ crystalline proteins frequently lead to early-onset cataracts. Often associated with high intraocular pressure (IOP), glaucoma is an optic neuropathy that, if left untreated, can result in permanent blindness. Aging, diabetes, and fungal infections are also linked to vision loss. A few more prominent eye conditions are fungal keratitis, retinoblastoma, diabetic retinopathy (DR), and age-related macular degeneration (AMD) [1].

Approximately 76 million people have glaucoma, 196 million have AMD, and 92.6 million have DR, according to a recent study. Many ocular disorders can be effectively treated with strong medications, but their therapeutic efficacy is restricted by a number of barriers,

***Author for Correspondence**
Atish Sandeep Dabade
E-mail: atishdabade07@gmail.com

[1]Research Scholar, Department of Pharmacy, Dr. Shivajirao Kadam College of Pharmacy, Kasbe Digraj, Sangli, Maharashtra, India.

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including the tear film, cornea, conjunctiva, and blood-ocular barriers [2]. For instance, blinking and tear flow cause conventional eye drops to lose most of their potency, which lowers the drug's bioavailability to less than 5%.

Drug absorption is greatly aided by the cornea, which is made up of the stroma, endothelium, and epithelium. Medicines that are tiny and lipophilic can pass through the epithelium, but hydrophilic medicines are easier to absorb through the stroma. The endothelium keeps the cornea transparent and allows hydrophilic medications and macromolecules to enter the aqueous humor only on a specific basis. Despite having a smaller role in drug absorption than the cornea, the conjunctiva permits certain peptides, oligonucleotides, and macromolecular nanomedicines to reach deeper layers of the eye. Further limiting the admission of foreign chemicals into the bloodstream are blood-ocular barriers, which include the blood-aqueous barrier (BAB) in the anterior segment and the blood-retinal barrier (BRB) in the posterior segment [3, 4].

Ocular formulations can be supplied in conjunction with ocular devices, applied topically to the anterior surface of the eye, or administered intraocularly. These dose forms come in three different forms: semi-solids (gels, ointments), solids (powders, inserts, therapeutic contact lenses), and liquids (eye drops, suspensions, emulsions). The anterior portion of the eye is the main target of eye drops, which account for more than 95% of marketed ocular products. However, their residence durations are brief. While hydrophobic medications can be effectively delivered via suspensions and emulsions, they may result in impaired vision. Gels and ointments extend residence time because they are semi-solid forms. Solid dosage forms have advantages, such as regulated release (for inserts), protection for medications that are sensitive to water, and extended drug residence time (for therapeutic contact lenses) [5].

Significant drug concentration must be maintained while reducing the active ingredient, which calls for significant corneal penetration and an extended precorneal residence time for optimal ocular medication absorption. In order to improve corneal permeability, shield medications from biological environments, overcome ocular obstacles, and extend drug residence times, nanosystems have developed as cutting-edge technology. To guarantee these nanosystems work as intended, they must be characterized. To do this, a variety of techniques are used, including assessing the nanosystems' size, stability, visual appeal, zeta potential, interactions, and pH [6,7]. This review highlights the gaps in the literature on ocular drug delivery by providing an extensive analysis of the anatomy of the eye, common ocular diseases, and delivery barriers. It also covers dosage form classifications, administration routes, characterization methods, nanostructured platforms, and upcoming developments in ocular drug delivery.

ANATOMY AND PHYSIOLOGY

The eye is a very complicated and sensitive organ. The anterior and posterior chambers of the eye are depicted in Figure 1 to illustrate its anatomy. The tear film, cornea, pupil, lens, and ciliary body are all part of the anterior segment, whereas the conjunctiva, sclera, choroid, retina, vitreous humor, and optic nerve are all part of the posterior segment. The orbital glands and the secretions of the epithelium control the amount and nature of tears [8].

The translucent cornea of the nearly spherical eye extends somewhat forward. Tears, eyelids, lashes, and the reflexive blinking reflex all work to shield the eye. The act of blinking facilitates the removal of mucus and replenishes the corneal surface with tears produced by the lachrymal glands. In order to prevent damage, the blink reflex also shuts the eyelids, and the eyelashes capture dust and debris. Tears are bactericidal, meaning they assist clear the eye of irritants and shielding it from infections. Unless foreign material is supplied in modest volumes and is both physiologically and chemically compatible with the surface tissues of the eye, its defensive functions are combined by the

lachrymal system and the eyelids to ensure that foreign material entering the eye is promptly eliminated [9].

Communication between the anterior and posterior regions of the eye is facilitated by the stroma, ciliary muscles, and capillaries in the ciliary body. Between the lens and retina is a clear, gel-like connective tissue called the vitreous humor. It is made up of 99.9% water, hyaluronic acid, ions, and collagen. The conjunctiva is a thin, translucent membrane that covers the front of the sclera and borders the interior of the eyelids. It is composed of three layers: a submucosa that joins the sclera, an outer epithelium, and a large propriety that houses blood vessels, lymphatic, and nerve tissue. Collagen and mucopolysaccharides make up the sclera, which is the cornea's extension [10, 11].

The retina, a thin layer of neural and glial tissue, covers the back of the eye and converts visual information into electrical signals, which are transmitted to the brain via the optic nerve.

Structure of the Eye

The muscles of the extrinsic eye and the lachrymal system are both designed. The lachrymal apparatus's structures are in charge of producing and expelling lachrymal fluid, or tears (Figure 1).

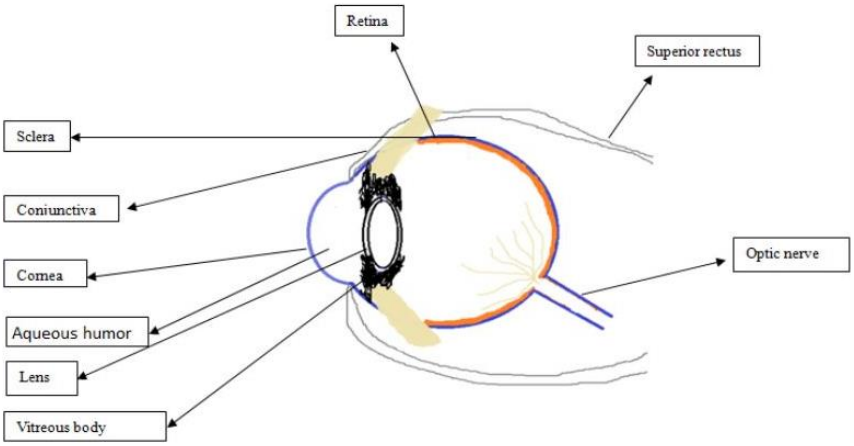

Figure 1. Structure of the eye.

The vitreous chamber, the largest of the three chambers in the eye, is filled with vitreous humor, a translucent fluid that resembles jelly. This fluid helps to control IOP, preserve the shape of the eyeball, and enable light refraction inside the eye. It also keeps the retina and lens in place. Three layers make up the eye: the neuronal, fibrous, and vascular layers [12]. The sclera and cornea belong to the outer fibrous layer. The portion of the eye that receives light and focuses it is called the cornea. The epithelium, stroma, and endothelium make up its three primary layers. A compact layer packed with water makes up the stroma, whereas the epithelium is made up of five to seven layers of closely spaced cells. The epithelium consists of five to seven layers of tightly connected cells, while the stroma is a compact layer filled with water. The endothelium plays a crucial role in maintaining the cornea's transparency. The middle vascular layer contains the choroid, ciliary body, and iris. The iris, the colored portion of the eye, regulates the amount of light that enters through the pupil, the dark central opening. The size of the pupil adjusts in response to varying light conditions. The lens, which is transparent, further focuses light onto the retina. The ciliary body comprises pigmented and non-pigmented ciliary epithelium [13, 14].

The uveal coat, the middle layer, the retina, and the outer coat, which consists of the cornea and sclera, make up the three layers that make up an eyeball. The sclera, which resembles the segments of the two spheres created by the cornea and sclera, is composed of fibrous fibers that offer structural stability and support. The pliable anterior segment of the eyelids, which may open and close to

modify the scleral fissure, shields the outside of the eye. Reflexes and voluntary blinking allow for the automatic and conscious regulation of the eyelids. Additionally, by distributing tear fluid throughout the eye's surface, they aid in giving the cornea an optically smooth surface [15].

THE EYE-FIBROUS LAYERS

The Cornea

The cornea makes up one-sixth of the transparent, fibrous outer layer of the eyeball. The stroma, Descemet membrane, endothelium, Bowman membrane, and epithelium are its five separate layers. The human cornea's outer epithelium is composed of five sublayers and has a thickness of 50–100 micrometers. Only 10% of the barrier against hydrophobic drug penetration is provided by its lipophilic character, whereas 90% of the barrier against hydrophilic drug penetration is provided by it [16].

With a total thickness of 8–14 micrometers, Bowman's membrane, which is located beneath the epithelium, is noticeably thinner. This layer loses its capacity to prevent drug penetration if it is destroyed since it is incapable of growing again. Mucopolysaccharides, collagen, and other proteins make up the stroma, which makes up around 80% of the cornea's dry weight. The stoma's ability to stop lipophilic medication absorption through the cornea is enhanced by its makeup. The Descement membrane is a thin, regenerating layer that follows the stroma and is around 6 micrometers thick. Research suggests that its impact on the absorption of ophthalmic medicines is not statistically significant [17–18].

Last but not least, the endothelium consists of a single layer of cells that covers the cornea's whole posterior surface. This layer is around 200 times more permeable than the epithelium because of the gap junctions that exist between its cells. To keep the corneal environment balanced, the bicarbonate-dependent Na^+/K^+-ATPase pump controls the passive flow of fluid into the stroma and the active removal of fluid from it [19].

The Sclera

About five-sixths of the eyeball is composed of the sclera, also known as the "white of the eye." Due to the structure's combination of elastic fibers and dense collagenous connective tissue, it has an opaque, white appearance. The sclera is responsible for three main things: (i) keeping the eyeball shaped, (ii) shielding the interior tissues of the eye, and (iii) acting as a surface where ocular muscles can be attached. Studies reveal that the sclera is extremely receptive to hydrophilic medications, with permeability being significantly impacted by molecule size. As a result, the sclera's pores and cytosolic spaces can accommodate the passage of water-soluble compounds with lower molecular weights more efficiently [20].

The Conjunctiva

This multilayered epithelial structure is composed of three main regions: (i) the anterior epithelium, (ii) the integrative epithelium, and (iii) the neurogenic epithelium. The conjunctiva is more permeable to hydrophilic substances than the cornea, despite the strong connections binding these cells together. There are more paracellular epithelial pores and larger epithelial pores overall, which results in enhanced permeability [21].

The Neural Layer of the Eye

A light-sensitive neural layer on the inside and a layer of pigmented cuboidal cells on the outside make up the retina, which is the innermost layer of the posterior segment of the eye. Relay neurons, 6–7 million photoreceptor cone cells, and about 120 million photoreceptor rod cells make up the neural layer. For vision, the fovea and the macula, two important areas of the retina, are essential. Focusing light on the fovea yields the best level of visual acuity because it contains the highest

concentration of photoreceptors. The optic disc, sometimes called the blind spot, is where the retinal artery and vein enter and leave the retina. It is devoid of photoreceptors.

The Vascular Layer of the Eye

The melanin pigments present in a large number of the vascular layer's cells are what give it its dark color. The ciliary arteries, which are short arteries that round the optic nerve and the branches of the ophthalmic artery, supply blood to the eye. The choroid, ciliary body, and iris comprise the vascular layer, which contains the bulk of the blood vessels in the eye. The vascular layer's posterior part is called the choroid, and it lines the inside surface of the sclera. This layer creates the blood-ocular barrier, which strictly regulates the amount of chemicals from the blood that can enter the eye [22].

OCULAR DISEASES

Conjunctivitis

Numerous substances, such as smoke, pollution, pollen, germs, viruses, and other allergens, can cause corneal inflammation. Secretions and cellular invasion are the hallmarks of this illness. While *Haemophilus influenza* and *Streptococcus pneumonia* can also cause conjunctivitis, *Staphylococcus aureus* is the most common cause of bacterial conjunctivitis and blepharoconjunctivitis. Redness, pain, weeping, and excessive secretions from the eyes are common symptoms. Roughly 40% of people worldwide suffer from allergic conjunctivitis. When conjunctivitis is infectious, topical antibiotic therapy is frequently recommended as a form of treatment [23].

Glaucoma

Increased pressure in the anterior and posterior chambers of the choroid layers is the result of improper drainage of the aqueous humor, which causes glaucoma. The optic nerve, which is in charge of sending visual information from the eyes to the brain, can be harmed by elevated IOP. Untreated glaucoma can cause irreparable visual loss and, in a few years, may result in total and permanent blindness. Glaucoma can be classified into two main categories: (i) closed-angle and (ii) open-angle. The cupping of the optic disc and loss of visual field resulting from impaired aqueous humor outflow through the trabecular meshwork are the hallmarks of open-angle glaucoma, which usually presents no symptoms. On the other hand, when outflow channels are blocked, closed-angle glaucoma produces increased pressure. Say, 76 million The aqueous humor contains several antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. The levels of these enzymes tend to decrease with age, contributing to elevated IOP. An imbalance between oxidants and antioxidants can influence the progression of glaucoma. Anti-glaucoma medications work to regulate either the formation or drainage of aqueous humor. Numerous studies have been published to improve glaucoma treatment options. Many studies were published to enhance glaucoma treatment [24].

Keratitis

A fungal, bacterial, or viral infection that affects the eyes. In most cases, viral pathogens are the source of bacterial corneal ulcers. Corneal ulcers are commonly linked to *Staphylococcus aureus*, Proteus, *E. coli*, and *Pseudomonas pyocyanin*.

Ocular risk factors include contact lenses, leprosy, HIV positive, trauma, and previous corneal surgery. Systemic risk factors include diabetes and topical corticosteroids. Corneal ulceration, stromal inflammatory infiltration, and compromised wound healing are the outcomes of fungal keratitis. MiRNA expression may change as a result of ocular irritation. Antifungal medications, either topical or oral, are used to treat fungal keratitis. In cases where medication is ineffective, corneal surgery may be needed. Sometimes, even after surgery, vision may not recover. A large number of studies address the management of fungal keratitis. Topical cubosomes filled with sertaconazole nitrate and blended [25].

Iritis (Anterior Uveitis)

Usually, DR begins suddenly and is marked by inflammation and irritation in the eyes. Other associated disorders are blepharitis (inflammation of the eyelid edge), chalazia (meibomian cysts of the eyelid), and ophthalmic variants of rosacea. Effective blood pressure and glucose control, in addition to early diagnosis and treatment, can help avoid these disorders. Diabetes can cause proliferative or non-proliferative DR, both of which eventually result in progressive retinal degeneration. Currently available therapies for DR include vasectomy, laser photocoagulation, and medication [26].

Leaky blood vessels are sealed with laser photocoagulation, which can help avoid blindness but may leave laser scars behind. The surgical removal of the vitreous gel and blood from leaking ocular vessels is known as a vasectomy; however, this technique only stops the bleeding temporarily and cannot stop it from happening again. Drug therapies include sustained-release corticosteroid implants that target inflammatory pathways and intravitreal injections of corticosteroids to lessen macular edema. Blood leakage and edema can be lessened by contemporary therapy options that use anti-VEGF drugs, such as ranibizumab and aflibercept, to decrease the expression of VEGF [27].

CHALLENGES OF THE OCULAR DRUG DELIVERY SYSTEM

The eye is the most accessible location for topical drug administration, enabling precise drug delivery to the internal or external surface of the eye. However, the ocular bioavailability of medications given topically, like eye drops, is frequently quite poor. The dosage that has been delivered can more easily drain into the nasopharynx thanks to the nasolacrimal system [28].

Various ophthalmic formulations, such as viscous solutions, ointments, gels, and polymeric inserts, have been created to improve ocular bioavailability and drug action duration. While these vehicles can extend corneal contact time to varied degrees, they confront patient acceptance issues. Ointments can induce clouded vision, polymeric inserts frequently lead to low patient compliance, and gels can cause lid sticking, making them less popular among users (see Figure 2) [29].

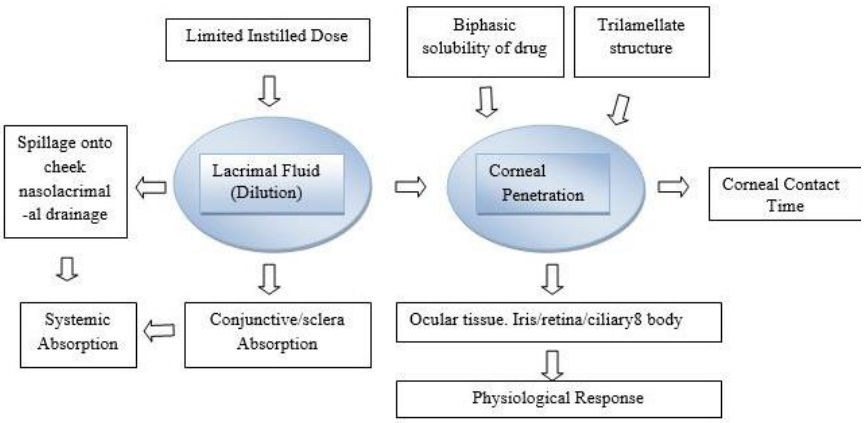

Figure 2. Fate of ocular drug delivery system.

To overcome the difficulty of limited ocular bioavailability, polymer-based in-situ gel-forming drug delivery devices can be used. Specific physicochemical changes in the cul-de-sac cause these systems to undergo sol-to-gel phase transitions. In recent years, a number of pH-sensitive systems (such as cellulose acetate phthalate and carbopol) and temperature-sensitive systems (such as poloxamer) have been developed to maintain ophthalmic drug delivery. In-situ gel-forming technologies can improve ocular bioavailability by increasing a drug's precorneal residence duration [30].

Efforts are also being made to increase the topical bioavailability and therapeutic response of ophthalmic medicines, especially those with low solubility and permeability. Increasing the viscosity

of the formulation has been proven to improve both ocular residence time and medication absorption at the ophthalmic site. This technique relies heavily on hydrophilic viscosity enhancers, such as cellulose, polyalcohol's, and polyacrylic acid. Sodium carboxymethyl cellulose, a highly cohesive polymer, is particularly useful due to its great adhesive qualities. Carbomer is often used to increase viscosity in both liquid and semi-solid compositions. Viscosity boosters are also useful in ophthalmic medications like lotions, gels, and ointments. Polycarbophil, a water-insoluble cross-linked polyacrylic acid, improves medication retention in the eye [31, 32].

The ocular route is a straightforward, non-invasive, and cost-effective alternative to existing systemic peptide administration modalities, such as buccal, nasal, rectal, vaginal, and dermal. This strategy avoids the pain of parenteral injections as well as the deterioration that occurs in the gastrointestinal tract. Adding a viscosity enhancer to an ophthalmic solution can assist reduce the size of the instilled drop while boosting viscosity, resulting in better drug absorption [33].

Various excipients and viscosity enhancers have been employed in ocular formulations, including chitosan, xyloglucan, arabinogalactan, cellulose derivatives (methylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethylcellulose), hyaluronic acid, alginic acid, and gellan gum. Using viscosity modifiers can extend the contact time between the drug and the ocular surface, further increasing bioavailability. Additional methods for improving drug delivery include diffusion, polymer degradation, chemical reactions, and the retention of particles at the delivery site after administration. However, challenges remain in designing therapeutic systems that deliver optimal drug concentrations at target sites with high therapeutic efficacy [34]. The anatomy and physiology of the cornea, combined with its barrier functions, result in rapid absorption of drugs, necessitating quick instillations of eye drops to maintain therapeutic levels in the tear film or targeted sites. Frequent dosing can lead to side effects, such as toxicity and cellular damage at the ocular surface [35].

Precorneal loss mechanisms, such as solution drainage, lacrimation, tear dynamics, tear dilution, conjunctiva absorption, non-productive absorption, transient residence time in the cul-de-sac, and tear turnover all contribute to low bioavailability of most ocular dosage forms. Furthermore, the corneal epithelial membrane's relative permeability presents significant challenges for delivering drugs to the anterior segment after topical administration [36, 37].

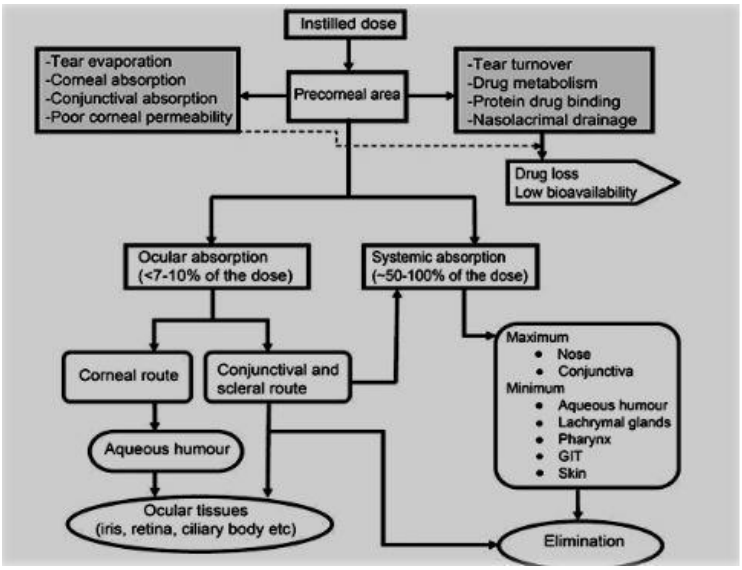

Figure 3. Challenges of ocular drug delivery system.

To achieve better clinical outcomes, topical dosage forms must strike a balance between lipophilicity and hydrophobicity, as well as have a longer contact time (Figure 3). As a result of various anatomical and physiological obstacles, only about 1% of the drug's instilled dose reaches intraocular tissues [38].

CHALLENGES IN OCULAR DRUG DELIVERY SYSTEMS

Anterior Segment Delivery Challenges

For ocular distribution, topical formulations are typically chosen over systemic formulations because of the particular difficulties caused by the structure of the eye. The conjunctiva and tear film are two precorneal obstacles that a medication must first pass through when it is applied to the eye. These barriers can seriously hinder the drug's ability to reach the active chemicals in the medication. The low bioavailability found in many ocular formulations is mostly caused by these precorneal loss mechanisms [39].

Often, repeated instillations of eye drops are necessary to maintain therapeutic medication levels in the tear film or at the target site. On the other hand, using extremely concentrated medication solutions frequently may result in hazardous side effects and even possible eye surface cellular damage [40,41]. This emphasizes the necessity of efficient methods to improve medication delivery while reducing side effects.

Posterior Segment Delivery Challenges

Ocular medications given topically have limited access to the posterior portion of the eye due to the BRB. The poor bioavailability of ocular drugs is often caused by a number of reasons that restrict drug delivery at the posterior ocular tissue. The BRB is essential for restricting the efficacy of intravenous medication delivery at the posterior location because it prevents pharmaceuticals that are delivered systemically from penetrating the retina. To effectively treat diseases affecting the posterior segment, it is essential to achieve high concentrations of vitreous drugs [42]. The BRB is more permeable to lipophilic molecules, allowing these drugs to enter the posterior segment more easily. However, frequent administration of high-concentration drugs can lead to systemic side effects, as summarized in (Table 1).

Preserving therapeutic concentrations for long periods of time while reducing the number of injections is a major difficulty when administering medications to the posterior region. Medications can be removed using the anterior route, which involves going through the aqueous humor and eventually coming out of the anterior chamber. A lot of drugs are also eliminated by the posterior route, which goes through the BRB and then into the bloodstream [43].

Table1. Marketed formulations of ophthalmic preparations with their role.

S. N.	Brand Name	Role	References
1.	Optimox	Bacterial conjunctivitis.	[33]
2.	BIOGRAN	Astringent at ophthalmic levege.	[27]
3.	Rugby	Relieve dry and irritated eyes.	[9]
4.	Lubifresh	Relief from burning.	[60]
5.	LACRYMED	Relieves dryness and soreness.	[13]
6.	COSS-HPMC	Prevent conjunctival and corneal damage.	[68]

APPROACHES TO ENHANCE OCULAR DRUG DELIVERY

Improvement of Corneal Permeability

Enhancing corneal permeability is one way to increase medication absorption following topical application. This can be accomplished by utilizing surfactants, permeation enhancers, calcium chelating agents, or ion pairs to change the physicochemical characteristics of ionized medicines, or

by manipulating the components of membranes or breaking epithelial tight junctions. Furthermore, prodrugs can be transformed into their active forms by enzymatic means after sufficient penetration has occurred [44]. Iontophoresis is another useful technique that uses a low-intensity electrical current to increase drug penetration by producing electro-osmosis and electro-repulsion effects.

Improvement of Corneal Retention Time

The use of excipients, especially viscosity-increasing polymers, is a useful method for prolonging corneal retention duration. Highly viscous eye drops, however, can lead to incorrect dosing, discomfort for a large number of patients, and obscured vision. In situ gels, on the other hand, provide a longer contact period than conventional solutions. Temperature-sensitive, ionic-sensitive, and pH-sensitive in-situ gels are the three categories into which they fall according to their transition characteristics. An ion-sensitive polymer called sodium alginate, along with HPMC and ciprofloxacin in a gel formulation, for instance, showed better residence time and prolonged drug release [45].

A mucus gel layer, made up of at least twenty anionic O-glycosylproteins known as mucins, covers the surface of the eyes. Residence time can be considerably increased by excipients that help bind to this mucus gel layer. The polycationic structure of chitosan and its abundance of reactive amino groups, which allow it to interact with the mucin layer, make it a popular mucoadhesive polymer. The niosomal system that Kaur et al. studied had higher activity, less adverse effects, and longer drug release. It was composed of Span 60, cholesterol, and chitosan. Because they can improve drug solubility and create covalent bonds with mucoadhesive polymers to extend residence time, cyclodextrins—cyclic glucopyranose oligosaccharides—are also frequently used in ocular formulations.

To improve the administration of drugs into the eyes, a number of colloidal delivery nanosystems have been created. Various medications can be transported using these systems, which can also boost bioavailability, decrease dosage frequency, minimize possible side effects, and enhance patient compliance [46]. Moreover, solid polymeric devices have been created as approved sustained-release ocular dosage forms. However, patients often reject solid strategies due to discomfort and interference with vision. For example, the sustained activity of bimatoprost was observed for several months following its incorporation into an insert, while a dexamethasone contact lens prepared via encapsulation demonstrated a 200-fold drug retention in the retina compared to conventional eye drops [47,48].

Use of Viscosity Enhancers

Because they can increase viscosity, which helps drugs enter the anterior chamber of the eye, viscosity-increasing polymers are frequently used as additives in ophthalmic formulations. Although these polymers are not very effective in increasing bioavailability in humans, they do enhance precorneal residence duration and transcorneal penetration by decreasing the clearance rate from the preocular area. Typical instances of these polymers are methylcellulose, hydroxyethylcellulose, HPMC, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) [49].

Because PVA has adhesive qualities and thickens the precorneal tear film, it was determined that, of formulations with a viscosity of 20 cSt, the tropicamide solution was the most effective. Along with surface spreading characteristics and the polymer's capacity to use water as it spreads across the ocular surface during blinking, these factors all affect drug retention in the precorneal tear film [50].

Gel Formulation

In their steady state, gels are defined as highly dilute cross-linked systems with stiffness. Gels have a three-dimensional cross-linked structure that makes them behave like solids even though they are mainly liquid. On the other hand, very viscous gels might not improve bioavailability. Rather, they have the ability to control the release of the medication, which results in a lower frequency of

dosage—typically just once daily. Drastically reduced patient compliance can result from high-viscosity solutions causing impaired vision and matted eyelids. Aqueous gels are frequently blended with viscosity-building agents such PVA, polyacrylamide, poloxamer, HPMC, carbomer, polymethylvinylether, maleic anhydride, and hydroxypropyl ethylcellulose. Further advances in controlled drug delivery systems are made possible by hydrogels, or swellable water-insoluble polymers [51].

Pro-Drug formulation

Prodrugs have the potential to improve many aspects of medication formulations, increasing their suitability for enhancing permeability through the cornea. In order to provide the active moiety with new properties like selectivity and site-specificity, the chemical structure must be changed. Timolol, pilocarpine, epinephrine, and phenylephrine are a few prodrugs. As a prodrug, dipiverine–a diester of pivalic acid and epinephrine–stands out for having an astounding seventeen times higher corneal permeability than epinephrine. Dipiverine's six-hundred-fold higher lipophilicity at pH 7.2 is the cause of this increased permeability. As a result, dipiverine can efficiently cover the entire eyeball with a lower dosage, producing a therapeutic effect similar to that of adrenaline. Conventional eye drops contain 2% adrenaline, whereas a 0.1% solution of dipiverine only has a little effect [52, 53].

Penetration Enhancers

When it comes to permeability, the corneal epithelial membrane is crucial. Thus, it is possible to improve the transport property around the cornea by increasing its permeability. Chelating agents, surfactants, bile acid salts, and preservatives (such as benzalkonium chloride) are examples of agents exhibiting these qualities; however, their use in the production of ophthalmic formulations is precluded due to local toxicity (Table 2) [54].

Liposomes

It is known that liposomes are minuscule vesicles made up of one or more lipid bilayers that are concentric and divided by aqueous buffer or water. Their capacity to form close contact with the surfaces of the eye, especially the cornea and conjunctiva, makes them popular in formulations intended for the ocular route, where they improve the absorption of drugs. It is possible to manufacture liposomes with a variety of ingredients, such as stearylamine, α-L-dipalmitoyl-phosphatidylcholine, phosphatidylcholine, and varying concentrations of lecithin or cholesterol. Biocompatibility, biodegradability, amphiphilicity, and comparatively low toxicity are the main benefits of liposomal delivery systems. They provide prolonged release of the medicine along with tailored delivery and site-specificity [55]. Drugs having low partition coefficients, poor solubility, low absorption, and medium to high molecular weights benefit most from liposomes. And when it comes to creating ocular delivery systems, liposome surface charge is quite important. It is the negatively charged corneal surface that preferentially captures positively charged liposomes; neutral or negatively charged liposomes are less likely to stick to the cornea. Numerous active pharmaceutical substances, such as acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin, have been found to be employed in liposomal ophthalmic formulations [56].

Table 2. General considerations for the design of ocular drug delivery formulations.

Component	Properties	References
Drug molecule	In order to pass through the corneal epithelium and stroma, the optimal partition coefficient must be maintained. Both lipophilic and hydrophilic, and tiny enough (less than 10 Å) to pass through the corneal epithelium. It's possible that the stroma will block macromolecules more effectively than the endothelium. Ideal partition coefficient within the interval of 10–100. To prevent irritation and the ensuing lacrimation, the pH should be 7.4.	[25]
Carrier	The drug particle size is less than 10 μm, with a diameter of less than 10 mm. Provide the medication for an extended duration without experiencing any negative effects. Dosage dumping should never happen.	[30]

	To aid in the drug's release, drink plenty of water while crying.	
Buffers	Low doses are used to prevent irritation.	[32]

Niosomes and Discosomes

Using non-ionic surfactants, niosomes are bi-layered, chemically stable nanocarriers that can carry both hydrophilic and hydrophobic medications. Niosomes have many benefits over liposomes, which are frequently unstable and expensive phospholipids made of. Liposomes can also be chemically unstable and prone to oxidative destruction. Because they are non-immunogenic, biodegradable, and biocompatible, they assist prolong the period of time the medication is in touch with the cornea, hence increasing the drug's bioavailability. Moreover, discosomes a modified form of niosomes act as a vehicle for eye medications. Discosomes usually have a size between 12 and 16 μm, which helps keep them out of the bloodstream and makes them fit better inside the conjunctival sac due to their disc-like form. Discosomes are different from niosomes in terms of their size and makeup [57].

Nanoparticles

Drugs can be dissolved, entrapped, encapsulated, or adsorbed within polymeric colloidal particles known as nanoparticles, which have a size range of 10–100 nm. Metals, lipids, phospholipids, natural or manufactured polymers, and other biodegradable substances make up these nanoparticles. Drugs can be incorporated into a matrix or affixed to the surfaces of biodegradable polymers that are utilized in the manufacture of nanoparticles using a variety of formulating techniques. Polylactides (PLAs), polycyanoacrylate, poly (D, L-lactides), and natural polymers, such as chitosan, gelatine, sodium alginate, and albumin are among the nanoparticle kinds that have been used in ocular drug delivery. In the last 10 years, nanoparticles have shown great promise as drug delivery vehicles for eye illnesses [58,59].

Nanocapsules, which are tiny capsules with a core chamber encircled by a polymeric membrane, and nanospheres, which are solid matrix spheres, are the two distinct forms of nanoparticles. Betaxolol and carteolol, which are present in the oily core of nanocapsules in their unionized form, diffuse more easily into the cornea, making them more effective than nanospheres. Numerous investigations have demonstrated that the mucoadhesive characteristics of nanocapsules can lengthen residence times and improve biological responses, which in turn improve drug bioavailability at the eye location and decrease dose frequency. The cyclosporine-containing poly-ε-caprolactone nanoparticles demonstrated better corneal absorption than the medication's greasy solution [60].

Nanosuspension and Nanodispersions

Drugs that dissolve poorly in water are suspended at the nanoscale in an appropriate dispersion media using a formulation known as a nanosuspension. For medicinal compounds that form high-energy crystals and become insoluble in both lipophilic and hydrophilic environments, this method is especially helpful [61]. Inert polymeric resins are utilized to make polymeric nanoparticle solutions, which are efficient means of delivering drugs. Both medication release and bioavailability may be enhanced by these carriers. They are suited for ophthalmic medications due to their inert nature, which prevents irritation of the iris, cornea, or conjunctiva. One such carrier is a dispersion of polymeric nanoparticles that contains flurbiprofen (FLU) as the active component, with the polymers being Eudragit RS 1001 and RL 1001 [62].

Additionally, alginate-chitosan nano-dispersions have been developed for sustained drug delivery and improved transcorneal permeation.

Microemulsion

The term "microemulsion" refers to a stable dispersion of water in oil that is produced by lowering interfacial tension with the addition of a combination of surfactants and co-surfactants. In addition to reducing the frequency of administration, this formulation improves the bioavailability of eye

medications. Microemulsions have a small droplet size (about 100 nm), a clean appearance, and great thermodynamic stability as their main benefits. An oil-in-water system comprising propylene glycol, lecithin, PEG 200, and pilocarpine as the active medication, as well as isopropyl myristate as the oil phase, is an illustration of a microemulsion formulation [63].

Dendrimers

Recently, dendrimers – symmetric structures made of repeatedly branching molecules encircling a central core – were suggested as efficient delivery systems for topical ocular medications. Phosphorus dendrimers, poly-L-lysine (PLL), polypropylenimine (PPI), and poly (amidoamine) (PAMAM) dendrimers are frequently used in ocular applications. In addition to delivering nucleic acid-based medications to the eye, these dendrimers work well with hydrophilic (such as antibiotics) and lipophilic (such as anti-glaucoma) medications. According to research, these carriers' surfaces can be modified through acetylation or PEGylation, which can also assist to lower their toxicity and improve their effectiveness. Longer drug residence times in the precorneal region, higher bioavailability, and longer therapeutic effects are benefits of employing dendrimers as drug carriers for topical treatments [64, 65].

In-Situ Forming Gel

Early in the 1980s, researchers proposed the idea of using in situ gel to deliver drugs directly to the eye. Increasing viscosity is the main goal of this novel strategy, which will lessen medication drainage from the cornea. At the time of application, these pourable gels are liquid. They go through a phase transition and become a viscoelastic gel as they reach the cul-de-sac of the eye. This allows them to adapt to changes in the surrounding environment and enhances the drug's bioavailability. There are certain disadvantages to in situ gels, though, since variables like pH, temperature, and ion concentration can affect how well they work. When comparing in-situ gelling devices to traditional eye drops, the former provides a more potent and longer-lasting therapeutic impact [66].

Microparticles

Isotropic, clear to translucent systems consisting of water, surfactant, and oil droplets, microparticles range in size from 20 to 200 nm. Drugs are either covalently linked to the polymer's backbone or uniformly disseminated inside a polymeric matrix in these micron-sized polymeric particles. Following topical administration to the eye, these particles reach the ocular cul-de-sac, where a variety of mechanisms, including diffusion, chemical reactions, and polymer degradation, cause the medication to be released. By lengthening the precorneal residence duration, microparticles enable long-term and continuous medication release [67]. This leads to a decrease in the frequency of dose and an increase in ocular bioavailability. However, because microparticulate preparations can irritate eyes due to their relatively high particle size, it is typically not advised to use them for ocular delivery. The beneficial characteristics of microparticles include their biodegradability [68].

Ocular Inserts

Designed to be inserted into the conjunctival sac of the eye, ophthalmic inserts are solid patches that substantially slow down the rate of medication release. Due to their ability to maintain a constant drug concentration and enable continuous, regulated delivery of the medication, these inserts successfully address the problem of frequent dosing [69]. By extending the duration of contact, ocular inserts can enhance drug absorption while lowering the required dosage and frequency of administration. This is one of its key benefits. The sensation of a foreign object in the eye, difficulties with self-insertion, and worries about the insert coming loose are some of the disadvantages, though, and may lead to patient noncompliance. There are several methods for creating ocular inserts, and the end products are hydrogel-based formulations that are soluble and erodible [70].

Iontophoresis

Because it is a non-invasive method of delivering medication to the front and posterior parts of the eye, ocular iontophoresis is a promising field in drug delivery research. With the help of this

technology, ionized pharmaceuticals can be transferred across membranes with a modest electrical current. Electro-osmosis and migration are the two main mechanisms that assist drug mobility. Transcorneal, corneoscleral, and transcleral iontophoresis are the three varieties of iontophoresis; transscleral iontophoresis is thought to be very beneficial. For this reason, the OcuPhorTM system – which includes an applicator, a dispersive electrode, and a dose controller – was created expressly to transport the active drug moiety into the retina-choroid. Similar to this, the VisulexTM tool facilitates the deliberate passage of ionized molecules through the sclera [71]. Ocular iontophoresis has been used successfully in the following cases: For this reason, the OcuPhorTM system which includes an applicator, a dispersive electrode, and a dose controller was created expressly to transport the active drug moiety into the retina-choroid. Similar to this, the VisulexTM tool facilitates the deliberate passage of ionized molecules through the sclera. Antibiotics, such as gentamicin, tobramycin, and ciprofloxacin have been successfully treated with ocular iontophoresis; vancomycin, on the other hand, is not effective because of its large molecular weight. Positive outcomes have also been reported with drugs, such as antisense oligodeoxynucleotides (ODNs) and dexamethasone [72].

Future Prospects

When it comes to treating eye problems in both the anterior and posterior segments, non-invasive, sustained-release devices are crucial since the challenges involved in drug delivery to the eye are larger than those pertaining to the skin. Maintaining therapeutic drug concentrations at the targeted region for a prolonged duration while avoiding systemic exposure is the desirable feature of an ocular drug delivery system. Better patient compliance is a crucial consideration in the development of future ocular medication delivery technologies, and such systems would improve comfort and convenience of use in the process. Researchers are coming up with pertinent solutions that either integrate many technologies or enhance individual approaches in order to overcome the shortcomings of the current technology. Droppable gels containing liposomes and nanoparticles have been the subject of recent research on ocular delivery techniques.

The challenges to be faced by topical ocular drug delivery systems in the future are as follows:

- Usually, the bioavailability of the ocular route is limited to 15–20% of the administered dose.
- The majority of commercially available ocular formulations exhibit a significant degree of non-specificity, underscoring the necessity of creating novel therapeutic candidates with ocular application specificity.
- More investigation is needed into non-corneal pathways, especially for ionic or water-soluble substances. Additionally, medication molecules that preferentially absorb through the cornea and limit absorption via the nasal mucosa must be the focus of this research.
- To ensure that delivery systems are designed and packaged appropriately, more research is required. Considerable progress in scientific and technological domains, namely in the areas of nanotechnology and biomaterials, is imperative for enhancing ocular medication delivery mechanisms.

CONCLUSIONS

Because viscosity enhancers can increase patient compliance and make self-medication easier, ocular drug delivery formulations including them are generally recognized. Enhancers of this kind minimize drug loss through tears and lachrymal fluid, while simultaneously increasing precorneal residence duration and ocular bioavailability. The principal purpose of viscosity enhancers is to increase the viscosity of the formulation, hence facilitating its prolonged retention at the ocular site. Furthermore, pharmacological qualities including penetration and precorneal residence time can be improved by altering polymers.

In order to decrease surface tension, extend corneal contact duration, impede drainage, and eventually boost bioavailability, viscosity-increasing compounds are used. Their efficacy has been observed especially in the treatment of aqueous tear deficiency-related dry eye symptoms. High

efficacy and a prolonged residence duration are provided by viscous topical ophthalmic solutions, which also slow down the rate at which the ocular surface drains.

Optimizing the concentration of these solutions is crucial to prevent problems like impaired vision and make sure they don't get too viscous. By changing the integrity of the corneal epithelium, viscosity enhancers have been demonstrated to improve corneal absorption and act as drug-delivery vehicles by extending the duration of contact at the ocular location

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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