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A REVIEW ON ADVANCED AND CHALLENGES IN OCULAR DRUG DELIVERY SYSTEMS

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ABSTRACT

Eye conditions that are frequently encountered in daily life can be prevented or treated with routinely used dosage forms, such as eye drops and ointments. Because of the eye's protective and anatomical structure, delivery to the internal components of the eye is still problematic. One of the most intriguing and difficult issues facing pharmaceutical firms today is ocular medication delivery. The primary issue with traditional dose regimens is the drug's bioavailability. In-situ-forming ophthalmic drug delivery systems made from polymers that display reversible liquid-gel phase transition can overcome the poor bioavailability of ophthalmic solutions brought on by dilution and drainage from the eye. To address these issues, other kinds of dosage forms, including liposomes, nanoparticles, and There are now micro emulsions available. In terms of increasing medication bioavailability, lowering toxicity, and lowering dosing frequency, controlled drug delivery systems are superior to traditional dosage forms in many ways. More recent studies on ophthalmic drug delivery systems focus on combining multiple drug delivery technologies, such as build-up systems that slow down the drug's removal while simultaneously extending the vehicle's contact time at the ocular surface. This review concentrates on new advancements in both traditional and unconventional ocular dose formulations and items that extend medication contact times. contact the cornea, improve their bioavailability, and use various goods and techniques for both delivery methods.

KEYWORDS: Ophthalmic drugs, nanoparticles, eye drops, micro-emulsions, ointments.

INTRODUCTION

OCULAR DRUG DELIVERY SYSTEMS

The well-established method of administering medications for the treatment of many eye conditions, such as dry eye, conjunctiva, eye flu, etc., is topical application to the eye.[1] Topical administration is typically preferable to systemic administration for eye diseases because any drug molecule supplied through the ocular route first passes through the pre-corneal barriers before entering the cornea's anatomical barrier. These first barriers, which are made up of the conjunctiva and tear film, delay the drug's entry into the eye.[2] Blinking, baseline and reflex lacrimation, and drainage are some of the eye's defence mechanisms that reduce a drug's bioavailability and aid in the quick removal of foreign objects from the surface of the eye, such as dust particles, bacteria, and medications. Regarding 70% of the eye dose formulations on the market, the most widely accessible ophthalmic medications are drops and ointments. However, these preparations are quickly removed from the ocular surface after being injected into the eye because of the eye's lachrymal nasal drainage and blinking tear flow1. A typical dropper for traditional ophthalmic solution delivers 50–75 µl of solution per drop, and some of these drops quickly drain until the eye returns to its normal resident capacity of 7 µl. Very little medication is able to reach the cornea and inner tissue of the eye as a result of this drug loss in the front of the eye. The drug's actual corneal permeability is quite low, and the implanted solution typically has a corneal contact time of 1-2 minutes in people, which is less than 10%. As a result, very little medication truly enters the cornea and reaches the intraocular tissue. Owing to these restrictions, more recent pharmaceutical ophthalmic formulations have been developed in the last three decades, including in-situ gel, nanoparticles, liposomes, nano-suspensions, micro-emulsions, iontophoresis, and ocular inserts. These formulations increase the drug's bioavailability in a controlled and sustained manner. The optimal ocular medication delivery system must be able to release the medication continuously and stay in the region in front of the eye for an extended amount of time. Optimizing ocular medication delivery is therefore required; the best methods for doing so include the addition of polymers of different grades, the creation of colloidal suspension or the use of erodible or non-erodible inserts, and the creation of viscous gel to extend the pre-corneal drug retention. Bio adhesive systems

might be polymeric solutions or suspensions of micro particles.[1–2]

Because of its intricate anatomical and physiological makeup, the human eye is a special organ with distinct physiological functions. Its many different structures make it difficult to create drug delivery systems for it. The main issue with the traditional ocular drug delivery method utilizing eye drops is that they are quickly and widely removed from the eye, which results in a significant loss of the medication.[3,4] Only a tiny percentage of a medication in eye drops makes it past the corneal layer and into the interior tissues of the eye.[5,6] The two methods of ocular drug delivery that fall under this broad category are those that deal with the anterior and posterior portions. Conventional drug delivery methods such eye drops, suspensions, and ointments are ineffective for treating vision-threatening ocular disorders.[7] The disorders that affect the anterior portion of the eye are the sites of action for about 90% of the ophthalmic formulations on the market, which are in the form of eye drops.[8] The posterior portion of the eye cannot be reached by topical medication delivery using traditional methods. When applied in the cul-de-sac, formulations such as eye drops and ointments are rapidly removed from the eye area due to lachrymal nasal drainage and tear flow. It requires frequent dosage to produce a therapeutic effect because the majority of the drug is drained away and only a little percentage reaches the site of action. The retina, vitreous humour, and choroid are all parts of the posterior segment of the eye; conditions affecting these areas can be treated with intravenous and intravitreal drug delivery systems, implants, or by delivering the medication through the periocular route; however, a high concentration of the medication is also required.

When it comes to ophthalmic drug delivery, the posterior portion of the eye is often a target for innovative drug delivery techniques.[9] The purpose of this review and this study's novelty is to draw attention to the most recent advancements in pharmaceutical ophthalmic formulations, including the creation of in-situ gels, nanoparticles, liposomes, and nano-suspensions, micro emulsion, ocular inserts, and so forth, and their advancements to address the issues with the current conventional dosage forms while simultaneously enhancing the drug's bioavailability and sustained release at the intended site.[10]

Physiology of eye

The transparent cornea, lens, and blood vessel-free vitreous body make up the eye. Aqueous humour, which has the same osmotic pressure as blood and high oxygen content, carries nutrients and oxygen to this non-vascular tissue. The anterior chamber of the eye, which is in front of the lens, is filled with 300 µl of human aqueous humour. At the cornea-sclerotic junction, a thin layer of epithelium covers the cornea and is continuous with the conjunctiva. The cornea's primary bulk is made up of collagen layers that cross over one another, and it is surrounded on both the front and back by elastic lamina. An endothelial layer covers its posterior surface. There are many free nerve terminals in the cornea. The opaque white sclera, which is made of stiff fibrous tissue, continues posteriorly from the transparent cornea. The intraocular tension that is continuously maintained in the eye is tolerated by the cornea and sclera. The four structures that make up the lacrimal apparatus are responsible for continuously cleaning and lubricating the eye.

1. Lacrimal glands.
2. Lacrimal canals.
3. Lacrimal sac.
4. Nasolacrimal duct.

At a turnover rate of 16% per minute, the lacrimal fluid released by the lacrimal glands is drained onto the upper eye lids conjunctiva. It passes over the eyeball before being picked up by the eyelids' blinking motion. The lacrimal sac is compressed by muscles linked to blinking reflux; when these muscles relax, the sac swells and draws lacrimal fluid from the margins of the eyelids along the lacrimal canals into the lacrimal sacs. Human lacrimal fluid, an isotonic aqueous solution of sodium chloride and bicarbonate with a pH of 7.4 has a volume of 7 µl. It is used to remove foreign objects from the conjunctival sac or to dilute irritants. It has lysozyme, which lowers the number of germs in the conjunctival sac due to its antibacterial action. The pre corneal and corneal gaps include physiological barriers that prevent the medicine from diffusing and being productively absorbed when administered topically. The pre-corneal limitations of solution drainage, lacrimation, tear dilution, tear turnover, and conjunctival absorption are the causes of the low bioavailability of traditional ocular dose forms.[11]

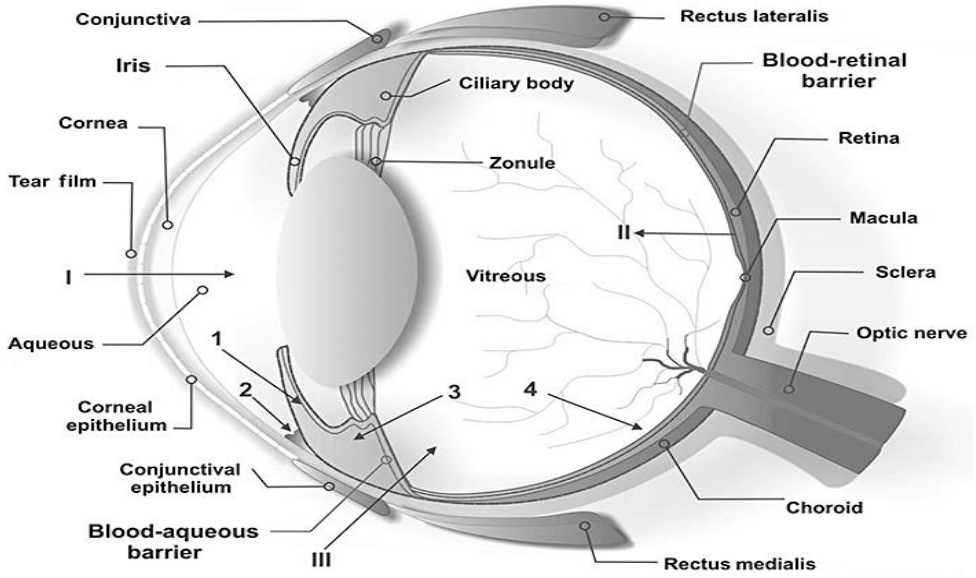

Fig. Eye anatomy and physiology.

The Cornea

In front of the iris and pupil, the cornea is the most anterior component of the eye. The majority of corneal nerves are sensory nerves that originate from the ophthalmic branch of the trigeminal nerve, making it the body's most densely innervated tissue.[12] An adult human eye's cornea has a curvature that is relatively stable throughout life, with an average horizontal and vertical diameter of 11.5 mm and 10.5 mm, respectively.[13] In photopic conditions, the optic zone (pre-pupillary cornea), which supplies the majority of the cornea's refractive function, is situated in the centre of the cornea, anterior to the pupil, and has a diameter of 4 mm. The branches of the anterior ciliary arteries terminate at the cornea's avascular surface. They create arcades that supply the peripheral cornea in the limbus.[14] As a result, the physiology and pathology of the central and peripheral corneas differ greatly.

The epithelium, Bowman's membrane, the lamellar storm, Descemet's membrane, and the endothelium are the five distinct layers that make up the human cornea (Fig. 3).[15] The tear film covers the surface of the corneal epithelium, smoothing out micro-irregularities as well as protecting the cornea from microbial invasion and harm from chemicals, toxins, or foreign bodies.[10] It is composed of an inner water-mucous layer and an outer lipid layer. With every eyelid blink, the tear film spreads because of interactions between the mucous layer and the epithelial cells.

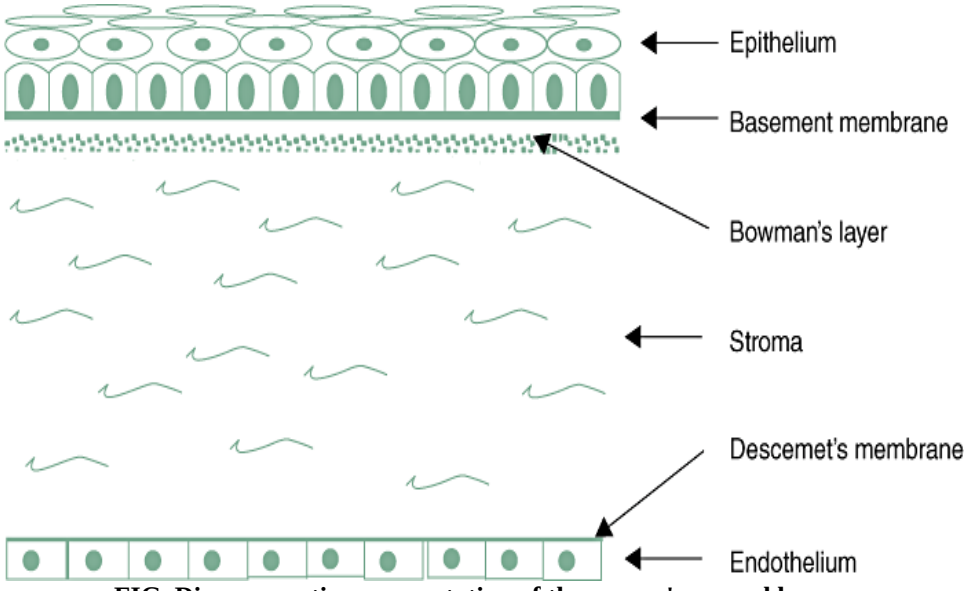

FIG. Diagrammatic representation of the cornea's several layers.

Two to three layers of surface cells, two to three layers of wing cells, and one layer of basal cells make up the corneal epithelium.[15] Because of the existence of micro place, which are ridge-like folds of the plasmalemma that interact with the tear film on top, the surface of the superficial epithelial cells is uneven. Every seven to ten

days, a population of pluripotent stem cells that live in the palisades of Vogt near the corneoscleral limbus renews the corneal epithelium's cells.[15] After migrating to the central cornea, the stem cells undergo differentiation into transient amplifying cells.[16,17] Recent studies have also found oligopotent stem cells in the corneal epithelium of pigs and mice, indicating that corneal stem cells are not limited to the limbus.[18] Cell connections provide the corneal epithelium its exceptional stability and impermeability.[15] Additionally, it has a strong connection to the basal lamina. The latter is primarily composed of type IV collagen and laminin and is released by the basal cells. Nearly every epithelial cell interacts with nerve cells because innervations are necessary for the functioning of the epithelium.

The cornea's structural integrity is provided by the corneal lamellar stroma, which is 500 µm thick. Collagen and proteoglycans, which are ultimately essential for the cornea's clarity and moisture, are secreted by stroll keratocytes. The Bowman's layer, an acellular zone 10–15 µm below the basal lamina, separates the stroma from the epithelium. From limbus to limbus, collagen fibrils are organized in 200–250 parallel lamellae, making up the majority of the stromal extracellular matrix.[19] The cornea's mechanical strength is attributed to the network of collagen fibrils, and corneal transparency depends on its regular arrangement. The cornea's mechanical strength and dioptric stability are likely influenced by the pre-pupillary cornea's more compactly packed fibrils compared to the peripheral cornea.[20] Proteoglycans with side chains of keratan suffocate or chondroitin sulphate/derma-tan sulphate envelop the stromal collagen fibrils. These proteoglycans aid in hydration regulation and have a crucial structural role. The stroma's main cell type, keratocytes, contribute to the organization of the tissue. These star-shaped cells interact with the corneal epithelium and are connected to one another by lengthy cytoplasmic extensions called morphologic and functional syncytium.

The Retina

The tissue that surrounds the vitreous chamber on the inside of the eye is called the retina. The optic cup gives rise to the vertebral retina during development. The latter is created when the optic vesicle, an extension of the embryonic forebrain, invaginated. The outside wall of the optic cup, which is encircled by the choroid and sclera, develops into the retinal pigment epithelium (RPE), whereas the inner wall, which surrounds the vitreous cavity, eventually becomes the neural retina.[21,22] The cornea and sclera around the retina protect it and keep it in the proper posture. The Müllerian glia serve as the structural core of the neural retina, while photoreceptors, bipolar cells, horizontal cells, amacrine cells, and ganglion cells comprise the six main types of neurons that make up the neural retina. The neuronal retina's cells are organized in multiple parallel layers (Fig. 4).[21–23] The photoreceptor cells' outer segments are located near the RPE, proximal to the nuclei, which are located in the outer nuclear layer. Within the inner nuclear layer of the retina are the nuclei of the amacrine, bipolar, horizontal, and Müllerian glia. There are plexiform layers on either side of the inner nuclear layer. The photoreceptors of the outer plexiform layer are connected to bipolar and horizontal cells, while amacrine and bipolar cells create synapses with ganglion cells in the inner plexiform layer. The ganglion layer contains the ganglion cells' nucleus, while the nerve fibre layer contains their axons. The retina is covered in Müllerian glia processes. Through the formation of junctional complexes with photoreceptors and one another, the apical processes create the outer limiting membrane. The inner limiting membrane is made up of the vitreal processes' opposing end-feet. The Müllerian glia's lateral processes make contact with blood vessels and neurons, and they establish synapses with axons in the nerve fibre layer and dendrites in the plexiform layers.[21]

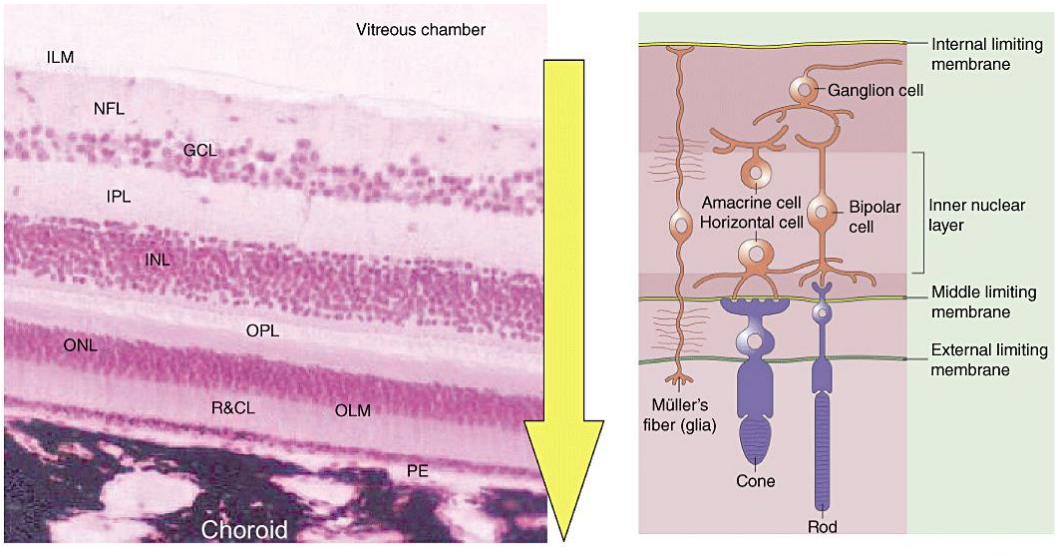

FIG. The cells and layers of the retina.

Rods and cones are the two types of photoreceptors found in the eyes of the majority of vertebrates. Rods are around 20 times more common than cones in humans.[21] Phototransduction, or the transformation of light into an electrical signal, is carried out by the photoreceptors. Pigments are present in the membranes of the photoreceptors' outer segment discs for this reason. The pigments in cones, which are in charge of colour vision, have absorption peaks in the blue, green, or yellow regions of the spectrum. The absorption peak of the rod pigments is located in the blue-green region of the spectrum. Rods are not involved in colour vision and become active in low light levels.

The Tear

The tear film is one of the precorneal barriers that lowers the effective concentration of the medications administered because to the tear's dilution[24], faster clearance, and drug molecule binding to the tear proteins. The turnover rate is about 1 µL/min.[25] Furthermore, the cul-de-sac size is just 7–10 µL, while the instillation dosage amount is typically 20–50 µL. The extra volume can either leave through the nasolacrimal duct or flow out onto the cheek.[26]

Blood-Retinal Barrier

Drug transport from the blood into the retina is restricted by the blood-retinal barrier (BRB). The tight connections of RPE and retinal capillary endothelial cells, known as iBRB for the inner BRB and BRB for the outer BRB, make up the BRB. There are few vesicles and no fenestration in the retinal capillary endothelial cells. Endocytosis or transcytosis, which may be receptor-mediated or fluid phase needing adenosine triphosphate, has been defined as the function of these endothelial vesicles. Müller cells and retinal capillary capillaries have a close spatial interaction that keeps the iBRB functioning normally during nutrition intake and metabolite disposal.[27]

Routes of Ocular Drug Delivery System

Topical Administration

Over 95% of marketed ocular medications are administered topically, making it the most popular method of delivering ocular drugs. Although it is a non-invasive method, its short residence time and inadequate corneal penetration result in a low bioavailability (<5%).[28] Additionally, blinking, tear drainage, and entering the systemic circulation through the nasolacrimal route all lower bioavailability. Frequent and high dose concentrations are required for topical delivery, which may cause major adverse effects. Additionally, patient compliance may be impacted by frequent doses.[28,29] Elderly and disabled patients should not use topical routes.[30] Terconazole used topically as bilosomes demonstrated improved medication safety and penetration.[31] High corneal absorption and corneal retention were seen when sertaconazole nitrate was applied topically as mixed micelles or cubosomes.[32,33] Higher antifungal activity and more itraconazole penetration both in vivo and ex vivo were demonstrated by the β-cyclodextrin-based micellar system.[34] Dorzolamide hydrochloride applied topically as proniosomal gels demonstrated regulated ex vivo penetration, enhanced bioavailability and stability.[35]

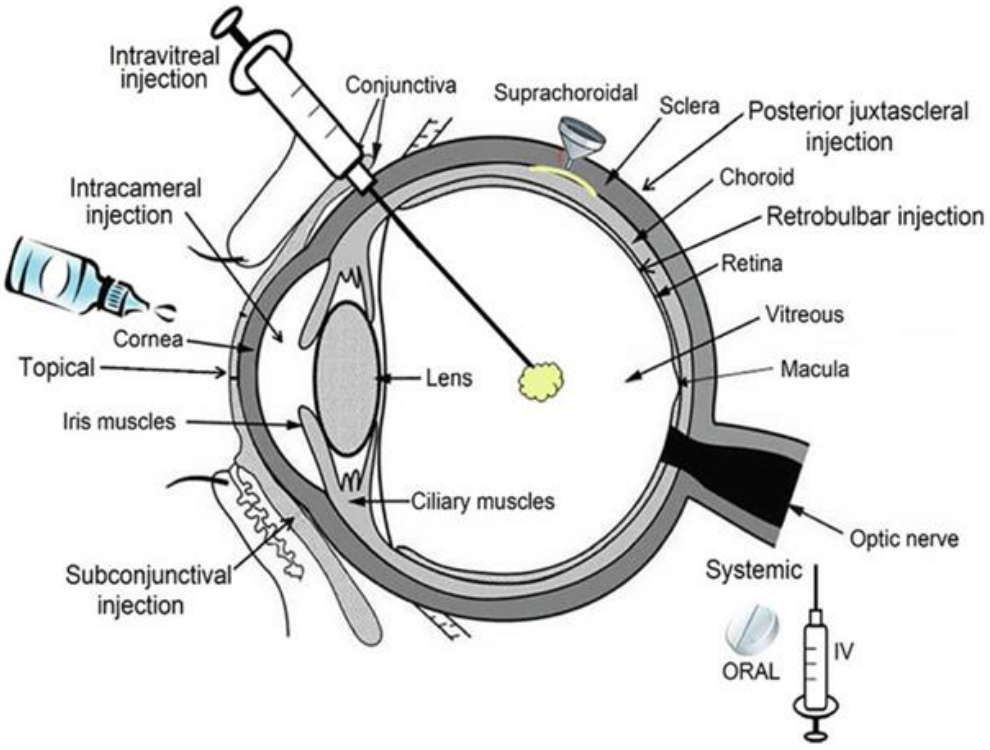

Fig. Different routes for ocular drug delivery.

Intracameral Injections

Intracameral injections entail administering an antibiotic straight into the vitreous cavity or the anterior part of the eyeball. It is typically carried out following cataract surgery to prevent endophthalmitis, which can be brought on by an eye infection. It was recently reported that hydrogel functionalized with vinyl sulfone and thiol groups could be used for intracameral injection to treat glaucoma.[36]

Intravitreal Injections/Implants

An intravitreal injection is a method of administering medication to the vitreous near the retina at the rear of the eye. One intravitreal injection of vitamin E/polylactic-co-glycolic acid microspheres containing neurotrophic factor produced from glial cell lines is part of a novel therapeutic strategy for glaucoma. For six months, this method offered a lasting release. Following intravitreal injection of polymer-free dexamethasone dimer implants, comparable outcomes were seen.[37] For the treatment of diabetic macular oedema and neovascular age-related macular degeneration, intravitreal injection of the biodegradable Rho kinase and protein kinase C inhibitor demonstrated persistent release for roughly six months.[38]

Retrobulbar Injection

In order to administer the drug behind the globe into the retrobulbar space, a needle is injected via the orbital fascia and eyelid. Compared to intravenous administration, amphotericin B administered retrobulbar had greater antifungal activity.[39] Chlorpromazine injections administered retrobulbar Ly are used to treat painful blind eyes.[40] Macular oedema caused by retinal vein blockage is treated with a retrobulbar injection of triamcinolone.[41]

Subconjunctival Injection

When topical medication treatment results in very poor drug penetration into the anterior portion of the eye, subconjunctival injection is commonly employed. Steroid injections under the eyes produced as PEGylated liposomes to treat uveitis shown long-lasting anti-inflammatory action and at least one month of ocular tissue targeting.[42]

When brinzolamide PLGA nanoparticles were injected subconjunctivally, the IOP was successfully managed for ten days.[43] In mice with graft versus host disease, subconjunctival injection of human mesenchymal stromal cells guaranteed a significant reduction in corneal inflammation and squamous metaplasia.[44]

Juxta scleral Injections

Some posterior portion symptoms that cannot be treated with a traditional topical approach are treated with juxta scleral injections. It is used to treat conditions associated to diabetes, trauma, and cystoid macula oedema. Juxta scleral injections of anecortave cortisone, which demonstrated prolonged release for six months in the choroid and retina, are a novel therapy option for AMD.[45] To address retinal genes, sophisticated trans-scleral microneedles have been developed to deliver adeno-associated viruses.[46]

Table: Examples of Different Routes of Ocular Drug Delivery. Description of the Investigated Drug, Route of Administration, and Major Outcome.

Model drug	Route of administration	Major outcome
Terconazole	Topical	Enhanced drug permeation and safety
Sertaconazole nitrate	Topical	high corneal uptake and corneal retention
Itraconazole	Topical	higher ex vivo and in vivo permeation
Dorzolamide hydrochloride	Topical	controlled ex vivo permeation, increased stability and improved bioavailability
Agomelatine	Topical	Sustained drug activity and prolonged drug retention
Ketoconazole	Topical	Improved corneal permeation, prolonged ocular action, and increased bioavailability
Voriconazole	Topical	Increased drug solubility, efficacy, stability, and duration of action
Amphotericin B	Retrobulbar injection	Higher antifungal efficacy
Chlorpromazine	Retrobulbar injection	Manage blind painful eyes
Triamcinolone	Retrobulbar injection	Handle macular edema resulted from branch retinal vein occlusion
Dexamethasone	Iontophoresis	higher efficacy in managing non-infectious anterior uveitis
Besifloxacin	Iontophoresis	Increased bioavailability
Acyclovir	Iontophoresis	higher permeation and bioavailability

Irrigating Solutions

These solutions are aseptically prepared without the use of preservatives. Surgeons employ them as balanced salt to remove blood and cellular waste and keep the eye's hydration volume at the proper level.[47] There are numerous instances that highlight how crucial these solutions are. For instance, employing ketorolac (0.3% w/v) and phenylephrine (1% w/v) in the irrigation solutions can reduce the length of time needed for cataract surgery and prevent pupil miosis.[48]

Iontophoresis

A method for delivering drugs into the back of the eye is called iontophoresis. A voltage gradient is used in this process. Instruments based on microneedles are used in novel systems. In comparison to suprachoroidal injection, they had increased the amount of formula that was administered to the back of the eye.[49] Compared to drug uptake into choroidal capillaries, the duration of iontophoretic administration during contact lens use is 550–1300 times shorter.[50] Higher penetration and bioavailability were the outcomes of short-duration iontophoresis of the acyclovir prod drug.[51] Dexamethasone phosphate ocular iontophoresis shown improved effectiveness in treating non-infectious anterior uveitis.[52]

Dosage Forms

Liquid Dosage Forms

Eye Drops

Over 95% of the marketed ocular products are eye drops. They administer the drug to the eye's anterior region. Their benefits include recognized stability and ease of administration. Nevertheless, its drawbacks include a short retention period (less than five minutes), low bioavailability, and severe adverse effects brought on by frequent high concentration delivery.[53] Several nano system platforms had been developed to solve their drawbacks. Cyclosporine was for mutated as a mucoadhesive nano system utilizing poly (D-L lactide)-b-dextran. Nanoprecipitation technique was adopted for the formulation. The final product demonstrated small particle size, enhanced permeability, and drug retention.[54] Formulation of the antibacterial hesperetin as micellar system showed minute particle size, high percentage entrapment efficacy, greater penetration, and enhanced efficacy.[55]

Eye Suspensions

Ocular suspensions are hydrophobic pharmacological dispersions in an aqueous solvent. Because of drug retention in the conjunctival cul-de-sac, they have longer contact times. During the preparation phase, the tear fluid's particle size, solubility, and rate of dissolution are crucial.[56] Particles smaller than 10 µm are typically more soluble, dissolve more quickly, and are less retained on the surface of the eye. On the other hand, particles larger than 10 µm may cause tearing and irritation of the eyes.[57] One of the drawbacks of ocular suspension is its lack of stability. Since the particles have a tendency to clump together and are difficult to disperse, they cannot be kept in a freezer. Additionally, alterations in crystal size during storage will affect the drug's solubility and bioavailability. Following their administration, hazy vision may also occur. Enhanced stability, antifungal activity, and extended retention were demonstrated by improved ocular delivery of Posaconazole in a polymer system of Carbopol 974P and xanthan gum utilizing a high-pressure homogenizing approach.[58] A high-speed liquid-liquid shear technique was used to create an ultra-fine ocular solution of rebamipide. This formulation demonstrated improved stability, small particle size, and increased transparency.[59]

Eye Emulsions

An emulsion is a biphasic system that has been solubilized by the addition of stabilizers or surfactants. Delivering hydrophobic medications is one of the benefits of ocular emulsions; oil-in-water (O/W) emulsion has improved contact time, bioavailability, and is less irritating to the eye.[60] The creation of a nano emulsion using high-pressure homogenization improved the ocular distribution of polymyxin B sulphate and dexamethasone acetate. To improve ocular adherence, a positive charge inducer was used. The final formulation demonstrated improved retention time, decreased particle size, and increased stability.[61] Triamcinolone acetonide microemulsion was created using the water titration method. It demonstrated enhanced permeability and reduced particle size.[62]

Semisolid Dosage Forms

Eye Gels

Eye gels are a semisolid medication with a significant water content. its viscosity contributes to its improved absorption and retention time. Blurred vision may still occur even though gels contain a lot of water. Ocular gels could be made from a variety of polymers, including carboxymethyl cellulose, hydroxypropyl methylcellulose, acrylic acids, and polyacrylic acid.[63] A pronioso mal gel of curcumin with improved anti-inflammatory action and a significant reduction in particle size was created using the coacervation process.[64] By creating a phytantriol-based lyotropic liquid crystalline gel, it was shown that pilocarpine increased its ex vivo permeability and retention time. The vortex approach was used to create that gel.[65]

Eye Ointments

White petroleum and mineral oil are ingredients in eye ointments, which are semisolid dosage forms. Because they impair vision, they are exclusively applied to the lower eyelid before sleeping. Younger patients frequently utilize them. They are a suitable option for medications that are lipophilic and moisture sensitive due to their anhydrous nature. Compared to solutions, they have a longer retention period and greater bioavailability.[66] The antiviral medication acyclovir is contained in the eye ointment Avaclyr®, which was authorized in 2019 to treat herpetic keratitis. Additionally, loteprednol etabonate, an anti-inflammatory drug, is enclosed in Lotemax®. They both demonstrated improved drug release and corneal penetration.[67]

Solid Dosage Forms

Eye Powders

They are sterile solid dose forms for medications that are sensitive to water.

Cefuroxime, moxifloxacin, and voriconazole are administered intracamerally as injectable formulations.

Voriconazole is reconstituted in water, whereas cefuroxime and moxifloxacin are reconstituted in saline. After reconstitution, cefuroxime and voriconazole solutions remain stable for seven days. Moxifloxacin solution, however, remains stable for 24 weeks.[68,69]

Ocular Inserts

Ocular inserts are biodegradable polymers in a solid dose form. They display a drug release model of zero order. High residence time, sustained drug delivery, continuous release, and fewer adverse effects are some benefits of inserts.[70] Triamcinolone acetonide-loaded nanofibers were created using the electrospinning process. They displayed decreased side effects, systemic absorption, and particle size.[71] Additionally, when the insert was implanted, sustained bimatoprost activity for several months was demonstrated.[72]

Therapeutic Contact Lens

According to recent research, a therapeutic contact lens's sustained residence time and close contact with the cornea could increase bioavailability by more than 50%.[73] Compared to traditional eye drops, their residence period is ten times longer.[74] Additionally, they lessen systemic absorption, the time between doses, and the necessary doses.[75] Numerous methods, including molecular imprinting, ion ligation, soaking, and the utilization of nanoparticles, can be used to contain the medication inside contact lenses.[76,77,78] Clinical use is hampered by protein attachment, ion and oxygen penetration, transmittance, medication loss during production or storage, and lens swelling.[79] The encapsulation process was used to prepare the Dexametha One contact lens. Compared to traditional eye drops, it demonstrated a 200-fold increase in drug retention in the retina.[80] Chips containing timolol, bimatoprost, or hyaluronic acid have been utilized to slow down fast medication release.[73]

Advanced Techniques in Ocular Drug Delivery Systems

1. Nanoparticles and Nanocarriers

Liposomes: These tiny lipid vesicles have the ability to encapsulate medications, increasing their stability and bioavailability while lowering their toxicity.

Polymeric Nanoparticles: Targeted drug administration to the ocular tissues and controlled release are made possible by the use of biocompatible and biodegradable polymers.

Solid Lipid Nanoparticles (SLNs): These can lengthen the duration of ocular residence and offer a regulated release profile.

2. Sustained and Controlled Release Systems

Implants and Inserts: By releasing medication over the course of days or weeks, implants and ocular inserts, such as punctual plugs, can offer prolonged drug delivery.

Systems based on hydrogel: These can expand in reaction to external stimuli (such as temperature or pH) and release medications as necessary.

3. Microneedles

By passing through the sclera or conjunctiva, transdermal microneedles can deliver medications to the eye while avoiding the obstacles seen in conventional delivery methods.

4. Smart Drug Delivery Systems

Smart nanocarriers: outfitted with materials that react to stimuli, such as Ph variation or enzyme activity, to release medications**.**

Bioelectronic devices: are those that use electrical stimulation to actively deliver medications.

5. Enhanced Penetration Technology (EPT)

In order to improve drug absorption across ocular biological barriers, this approach uses penetration enhancers.

Challenges In Ocular Drug Delivery System

To create ocular delivery systems with excellent therapeutic efficacy, the unique challenge of therapeutic system design is to attain an ideal drug concentration at the active site for the right amount of time. The cornea's structure, physiology, and barrier function all affect how quickly medications are absorbed. To keep the therapeutic drug level in the tear film or at the site of action constant, eye drops must be used frequently. However, prolonged use of extremely concentrated solutions may result in harmful side effects and ocular surface cellular damage.

Precorneal loss factors, which include solution drainage, lacrimation, tear dynamics, tear dilution, tear turnover, conjunctival absorption, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane, are the main causes of poor bioavailability of medications from ocular dosage forms. These factors also pose a significant challenge to anterior segment drug delivery after topical administration. Only a tiny portion of the medication—roughly 1% or less of the administered dose—is absorbed by the eyes as a result of these physiological and anatomical limitations. Topical formulations must balance hydrophilicity and lipophilicity with longer contact times in order to be clinically successful.[81]

Anterior segment delivery challenges

Because any drug molecule supplied by the ocular route must first traverse the precorneal barriers before reaching the cornea's anatomical barrier, topical treatment is typically recommended over systemic administration for eye disorders. The tear film and conjunctiva are the first barriers that prevent an active substance from entering the eye quickly. Precorneal loss factors are the primary cause of the poor bioavailability of medications from ocular dosage forms.

Posterior segment delivery challenges

The strong effectiveness of the blood-retinal barrier (BRB) prevents topical ocular drugs from reaching the posterior segment pharmacological targets. The same mechanisms that cause low ocular bioavailability also hinder medications from being delivered to the posterior region of ocular tissue. Furthermore, the BRB restricts the intravenous route's efficacy for posterior medication administration.[82] Systemically injected medications cannot enter the retina due to the tight connections of the BRB.[83] In order to cure illnesses of the posterior segment, high vitreal medication concentrations are needed. The admission of drug molecules into the posterior portion of the eye is primarily controlled by BRB, which is selectively permeable to more lipophilic compounds. This leads to the frequent administration of large doses of medication, which causes systemic side effects.[84]

The posterior portion also faces the difficulty of maintaining the reduce the frequency of injections and maintain a therapeutic medication concentration for extended periods of time. Drugs are removed through the anterior route, which involves first entering the aqueous humor and then exiting through the anterior chamber angle. Numerous medications are also removed from the body by the posterior route, which passes through the blood-retina barrier and into the systemic circulation.

Bioavailability Issues

- Drugs do not penetrate the corneal epithelium very well.
- The eye drains and washes out quickly.

Patient Compliance

- Difficulty with regular dosage schedules.
- Adherence problems brought on by intricate administration methods.

Formulation Stability

- The stability of sophisticated formulations in physiological settings presents certain difficulties.

Regulatory Hurdles

- New delivery system approval can be a drawn-out and challenging process.

Biocompatibility and Toxicity

- Ensuring that substances employed in innovative delivery systems don't cause negative side effects.

FUTURE TECHNOLOGIES

Smart Nano-Micro Platforms

Smart refers to a nano-micro matrix that can achieve sensor triggering roles with stimuli-responsive features and significantly alter its mechanical, thermal, and/or optical properties in a controllable or predictable manner. In contrast to traditional nanocarriers, smart nano-micro platforms can reveal precise reactions to endogenous (pH, reactive oxygen species, and biological molecules like DNA and enzymes) or exogenous (light, sound, and magnetic field) factors. This allows them to perform a variety of tasks, including site-specific drug delivery, bioimaging, and biomolecule detection. In recent years, these fascinating methods have been used to ocular administration. These ground-breaking technologies have generally been used to improve safety and efficacy, reduce side effects, increase drug/agent bioavailability, and diagnose and treat cancer.[85,86] Sunitinib microparticles, which significantly reduce intraocular inflammation in mice models for up to six months, were successfully administered by Tsujinaka et al.[87] Solid lipid nanoparticles containing miRNA were created by Rodriguez et al. as gene therapy.[88] Basuk et al. used visible light to demonstrate photo-modulated release of bevacizumab that had been pre-loaded.[89]

Extracellular Vesicles (Exosomes)

Different cell types create extracellular vesicles, a type of organelle. Extracellular vesicles contain a variety of bioactive substances, such as proteins, lipids, RNAs, and DNAs. Because of their nanosized, they act as potent intercellular triggers that can initiate a variety of physiological and pathological effects. They may be generated by immune cells in diseased conditions and regulate the course of inflammation. They are known to play a part in immune-mediated eye conditions such corneal allograft rejection and Sjogren's syndrome.[90] Additionally, by promoting the synthesis of certain matrix components, they might promote ocular tissue rejuvenation. Further research is necessary to create exosome-based ocular delivery devices. To speed up the corneal epithelium's healing process, Tang et al. created exosomes of mesenchymal stem cells produced from pluripotent stem cells.[91] To stop posterior capsular opacification, Zhu et al. created exosomes from lens epithelial cells that loaded doxorubicin.[92]

Tissue Engineering

There are two categories for tissue engineering experiments. Additive tissue engineering is the first kind, which replaces tissue or cells or attempts to allow the growth of anything that has vanished. Arrestive tissue engineering is the second kind, which stops atypical growth. Nano systems could be used for tissue engineering that is both additive and arrestive. Retinal ganglion cell viability testing[93], retinal ganglion cell repair[94], nanofiber scaffold creation[95], corneal endothelial cell transplantation[96], and suppression of retinal cell death[97] are a few instances of nano system-based tissue engineering. Researchers have started looking into the possibility of using nanotools and nanomaterials to help the nerve cells in the eye work normally again.

Innovations in Clinical Trials

The lead for innovative treatment comes from ongoing clinical trials for various dosage formulations. For instance, a semi-solid pilocarpine topical cream is used to treat presbyopia. This phase 2 trial, which is

multicentre, randomized, double-masked, placebo-controlled, and parallel group, assesses the cream's safety and effectiveness. The research will begin on January 3, 2022. and will go on through May 2023. Additionally, twice-daily Cequa™ (Cyclosporine) ophthalmic emulsion. This is a 12-week, single-arm, multicentred, phase 4 research. One example of a solid dose form is the eye insert Dextenza 0.4 Mg (dexamethasone). The purpose of the trial is to evaluate the Dextenza insert's safety and effectiveness in treating pain and inflammation after corneal transplant surgery.

CONCLUSIONS

The presence of numerous ocular impediments in the front and posterior regions of the eye makes it challenging to effectively manage ophthalmic illnesses.

To bring the drug into the intended site of action, a variety of ocular routes of administration are employed, including topical, intraocular, periocular, and in combination with ocular devices. Numerous strategies and technologies have been implemented to reduce the amount of time between doses, administered dosage, and adverse effects, as well as to improve ocular bioavailability, drug permeation effectiveness, and retention duration through regulated and prolonged drug delivery methods. These cutting-edge technologies may find extensive use in the management and treatment of eye illnesses due to their enhanced medication efficacy and demonstrated biocompatibility. More advancements in ocular medication delivery systems are anticipated in the future to increase patient compliance, maintain and improve eye health, and achieve better outcomes in the treatment of ocular illnesses.

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