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Ocular Drug Delivery System Challenges and New Advancements

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Abstract

Ocular medication delivery remains one of the most difficult areas of pharmaceutical science due to the eye's unique anatomical and physiological obstacles. Drug absorption and bioavailability are considerably limited by protective mechanisms including as tear turnover, blinking, nasolacrimal drainage, corneal epithelial tight junctions, and the blood-aqueous and blood-retinal barriers. Conventional dose formulations, such as eye drops and ointments mostly have a short residence time and low therapeutic efficacy, demanding frequent administration and resulting to lower patient compliance. Furthermore, posterior segment disorders such as age-related macular degeneration, diabetic retinopathy, and glaucoma necessitate focused and continuous drug delivery techniques that overcome both static and dynamic ocular obstacles. Recent advancements in ocular drug delivery systems have focused on improving bioavailability, prolonging precorneal retention, enabling controlled release, and enhancing tissue targeting. Innovative approaches include nanoparticle-based systems (polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers), liposomes, niosomes, dendrimers, micelles, and in situ gelling systems. Biodegradable and non-biodegradable implants, microneedles, ocular inserts, and contact lens mediated delivery have also demonstrated promising outcomes for sustained and site-specific therapy. Furthermore, emerging technologies such as stimuli-responsive systems, gene delivery vectors, and nanofiber-based platforms are expanding therapeutic possibilities for both anterior and posterior segment disorders.

Keywords: Ocular drug delivery, Ocular barriers, Bioavailability, Controlled drug release, Nanoparticles, Liposomes, In-situ gelling systems, Ocular inserts, Nanomicelles, Nanoparticles, Nanosuspensions, Implants, Microneedles, Intracameral Drug delivery, Punctal plug drug delivery system.

Introduction

The human eye is a complex organ, both anatomically and physiologically, with unique and independently functioning components. Its diverse and intricate structures also present significant challenges in developing effective drug delivery systems.

Ocular drug delivery remains a significant challenge for pharmaceutical scientists, despite the eye being one of the most sensitive and accessible organs for drug administration. A major limitation of conventional ocular

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delivery systems, such as eye drops, is the rapid and extensive elimination of the drug from the eye, leading to substantial drug loss and reduced therapeutic efficacy.

A major limitation of most eye drops is the rapid and extensive elimination of the drug from the pre-corneal lacrimal fluid due to solution drainage, reflex lachrymation, and non-productive absorption through the conjunctiva. As a result, the ocular residence time of conventional formulations is restricted to just a few minutes, with only 1–10% of the topically applied drug being absorbed. Initial strategies to improve the poor bioavailability of these drugs included the use of ointments and gels; however, these formulations often cause blurred vision, limiting patient compliance and clinical utility.

Approximately 90% of ophthalmic formulations on the market are in the form of eye drops, primarily targeting diseases of the anterior segment of the eye. However, conventional topical drug delivery methods are largely ineffective in reaching the posterior segment, as most of the drug is rapidly drained away, with only a minimal amount reaching the intended site of action. This necessitates frequent dosing to maintain therapeutic levels. The posterior segment of the eye which includes the retina, vitreous humour, and choroid is associated with several vision-threatening diseases. Treatment of these conditions typically requires intravenous or intravitreal drug delivery, implants, or administration via the periocular route, often at high drug concentrations. As a result, targeted delivery to the posterior segment has become a key area of focus in the development of novel ophthalmic drug delivery systems.

The rationale and novelty of this review lie in highlighting recent advancements in pharmaceutical ophthalmic formulations such as in situ gels, nanoparticles, liposomes, nanosuspensions, microemulsions, ocular inserts, and others and their potential to address the limitations of conventional dosage forms. These novel systems aim to enhance ocular bioavailability and provide sustained drug release at the target site.

Anatomy of the Eye

Human eye generally divided into two; anterior and the posterior segments. The anterior segment includes the cornea, conjunctiva, iris, ciliary body, aqueous humor and lens, the posterior segment comprises sclera, choroid, retina and vitreous humor.

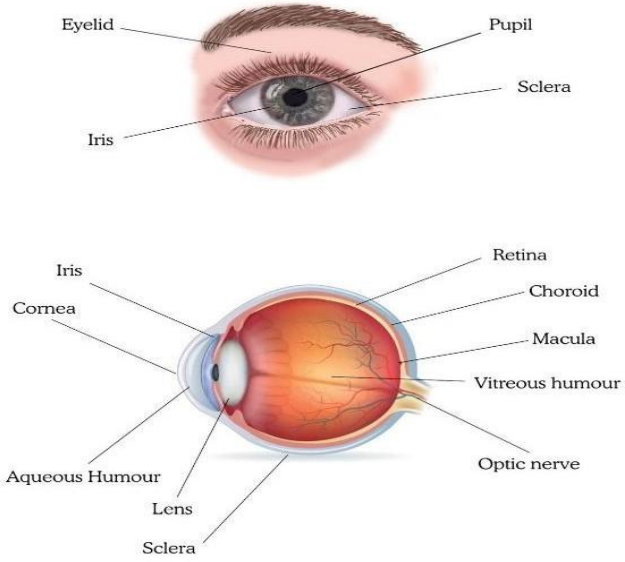

Figure 1: Anatomy of the Eye

The Cornea

The cornea, the outermost transparent and multilayered membrane of the eye, lacks a direct blood supply and derives its nourishment from the aqueous humor and the limbal blood capillaries.

The Orbit

A protective ring formed by fragments of several skull bones encircles the eye, culminating in a four-sided pyramidal structure that shields it from mechanical damage.

Upper and Lower Eyelids

The cornea, which forms the front surface of the eye, requires a consistently moist environment to function properly. The eyelids help maintain this by covering the eye during rest to reduce evaporation, and by blinking regularly while awake to spread the tear film—produced by the lacrimal glands and associated structures—across the corneal surface.

The Conjunctiva

The conjunctiva begins at the front of the eye and extends across its outer surface, serving as a protective membrane before terminating at the cornea—the transparent front portion of the eye.

The Sinewy Layer

The top's mechanical reliability is provided by the sinewy layer, which consists of the relatively stiff palpebral sash and the thick and somewhat inflexible tarsal plates that line the palpebral gap; the two parts together form the septum orbitale.

The Muscles of the Lids

One way to finish the tops is by flexing the orbicularis muscle, a singular, oval-shaped muscle that inserts into the covers from its origins in the temples and the face. There are two parts to it: the orbital and the palpebral; the top conclusion is primarily caused by the palpebral segment within the cover.

The Skin

In its outermost layer, the skin is characterized by characteristics that are generally consistent with skin anywhere on the body (maybe with a handful of big pigment cells), but which are considerably more diverse in the skin of the coverings.

The Glandular Apparatus

The lacrimal glands secrete fluid that keeps the eye moist. Underneath the tops, you'll find almond-shaped organs that open up internally from the outside corner of each eye.

Extraocular Muscles

Its growth is monitored by six muscles external to the eye. These include the mostly and secondarily angled quadriceps muscles as well as the average, horizontal, subpar, and common recti.

Ocular Drug Delivery

Delivering drugs to the eye poses significant challenges compared to other areas of the body, largely due to the eye’s distinct anatomy and physiology. Protective features like the tear film, blinking reflex, and blood-ocular barriers serve to shield the eye but also hinder drug absorption and retention. These natural defense mechanisms, while essential for eye health, often reduce the efficacy of treatments. Consequently, achieving precise and effective drug delivery to the intended ocular site remains a complex task. Enhancing the accuracy and success of ocular drug delivery continues to be a key area of research.

Traditional methods of administering ocular medications such as gels, ointments, solutions, and inserts often come with drawbacks. These can include nasolacrimal drainage, reduced corneal flexibility, unwanted systemic absorption, and temporary visual impairment. Such side effects limit the overall effectiveness and patient comfort associated with these delivery methods.

In recent decades, significant progress has been made in the field of ocular drug delivery. Improved treatment outcomes are being achieved by either extending the contact time of drug carriers on the ocular surface or enhancing drug penetration across the mucosal barrier. Currently, much of the research is centered on nano carrier-based systems, which have shown the greatest promise in overcoming traditional delivery limitations. These advanced systems—including particulate carriers like nanoparticles and vesicular carriers such as liposomes, niosomes, pharmacosomes, and discosomes—have demonstrated the ability to enhance both the pharmacokinetic and pharmacodynamic profiles of therapeutic agents. Dendrimers, micro emulsions,

hydrogels, iontophoresis medication administration, laser treatment, scleral plugs, stem cell technology, non-viral gene therapy, and siRNA driven techniques are some of the innovative controlled drug delivery systems that are on the horizon.

Topical administration is the most common and widely accepted method for treating ocular diseases. However, the eye's protective mechanisms and the cornea's barrier properties cause rapid drug drainage, leading to very short contact time with the cornea.

Numerous strategies have been developed to enhance the bioavailability of drugs for effective ocular delivery. Various formulations such as ointments, gels, matrix systems (including inserts and collagen shields), nanoparticles, and nanocapsules have been utilized to prolong the drug's residence time on the ocular surface. However, these dosage forms come with certain drawbacks. They can cause discomfort, dizziness, and a sticky sensation, particularly in older patients, which may reduce patient compliance.

Ocular drug delivery is broadly categorized into anterior and posterior segment targeting. Conventional delivery systems such as eye drops, suspensions, and ointments remain widely used but are suboptimal for managing sight-threatening conditions, particularly those affecting the posterior segment. Notably, eye drops constitute over 90% of commercial ophthalmic formulations, primarily addressing anterior segment disorders. However, due to anatomical and physiological barriers, topically applied drugs exhibit poor penetration to the posterior segment. Effective treatment of posterior eye diseases involving the retina, vitreous, or choroid typically necessitates more invasive approaches, including intravitreal injections, periocular administration, intravenous delivery, or surgical intervention. Continuous improvements in diagnostic methods and treatment agents have led to the creation of ocular delivery systems that are highly effective in treating eye diseases.

Physiological Considerations

The absorption of ophthalmic medications is significantly constrained by physiological barriers, with the cornea representing a major limiting structure due to its relative impermeability. The cornea comprises three principal layers; epithelium, stroma, and endothelium, each contributing to the restriction of drug penetration. The corneal epithelium, characterized by lipophilic cellular layers facing the tear film, presents a substantial barrier to ionized and hydrophilic compounds. Moreover, tight junctions between epithelial cells impede paracellular diffusion, permitting only small, selectively permeable molecules to traverse this route. Beneath the epithelium, the stroma accounts for approximately 90% of corneal thickness and is highly hydrophilic in nature, further limiting the permeation of lipophilic agents. Collectively, these structural features constitute significant obstacles to effective ocular drug delivery.

The corneal epithelium serves as the principal barrier in regulating transcorneal drug absorption. Due to its lipophilic nature, this layer poses significant resistance to hydrophilic compounds, whereas the underlying stroma and endothelium, being more hydrophilic, offer relatively less resistance to drug permeation. Conversely, lipophilic drugs encounter increased resistance within the hydrophilic stroma. The rate and extent of drug penetration through the corneal membrane, particularly from the cul-de-sac, are governed by multiple physicochemical properties of the drug, including lipophilicity, solubility, molecular size and shape, charge, and degree of ionization.

Pharmacokinetic Considerations

Ocular pharmacokinetics involves the evaluation of drug absorption, distribution, metabolism, and elimination within ocular tissues over time and in relation to administered dose. Drug concentrations within ocular tissues and fluids vary depending on the formulation and route of administration, highlighting the importance of dosage form and delivery method in achieving therapeutic efficacy.

The most important ways that drugs leave the body through the eyes are by various processes, which are as follows:

1. Drug penetration through the anterior uvea and conjunctiva,
2. Drug absorption through the transcorneal space from the lachrymal fluid into the anterior chamber,

3. The administration of drugs from the circulation into the anterior chamber via the blood-aqueous barrier,
4. The transition of the medication from the top chamber to the trabecular meshwork and Schlemm's canal through the aqueous humour turnover,
5. Crossing the blood-aqueous barrier for drug clearance into the systemic circulation from the aqueous humour,
6. Circulation of drugs into the back of the eye via the blood-retina barrier,
7. Distribution of drugs using intravitreal means,
8. The drug is eliminated from the vitreous by means of the posterior route, which passes through the blood-retina barrie,
9. The drug is eliminated from the vitreous by means of the anterior route, which leads to the posterior chambers.

Conventional Ocular Drug Delivery System

Putting eye drops into the small space between the lower eyelid and the cornea is a common and patient-friendly way to deliver medicines to the eye. However, most of the eye drop dose is lost because some of it spills out or is washed away when we blink. Only about 20% (around 7 microliters) actually stays in that pocket. The amount of drug that remains there helps push the medicine into the cornea by passive diffusion.

For eye drops to work well, the drug needs to pass easily through the cornea and stay in contact with it for a longer time. Many methods have been tried to help eye drops stay longer in the eye and enter the cornea better. These include iontophoresis, using prodrugs, adding ion-pairing agents, and using cyclodextrins.

There are many eye-care products available, but about 70% of prescriptions are still for regular eye drops. This is likely because they are easy to make in large amounts, liked by patients, effective, stable, and cost-efficient.

Topical Liquid/Solution Eye Drops

Topical eye drops are the easiest, safest, and most comfortable way to give medicine to the eye without any surgery or needles. When an eye drop is placed in the eye, the medicine starts working right away, but its amount in the eye decreases quickly.

To help the medicine stay in the eye longer, enter the cornea better, and improve its overall effect, certain additives can be mixed into the eye drops. These additives include viscosity enhancers and permeation enhancers.Viscosity enhancers improve precorneal residence time and bioavailability upon topical drop administration by enhancing formulation viscosity. Examples of viscosity enhancers include hydroxy methyl cellulose, hydroxy ethyl cellulose, sodium carboxy methyl cellulose, hydroxypropyl methyl cellulose and polyalcohol.

Permeation enhancers help more of the drug pass through the cornea by slightly changing the cornea’s structure. Several other additives—such as chelating agents, preservatives, surfactants, and bile salts—have also been studied to see if they can improve drug penetration into the eye. Benzalkonium chloride, polyoxyethylene glycol ethers, ethylenediaminetetra acetic acid sodium salt, sodium taurocholate, saponins and cremophor EL are the examples of permeation enhancers investigated for improving ocular delivery.

Emulsions

An emulsion-based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. Using an emulsion-based formulation is a useful way to improve how well a drug dissolves and how much of it the eye can absorb. There are two main types of emulsions used for medicines: oil-in-water (o/w) and water-in-oil (w/o).

For eye medications, oil-in-water emulsions are more commonly used because they cause less irritation and are better tolerated by the eye compared to water-in-oil systems. Many studies have shown that emulsions can help eye drugs stay longer on the eye surface, pass through the cornea more effectively, release the drug slowly over time, and ultimately improve how much drug reaches the eye.

Multiple novel drug delivery systems, such as nanoemulsions, microemulsions, self emulsifying systems, liposomes, nanoparticles, nanosuspensions, niosomes, micelles, nanofibers, dendrimers, solid lipid nanoparticles, spanlastics, and hydrogels, have been reported for ocular drug delivery with promising therapeutic activity.

Table 1: Advantages and Disadvantages of ophthalmic emulsions

Advantages	Disadvantages
Ease of sterilization of the formulation	Low viscosity and low ocular retention; hence, gelling agents are introduced to increase the viscosity.
Improved aqueous solubility	Potential for ocular cytotoxicity due to the large quantity of surfactants.
Capability to deliver both lipophilic and hydrophilic drugs	The oily or milky nature of emulsions can cause temporary blurred vision after application
Enhanced wettability	Some patients may experience a stinging or burning sensation when the emulsion is applied
Increased permeability	-
Improved physical and chemical stability of the formulation	-

Suspensions

Suspensions are another type of non-invasive eye drop system used to deliver drugs to the eye. A suspension is a mixture where tiny, undissolved drug particles are spread throughout a liquid with the help of agents that keep them evenly dispersed. In simple terms, the liquid part of the suspension holds as much dissolved drug as possible, while the rest stays as fine particles.

These particles stay longer in the precorneal pocket (the space between the eyelid and cornea), which increases the drug's contact time with the eye and makes the drug work for a longer period compared to a regular solution. The duration of drug action in suspensions depends on the particle size**,** smaller particles quickly replace the drug that is absorbed into the eye tissues. Larger particles remain in the eye for a longer time and dissolve more slowly, providing a longer-lasting effect.

Limitations of Ocular Suspensions

- ✓ Low bioavailability
- ✓ Multiple barriers restrict drug penetration to internal tissues.
- ✓ Poor Bioavailability
- ✓ Rapid Clearance

The suspended particles can cause eye irritation, a foreign body sensation, and temporary blurred vision, which affects patient comfort.

Ointments

Ophthalmic ointments are another type of eye medication used for topical (surface) application. These ointments are made from a mix of semi-solid and solid hydrocarbons (such as paraffin) that melt at the eye's natural temperature, around 34°C. The type of hydrocarbon used is chosen based on how safe and compatible it is with the eye.

Ointments help improve how much drug enters the eye and allow the medicine to be released slowly over time, giving a longer-lasting effect.

Problems With the Current Ocular Medication Delivery Method

Making sure a drug stays long enough at the place where it needs to work is an important challenge in designing eye medicines. The cornea's structure and natural barriers make it hard for medicines to be absorbed.

To keep enough medicine in the eye to be effective, eye drops usually need to be applied often, either in the tear film or directly at the site where the drug acts.

However, using very strong eye-drop solutions too often can damage eye cells and cause harmful side effects. Delivering drugs to the front part of the eye is difficult because many factors remove the medicine before it can be absorbed. These include tears washing the solution away, blinking, tear turnover, drainage, and the limited time the drops stay in the eye. In addition, the corneal surface does not easily let medicines pass through. Because of these natural barriers, only about 1% or even less of the applied dose is actually absorbed. Effective eye-drop formulas usually stay in contact with the eye for a longer time and have a good balance of water-loving and fat-loving properties.

Anterior Segment Delivery Challenges

Because the eye has several barriers in front of the cornea, medicines applied to the eye must pass through these obstacles before they can reach their target. For this reason, eye drops are usually preferred over oral or injected medicines when treating eye conditions. The tear film and the conjunctiva are the first barriers that stop a drug from entering the eye. Many precorneal factors remove or dilute the medicine, leading to poor absorption from eye-drop formulations.

Issues With the Delivery of Posterior Segments

The blood-retinal barrier (BRB) makes it very difficult for drugs applied to the eye to reach the back (posterior) part of the eye. Just like the barriers at the front of the eye reduce absorption, the BRB blocks drug delivery to the retina. Even drugs given through the bloodstream have trouble reaching the retina because the BRB's tight connections prevent most substances from entering.

To treat diseases in the back of the eye, high doses of drugs injected into the vitreous (the gel inside the eye) are often needed. The BRB mainly allows fat-soluble (lipophilic) drugs to pass through. Using large doses repeatedly can cause side effects throughout the body. Another challenge is keeping a stable drug level in the eye for a long time while reducing the number of injections. Drugs are removed from the eye in two main ways: the aqueous humor in the front of the eye carries drugs out through the anterior route, and drugs can also leave through the posterior route, passing through the BRB into the bloodstream.

The Perfect Ocular Medication Delivery System Would Have These Features

- ✓ Promoting effective penetration into the cornea. Encouraging prolonged contact with the corneal tissue to maximize ocular medication absorption.
- ✓ Ease of administration to the patient.
- ✓ The number of times medication is given is decreased.
- ✓ Patient adherence.
- ✓ Less harmfulness and adverse reactions.
- ✓ Reduce the loss of medication to the cornea.
- ✓ Form that is both pleasant and non-irritant.
- ✓ Should not lead to hazy eyesight.
- ✓ Very little oil is present.
- ✓ The viscous system's suitable concentrations and rheological characteristics.

Novel Ocular Drug Delivery Systems

Nanotechnology based ocular drug delivery

In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have

been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability.

Nanomicelles

Nanomicelles are the most commonly used carrier systems to formulate therapeutic agents in to clear aqueous solutions. In general, these nanomicelles are made with amphiphilic molecules. These molecules may be surfactant or polymeric in nature.

Currently, tremendous interest is being shown towards development of nanomicellar formulation based technology for ocular drug delivery. The reasons may be attributed due to their high drug encapsulation capability, ease of preparation, small size, and hydrophilic nanomicellar corona generating aqueous solution. In addition, micellar formulation can enhance the bioavailability of the therapeutic drugs in ocular tissues, suggesting better therapeutic outcomes. So far, several proofs of concept studies have been conducted to investigate the applicability of nanomicelles in ocular drug delivery. Researchers have also utilized nanomicelles for ocular gene delivery. Several attempts are also being made to utilize nanomicelles for the posterior ocular drug delivery.

Nanoparticles

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres (Figure 3). In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix. From past few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues.

Nanoparticles represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from precorneal pocket. Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time. Polyethylene glycol (PEG), chitosan and hyaluronic acid are commonly employed to improve precorneal residence time of nanoparticles. Chitosan coating is most widely explored for improving precorneal residence of nanoparticles. The chitosan is positively charged and hence it binds to negatively charged corneal surface and thereby improves precorneal residence and decreases clearance.

Nanosuspensions

Nanosuspensions are colloidal dispersion of submicron drug particles stabilized by polymer(s) or surfactant(s). It is emerged as promising strategy for delivery of hydrophobic drugs. For ocular delivery, it provides several advantages such as sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid. The efficacy of nanosuspensions in improving ocular bioavailability of glucocorticoids has been demonstrated in several research studies.

Liposomes

Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core. The size of liposomes usually range from 0.08 to 10.00 μm and based on the size and phospholipid bilayers, liposomes can be classified as small unilamellar vesicles (10–100 nm), large unilamellar vesicles (100–300 nm) and multilamellar vesicles (contains more than one bilayer). For ophthalmic applications, liposomes represent ideal delivery systems due to excellent biocompatibility, cell membrane like structure and ability to encapsulate both hydrophilic and hydrophobic drugs. Liposomes have demonstrated good effectiveness for both anterior and posterior segment ocular delivery in several research studies.

For drug delivery to anterior segment of the eye, efforts are mainly put toward improving precorneal residence time by incorporating positively charged lipids or mucoadhesive polymer in liposomes. The positively charged liposomes i.e., cationic liposomes have exhibited better efficacy in ocular delivery than negatively charged and neutral liposomes due to binding with negatively charges of corneal surface.

Dendrimers

Dendrimers are characterized as nanosized, highly branched, star shaped polymeric systems. These branched polymeric systems are available in different molecular weights with terminal end amine, hydroxyl or carboxyl functional group. The terminal functional group may be utilized to conjugate targeting moieties. Dendrimers are being employed as carrier systems in drug delivery. Selection of molecular weight, size, surface charge, molecular geometry and functional group are critical to deliver drugs. The highly branched structure of dendrimers allows incorporation of wide range of drugs, hydrophobic as well as hydrophilic. In ocular drug delivery, few promising results were reported with these branched polymeric systems.

In-situ gelling systems

In-situ hydrogels refer to the polymeric solutions which undergo sol-gel phase transition to form viscoelastic gel in response to environmental stimuli. Gelation can be elicited by changes in temperature, pH and ions or can also be induced by UV irradiation. For ocular delivery, research studies have been more focused toward development of thermosensitive gels which respond to changes in temperature. Several thermogelling polymers have been reported for ocular delivery which includes poloxamers, multiblock copolymers made of polycaprolactone, polyethylene glycol, poly (lactide), poly (glycolide), poly (Nisopropylacrylamide) and chitosan. These thermosensitive polymers form temperature dependent micellar aggregates which gellify after a further temperature increment due to aggregation or packing. For drug delivery, these polymers are mixed with drugs in the solution state and solution can be administered which forms an in situ gel depot at physiological temperature. These thermosensitive gels demonstrated promising results for enhancing ocular bioavailability for both anterior and posterior segment.

Contact lens

Contact lenses are thin, and curved shape plastic disks which are designed to cover the cornea. After application, contact lens adheres to the film of tears over the cornea due to the surface tension. Drug loaded contact lens have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines and antimicrobials. It is postulated that in presence of contact lens, drug molecules have longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops.

Implants

Intraocular implants are specifically designed to provide localized controlled drug release over a extended period. These devices help in circumventing multiple intraocular injections and associated complications. Usually for drug delivery to posterior ocular tissues, implants are placed intravitreally by making incision through minor surgery. Though implantation is invasive procedure, these devices are gaining interest due to their associated advantages such as sustained drug release, local drug release to diseased ocular tissues in therapeutic levels, reduced side effects and ability to circumvent blood retina barrier. Several implantable devices have been developed for ocular drug delivery especially for the treatment of chronic vitreoretinal diseases.

Microneedles

Microneedle based technique is an emerging and minimally invasive mode of drug delivery to posterior ocular tissues. This technique may provide efficient treatment strategy for vision threatening posterior ocular diseases such as age-related macular degeneration, diabetic retinopathy and posterior uveitis. This new

microneedle based administration strategy may reduce the risk and complications associated with intravitreal injections such as retinal detachment, hemorrhage, cataract, endophthalmitis and pseudoendophthalmitis. Moreover, this strategy may help to circumvent blood retinal barrier and deliver therapeutic drug levels to retina/choroid. Microneedles are custom designed to penetrate only hundreds of microns into sclera, so that damage to deeper ocular tissues may be avoided.

Intracameral Drug delivery

An intracameral (IC) injection directly delivers the drug into the anterior chamber of the eye. This targeted drug delivery technique overcomes the ocular barriers and offers a high therapeutic concentration of medication at the desired site and consequently better clinical outcomes. IC drug delivery is a safe and effective modality with many advantages over topical delivery. These include excellent bioavailability, reduced systemic risk, and minimal ocular toxicity. Agents delivered via IC injection have shown promising results against infection, inflammation, ocular hypertension, and neovascularization.

The approach usually involves the administration by direct injection of a substance (typically an antibiotic) into the anterior chamber of the eye to prevent eye infection or endophthalmitis after cataract surgery and in some cases eye surgeons have administrated anesthesia in this manner. The intracameral route of administration involves injecting a drug directly into the anterior chamber of the eye, the fluid-filled space between the cornea and the iris. This method bypasses the eye's natural barriers, providing rapid and highly localized drug delivery for a variety of purposes, such as preventing infection after cataract surgery or controlling inflammation. It is also used for other treatments, including certain glaucoma or cancer therapies.

Advantages

- ✓ Rapid and high concentration: Delivers medication instantaneously to the target area, bypassing the need for diffusion through the cornea and other tissues.
- ✓ Excellent bioavailability: Achieves high drug levels at the site of action.
- ✓ Reduced systemic risk: Limits systemic absorption, which can decrease the risk of side effects elsewhere in the body.
- ✓ Targeted effect: Allows for focused treatment of the anterior segment of the eye, including the cornea, iris, and aqueous humor.
- ✓ Improved patient compliance: Can replace a regimen of topical eye drops, which some patients find difficult to manage.

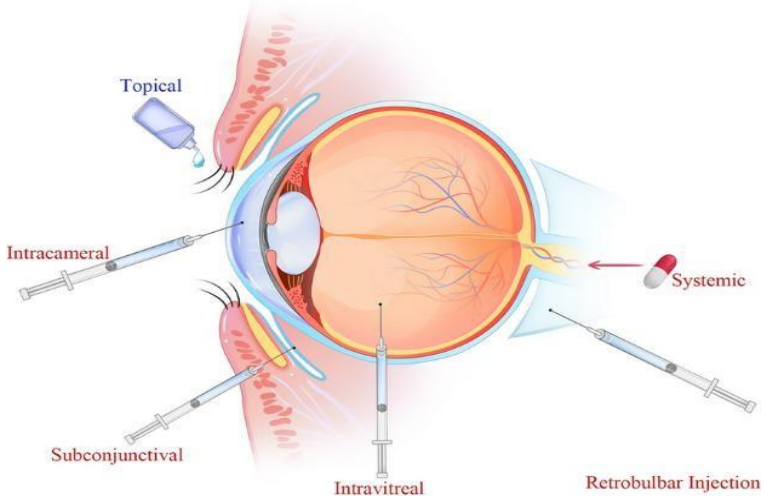

Figure 2: Ocular drug administrations

Punctal plug drug delivery system

A punctal plug drug delivery system is a medical device that uses a small plug inserted into the tear duct to provide sustained, long-term release of medication to the eye. This method is used to treat eye diseases like dry eye and glaucoma by keeping the drug on the ocular surface for longer periods than eye drops, improving drug bioavailability and potentially enhancing patient compliance. The plugs are made from polymeric materials and can be designed with different components, such as a drug-loaded core and an outer cap, to control the release rate of the medication.

Punctal plugs (PPs) are miniature medical implants that were initially developed for the treatment of dry eyes. Since their introduction in 1975, many PPs made from different materials and designs have been developed. PPs, albeit generally successful, suffer from drawbacks such as epiphora and suppurative canaliculitis. To overcome these issues intelligent designs of PPs were proposed (e.g. SmartPLUG™ and Form Fit™). PPs are also gaining interest among pharmaceutical scientists for sustaining drug delivery to the eye. This review aims to provide an overview of PPs for dry eye treatment and drug delivery to treat a range of ocular diseases. It also discusses current challenges in using PPs for ocular diseases.

PPs have recently been investigated for the controlled delivery of drugs to the tear fluid of the eye and the nasolacrimal duct. PPs can offer numerous advantages over topical drug delivery such as reduction in loss of drug and/or formulation owing to tear formation, reduction in lacrimal drainage of drug, ability to achieve controlled drug delivery.

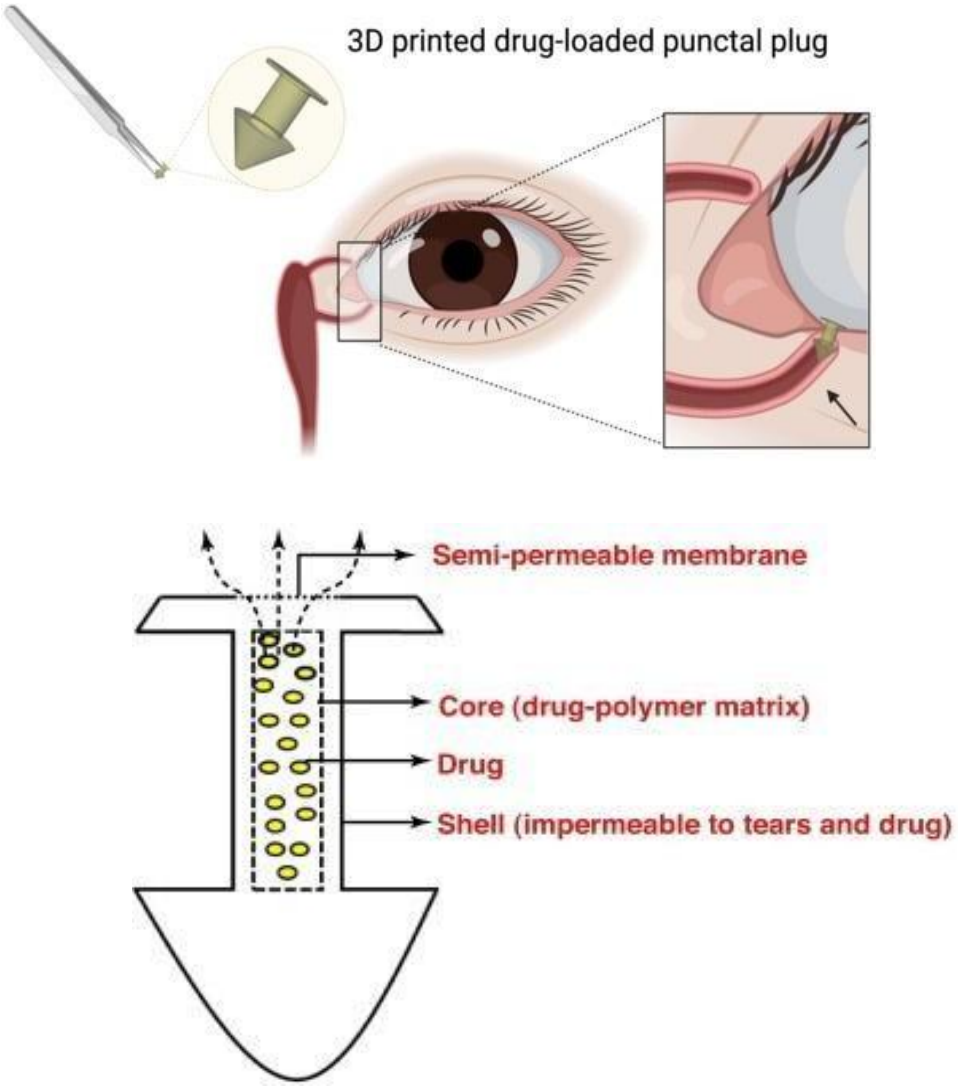

Figure 3: Drug loaded punctal plug

Conclusion

Ocular drug delivery continues to provide significant therapeutic hurdles due to the eye's distinct anatomical and physiological barriers, which include the corneal epithelium, blood-aqueous barrier, blood-retinal barrier, tear turnover, and nasolacrimal drainage. Conventional formulations, such as eye drops and ointments, are still hampered by poor bioavailability, quick precorneal clearance, and low patient adherence, especially in chronic ocular diseases.

Recent advancements in ocular drug delivery systems have demonstrated promising potential in overcoming these limitations. Novel approaches including nanoparticle-based carriers, liposomes, dendrimers, in situ gels, ocular inserts, microneedles, implants, and biodegradable polymeric systems have significantly improved drug retention time, targeted delivery, permeability, and controlled release profiles. These systems aim to enhance therapeutic efficacy while minimizing systemic exposure and adverse effects.

Furthermore, the integration of nanotechnology, stimuli-responsive materials, and sustained- release biodegradable implants marks a transformative shift toward precision and patient-centric ocular therapy. Advances in posterior segment delivery strategies are particularly noteworthy, addressing longstanding challenges in the management of retinal diseases such as age-related macular degeneration, diabetic retinopathy, and glaucoma.

Despite these encouraging developments, several hurdles remain, including long-term safety, scalability of manufacturing, regulatory approval pathways, patient acceptance, and cost- effectiveness. Future research should focus on translational studies, large-scale clinical validation, and the development of non-invasive, targeted, and patient-friendly delivery platforms.

In conclusion, while ocular drug delivery remains a complex and evolving field, emerging technologies are progressively bridging the gap between therapeutic need and clinical reality. Continued interdisciplinary collaboration among pharmaceutical scientists, clinicians, material scientists, and regulatory bodies will be essential to translate innovative research into safe, effective, and accessible ophthalmic therapies.

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