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NOVEL APPROACHES IN OPHTHALMIC DRUG DELIVERY: A COMPREHENSIVE REVIEW

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Abstract:
Ocular drug delivery has consistently posed a challenge for ophthalmologists and drug-delivery experts. Many eye conditions require prolonged and frequent drug treatments, but the effectiveness of topical drugs is often limited to less than 5% due to natural barriers in the eye. Recent advances in nanotechnology offer promising solutions. Novel ocular drug delivery systems encompass innovative approaches such as nanomicelles, nanoparticles, nanosuspensions, liposomes, drug-eluting contact lenses, ocular inserts, and specialized ocular devices. These systems are designed to prolong drug residence on the ocular surface and enhance the bioavailability of therapeutic agents, thereby improving the effectiveness of treatment. This comprehensive review explores the latest developments in novel ophthalmic drug delivery systems and strategies to improve therapeutic outcomes, patient compliance, and minimize side effects. We highlight the potential of these technologies to enhance drug bioavailability, prolong drug release, and target specific ocular tissues, offering promising solutions for various eye conditions. This review thoroughly examines the evolving landscape of ophthalmic drug delivery, offering insights into the future of ocular therapeutics.

Keywords: Ophthalmic drug delivery, Eye diseases, Ocular barriers, Novel drug delivery system, Posterior and anterior segment

Introduction

Ocular diseases seriously impact vision and quality of life. A global survey in 39 countries found that 285 million people suffer from visual impairment. Of them, 65% are aged 50 or older, and 80% of the blind are in the same age group. This highlights the need for effective treatments, especially for the elderly, to preserve and improve vision and quality of life.[1] The advancements in ocular drug delivery research hold the promise of introducing innovative approaches for more effective management of ocular diseases, along with the development of novel therapeutic methods. These emerging drug delivery systems are anticipated to provide sustained and prolonged drug action, achieving precise and targeted delivery, employing stimuli-responsive release mechanisms, and offering less invasive methods of administration.[2-4] They aim to enhance efficiency and safety levels significantly, representing a positive shift towards improved treatments for eye conditions.

The eye, a remarkably intricate spherical organ about 24mm diameter, has a distinct anatomical and physiological structure.[5] It can be categorized into two primary segments: the anterior and posterior segments, as depicted in Figure 1. Both segments of the eye feature a range of biological barriers

designed to safeguard the eye from foreign substances and potential harm. The anterior segment comprises the cornea, iris, lens, and aqueous humor, while the posterior segment encompasses the vitreous body, retina, choroid, and the rear section of the sclera. These components work together to maintain ocular integrity and function. The cornea is a transparent part of the eye with five layers: epithelium (outermost), Bowman's membrane, stroma (thickest), Descemet's membrane, and endothelium (innermost).[6-7] The human corneal epithelium is a crucial component of the corneal barrier. It consists of multiple layers of corneal epithelial cells that are interconnected by tight junctions. These tight junctions play a significant role in restricting the penetration of drugs into the eye, particularly hydrophilic molecules. The corneal stroma primarily consists of charged and highly organized hydrophilic collagen. This composition poses a barrier that can impede the passage of hydrophobic molecules through the cornea.[8-10]

Both the anterior and posterior segments are susceptible to a range of vision-threatening conditions. Diseases affecting the anterior segment of the eye include conditions like conjunctivitis, dry eye syndrome, keratitis, cataract, glaucoma (ocular hypertension), anterior uveitis, pterygium, corneal cystinosis, and keratoconus.[11] On the other hand, prevalent diseases like age-related macular degeneration (AMD) and diabetic retinopathy primarily target the posterior segment of the eye.[12]

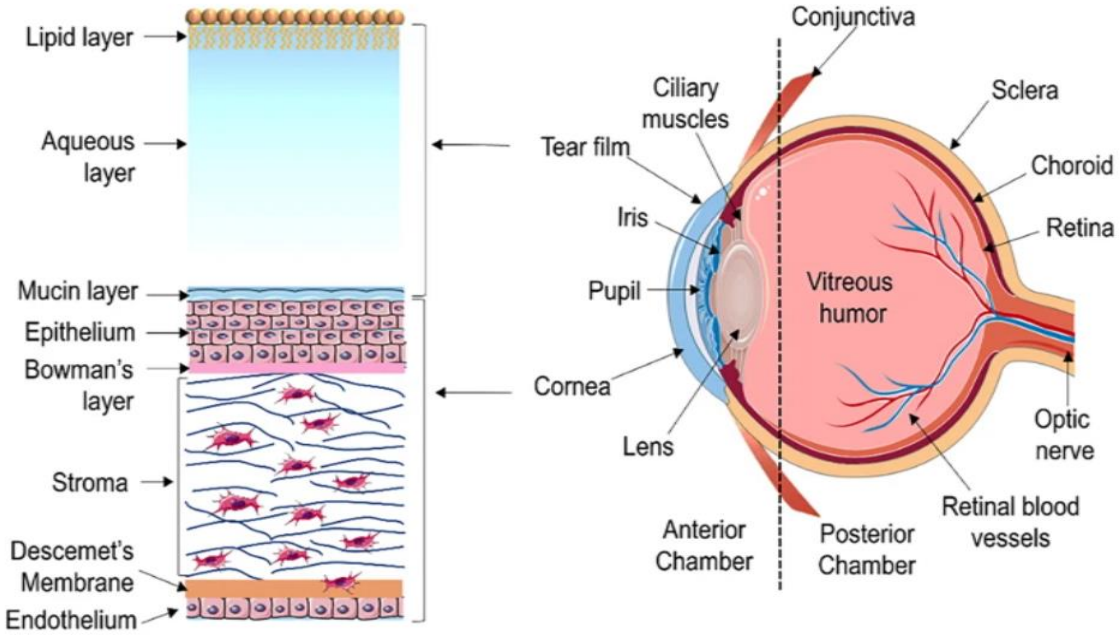

Fig 1: Structure of human eye[13]

Rationale for Novel Ophthalmic Drug Delivery

Traditional methods of administering drugs to the eye, face inherent limitations that hinder their efficacy. These limitations include poor drug bioavailability due to ocular barriers, short residence time on the ocular surface, and the requirement for frequent dosing, which often results in patient non-compliance. Furthermore, many ocular diseases affect specific tissues within the eye, necessitating targeted drug delivery. The emergence of new therapeutic agents, including biologics and gene therapies, also demands specialized delivery systems. Researchers and pharmaceutical companies are exploring innovative approaches such as nanoparticles, nanosuspensions, hydrogels, contact lenses, implants, and microneedles to address these challenges.[14] These advancements aim to enhance drug penetration, prolong drug release, and target specific ocular tissues while improving patient comfort and compliance. Additionally, regulatory considerations play a crucial role in driving the development of novel ophthalmic drug delivery systems to ensure safety and efficacy. Ultimately, the pursuit of innovative ophthalmic drug delivery methods is driven by the goal of providing more effective and patient-friendly solutions for treating a wide range of eye conditions.

Challenges in Ophthalmic Drug Delivery

Ophthalmic drug delivery presents a unique set of challenges due to the complex anatomy and physiology of the eye. The eye has multiple protective barriers that limit the entry of drugs into ocular tissues as shown in figure 1. Structurally, the front part of the corneal surface can be divided into three main layers: Epithelium, Stroma, and Endothelium. All three of these layers collectively function as barriers that can impede the absorption of drugs into the eye.[15] When administering topical formulations to the eye, several factors in the precorneal environment and anatomical barriers can significantly impact the bioavailability of the drug. Precorneal factors encompass aspects such as solution drainage, blinking, tear film dynamics, tear turnover rate, and induced lacrimation.

These factors collectively influence how effectively a drug is absorbed and retained on the ocular surface, affecting its therapeutic efficacy.[16] Designing drug delivery systems that can bypass or penetrate these barriers is a significant challenge. The limited drug absorption and penetration into target tissues often require frequent dosing, leading to poor patient compliance. Frequent dosing with eye drops can be inconvenient and uncomfortable for patients.[17] Non-compliance with prescribed treatment regimens is a common issue in ophthalmic therapy. Chronic ocular conditions, like glaucoma, require long-term treatment. Developing delivery systems that provide sustained drug release over extended periods is essential to reduce the frequency of dosing. Some drugs administered to the eye can be systemically absorbed, leading to potential systemic side effects. Designing delivery systems that minimize systemic exposure is critical. Researchers are continuously exploring innovative drug delivery technologies and formulations to overcome these hurdles and improve the treatment of various eye diseases.

Eye diseases affecting the anterior segment

Conjunctivitis

Conjunctivitis, commonly known as pink eye, is characterized by inflammation or swelling of the conjunctiva, a thin layer covering the eye white part and inner eyelids. Conjunctivitis can result from various factors including allergens, infections, or exposure to irritating chemicals.[18] Allergic conjunctivitis typically affects individuals with seasonal allergies, and contact lens wearers, particularly those who do not replace their lenses regularly are more prone to it. Infectious conjunctivitis is often caused by bacteria like streptococcus or staphylococcus and contagious viruses often associated with the common cold. Ophthalmia neonatorum, a severe form of infectious conjunctivitis, occurs in infants during their first month and can lead to permanent vision damage if not treated promptly.[19] Chlamydial conjunctivitis, caused by Chlamydia trachomatis, is responsible for over 40% of ophthalmia neonatorum cases and is transmitted from infected mothers during childbirth.[20] Chemical conjunctivitis can develop from exposure to harmful environmental chemicals. Treatment for conjunctivitis varies based on its cause and may involve topical antihistamines, non-steroidal anti-inflammatory drugs, antibiotics, or a combination of these therapies, including steroids when necessary.[21]

Dry eye disease

Dry eye disease, also referred to as keratoconjunctivitis sicca, is a condition that results from damage to the ocular surface due primarily to insufficient tear production for adequate lubrication. This condition is characterized by instability of the tear film, increased tear saltiness (hyperosmolarity), inflammation, and harm to the ocular surface.[22] Dry eye is a prevalent eye ailment, affecting anywhere from 5% to 50% of the global population.[23] Dry eye is a persistent condition with symptoms that encompass sensations of heat, pain, irritation, soreness, a feeling of a foreign body in the eye, and reduced visual clarity. Among the frequently employed treatments are artificial tears containing water-soluble polymers and the use of punctal plugs. These therapies aim to alleviate the discomfort and improve the condition associated with dry eye.

Keratitis

Keratitis is a serious inflammation of the cornea, which can pose a significant threat to vision and is considered an ocular emergency. It stands as the primary cause of corneal cloudiness and ranks fifth among the leading causes of blindness and visual impairment on a global scale.[24] This condition typically presents with symptoms such as severe eye pain, redness of the conjunctiva and eyelids, reduced vision, corneal ulceration, and infiltrates in the corneal tissue. Infectious keratitis can be attributed to various factors including bacteria, fungi, acanthamoeba, and viruses.[25] Additionally, non-infectious keratitis may arise from factors like corneal injuries, prolonged use of contact lenses, or severe dry eye conditions. The treatment for keratitis is contingent upon its underlying cause, ranging from the application of artificial tears and antibiotic eye drops to the possibility of corneal transplants. However, corneal transplant surgeries can be limited due to a shortage of available donor corneal tissue.[26] Furthermore, complications following such procedures may encompass issues like inflammation and the rejection of the transplanted cornea, necessitating the use of immunosuppressants, antibiotics, and anti-inflammatory medications to manage these challenges.

Cataract

Cataract is characterized by the clouding of the ocular lens leading to vision impairment, stands as a major global health issue. It ranks as the primary cause of blindness and the second most common cause of visual impairment worldwide.[27] While cataracts can develop as a result of eye injuries, they most commonly occur with age. The process involves the proteins within the lens clumping together over time, resulting in a cloudy lens that hinders the passage of light to the retina. The most effective treatment for cataracts is lens replacement surgery, which aims to restore clear vision by replacing the cloudy lens with an artificial one. However, lens replacement surgery is not without its challenges. Postoperative complications like endophthalmitis (eye infection) and suprachoroidal hemorrhage (bleeding in the eye) can occur, necessitating drug therapy to manage these adverse effects.[28]

Glaucoma

Glaucoma encompasses a group of eye conditions that pose a significant risk to vision, ranking as the second leading cause of global vision loss. The hallmark of glaucoma is the progressive damage to the optic nerves, ultimately leading to impaired vision.[27] This damage occurs gradually and is primarily driven by increased fluid accumulation in the front part of the eye. The root cause often lies in elevated intraocular pressure (ocular hypertension), which leads to fluid buildup. There are two main types of glaucoma: open-angle, which is a chronic form, and closed-angle, which tends to be acute and painful. Early detection and timely intervention are essential to prevent blindness or vision loss caused by glaucoma.[29] Various treatment options exist, ranging from medicated eye drops to laser surgery or a combination of these approaches. Reducing intraocular pressure is the most effective strategy for managing glaucoma. Topical eye drops, including prostaglandin analogues, carbonic anhydrase inhibitors, miotic agents, alpha agonists, and beta blockers, are commonly prescribed to lower intraocular pressure and preserve vision.[30]

Ophthalmic Formulation Considerations

Conventional eye drops are the most commonly used ophthalmic formulations. They are liquid preparations in which the drug is either completely dissolved (forming a true solution) or evenly dispersed (forming a suspension) in an aqueous carrier. Developing these eye drops involves considering various critical factors. Safety aspects like ensuring sterility, preventing ocular irritation or toxicity, and determining appropriate preservative levels are paramount. Additionally, factors related to the drug molecule such as its solubility in water, degree of ionization, and ability to partition between oil and water must be carefully assessed. Similarly, characteristics of the final product including pH, osmolality, buffering capacity, preservative concentration, and sterility play a crucial role. These aspects must be meticulously adjusted to ensure the drug effectiveness is not compromised. It is worth noting that rapid tear production, known as reflex tearing can lead to quick drainage of the applied eye drop reducing drug bioavailability.[31]

pH and buffer capacity are critical considerations when formulating ophthalmic drugs. The natural pH of tear fluid in the eye is around 7.4. Ideally, any ophthalmic formulation should fall within the pH range of 7.0 to 7.7 to minimize the risk of causing irritation to the eye. However, many ophthalmic medications are formulated outside of this pH range due to the need to maintain drug stability and solubility. One challenge in formulating ophthalmic drugs is that the tear fluid has limited buffering capacity, mainly due to the presence of bicarbonate and dissolved carbon dioxide. This limited buffering capacity restricts the pH range that can be effectively maintained by currently available liquid ocular products. Therefore, formulators must strike a balance between achieving the desired drug stability and solubility while minimizing the potential for irritation to the sensitive eye tissues.[32] The osmolality of lachrymal fluid typically falls in the range of 310 to 350 mOsm/kg, and this value is influenced by the number of dissolved ions in the tear fluid. When formulating ophthalmic drugs, it is crucial to ensure that the osmolality of the formulation falls within specific limits. Specifically, the osmolality of an ophthalmic formulation should not exceed 480 mOsm/kg or drop below 260 mOsm/kg. If the osmolality falls outside of these limits, the formulation can be irritating to the eye, potentially compromising the bioavailability of the administered drug.[33] Many commercial ophthalmic solutions are intentionally formulated to be slightly hypotonic, meaning they have a lower osmolality than the natural tear fluid. This is done because hypotonic solutions are generally better tolerated by the eye compared to hypertonic ones, reducing the risk of irritation when using these products.

Conventional ophthalmic dosage forms, including solutions, suspensions, and ointments, make up the majority, around 90%, of the currently accessible ophthalmic formulations in the market. These forms are favored because they are simple to create, easy to administer, and come with relatively low manufacturing costs. However, they have their limitations. Aqueous eye solutions, for instance, suffer from a very short contact time with the eye's surface and quick drainage through the nasolacrimal duct which ultimately results in poor drug bioavailability. Ointments, on the other hand can be problematic due to issues related to visibility and patient acceptability. Suspensions have their challenges too, often leading to unpredictable and inconsistent drug bioavailability when used in the eye.[34]

Novel-based ocular drug delivery systems

To address the challenges associated with delivering drugs to the eyes and to enhance the absorption of drugs in ocular tissues, a range of innovative drug delivery systems have been developed. These include nanoemulsions, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels, all designed to target and treat ocular diseases more effectively.[35]

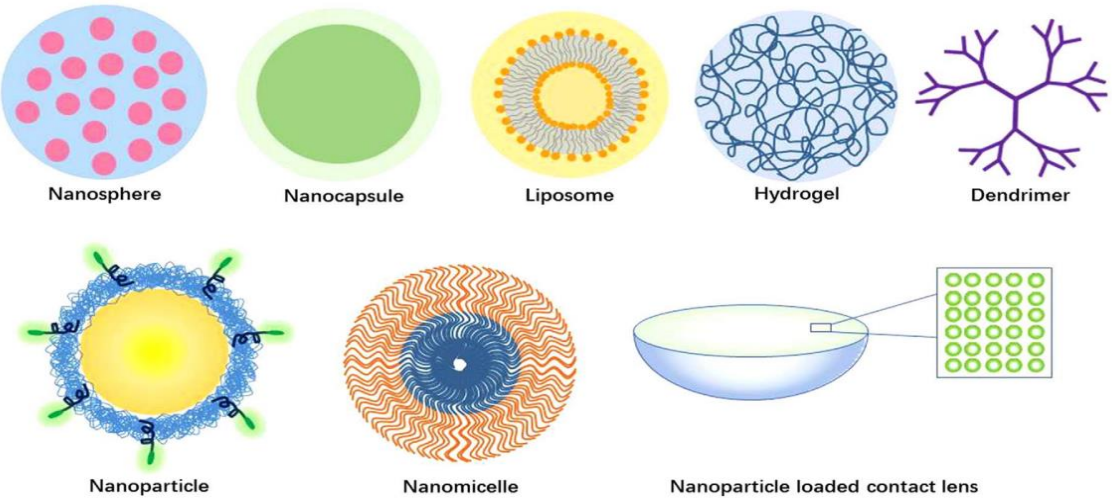

Fig 2: Various nano-carriers for ophthalmic drug delivery[36]

The development of novel drug delivery systems for ocular applications is imperative due to the inherent limitations of conventional ocular dosage forms. Traditional approaches face significant drawbacks, primarily characterized by poor ocular bioavailability. This means that a substantial portion of the administered drug is wasted with only a small fraction successfully reaching the intended target within the eye. This challenge is attributed to the ocular intricate anatomy and the distinctive characteristics of its tissues which hinder the efficient delivery of drugs. As a result, achieving effective drug delivery to the eye has consistently posed a formidable challenge in the field of ophthalmology. Several novel methods of drug delivery hold great potential in improving the treatment of various ocular diseases and conditions while addressing the limitations associated with conventional ocular dosage forms.[37]

Nanoparticles (nanospheres and nanocapsules)

Nanoparticles have emerged as a prominent nanocarrier system in extensive research over the past two decades. These minute particles typically range in size from 10 to 1000 nm. During the formulation process, drugs can be incorporated into nanoparticles through various methods including encapsulation, entrapment, adsorption, dispersion, or dissolution. Nanoparticles can be broadly categorized into two main types based on their composition: polymeric nanoparticles (PNP) and solid lipid nanoparticles (SLN). PNP can be designed using a variety of polymers, both biodegradable and non-biodegradable, along with copolymers. Examples include polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(lysine), poly(alkylcyanoacrylate) (PACA), and chitosan.[38-40] These nanoparticles offer versatile options for drug delivery systems and have opened up new avenues for therapeutic applications. They possess high drug loading capacity, ease of formulation, and scalability. They are minimally toxic, protect drugs from degradation, improve solubility and stability, provide sustained drug release, and remain stable in biological fluids. These qualities make them valuable for pharmaceutical and medical applications.[41]

Nanoparticles can be categorized into two main types, depending on the formulation process: nanospheres and nanocapsules. Nanospheres are characterized by a matrix structure where drug molecules are either dissolved within, dispersed throughout, or adsorbed onto the surface of the matrix. In contrast, nanocapsules have a different configuration, consisting of a polymeric wall or shell that surrounds an internal core. Typically, the drug is contained within this central core of the nanocapsule. These differences in structure offer distinct advantages and applications in drug delivery systems. Polymeric nanoparticles (PNP) can be formulated using various techniques, including ionic gelation, solvent evaporation, spontaneous emulsification/solvent desolvation, interfacial polymerization, and salting out/emulsification-diffusion. Among these methods, the ionic gelation approach is often preferred for PNP formulation. This preference arises from the method simplicity, ease of scalability, and the reduced risk of contamination during particle formation. It offers a practical and efficient means of producing polymeric nanoparticles for drug delivery applications.[42]

Liposomes

Liposomes are microscopic vesicles composed of one or more concentric lipid bilayers, with water or aqueous buffer compartments in between. In ocular formulations, liposomes are widely employed because they can intimately interact with the eye surfaces, particularly the cornea and conjunctiva. This interaction enhances drug absorption through the ocular route.[43] Liposome formulations can be created using components like phosphatidylcholine, stearylamine, cholesterol, lecithin, and α-L-dipalmitoyl-phosphatidylcholine.[44-46] These liposomes offer several advantages, including biocompatibility, biodegradability, amphiphilic properties, and low toxicity. [45,47] They facilitate targeted drug delivery and sustained release, making them suitable for drugs with poor absorption, low partition coefficients, limited solubility, and medium to high molecular weights.[48] It is essential to consider the surface charge of liposomes in ocular delivery; positively charged liposomes tend to adhere to the negatively charged corneal surface, while neutral or negatively charged liposomes do not. In various studies, liposomal ophthalmic formulations have been developed for active

pharmaceutical ingredients such as acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin.

Niosomes and discosomes

Niosomes are bi-layered nanocarriers composed of nonionic surfactants, serving as carriers for both hydrophilic and hydrophobic drugs. Unlike liposomes, which are chemically unstable and susceptible to oxidative degradation due to their phospholipid composition, niosomes offer a more stable and cost-effective alternative.[49,50] These advantages include biodegradability, biocompatibility, and non-immunogenicity. Niosomes enhance drug bioavailability by prolonging the contact time between the drug and the cornea. A modified version of niosomes called discosomes also serves as a carrier for ophthalmic drugs. Discosomes have a size ranging from 12 to 16 mm, preventing them from entering the general circulation. Their disc-like shape allows them to fit well into the conjunctival sac. Discosomes consist of nonionic surfactants and SolulanC, a lanolin derivative, along with a mixture of ethoxylated cholesterol and ethoxylated fatty alcohols. Niosomal carriers have been employed for drug delivery, including ganciclovir, cyclopentolate, and timolol.[51,52]

Nanoemulsion

A nanoemulsion, sometimes called a submicron emulsion, is a unique dispersed system consisting of two immiscible phases: an oily phase and an aqueous phase. These phases are held together and stabilized by one or more surfactants. In a nanoemulsion, the oily phase is dispersed into nano-sized droplets within the aqueous phase. It is important to distinguish nanoemulsions from microemulsions, which are thermodynamically stable, optically isotropic, and transparent colloids with droplets ranging from 20 to 200 nm in size. Nanoemulsions offer several advantages for ophthalmic drug delivery, including improved drug bioavailability, low viscosity, solubility of both lipophilic and hydrophilic drugs, reduced systemic absorption, resulting in fewer side effects. Additionally, nanoemulsions have excellent wetting and spreading properties due to their low surface/interfacial tension.[53,54] Nanoemulsions can be created using a variety of techniques, including high-pressure homogenization, ultrasonication, microfluidization, and spontaneous emulsification.[55] Sun et al. (2011) have developed a patented nanoemulsion composition for cyclosporine, designed for the treatment of ophthalmic diseases. This nanoemulsion is created by blending two solutions: one is an oily solution consisting of cyclosporine, propylene glycol monocaprylate, or oleoyl macrogolglyceride, while the other is an aqueous solution containing poloxamer, glycerine, and chitosan. This innovative formulation demonstrates excellent physicochemical stability and a prolonged shelf life, making it a promising option for ophthalmic drug delivery applications.[56]

Gels and *In Situ* Gelling Systems

Gels play a crucial role in ocular drug delivery due to their unique properties. They have the capacity to extend the corneal retention of drugs thanks to their thick and viscous consistency. Polymeric hydrogels, specifically, are defined as polymer-based systems that can swell when exposed to water and transform into a gel-like state. Hydrogels can be categorized into two main types: preformed hydrogels and in-situ gelling systems. Preformed hydrogels are essentially thick solutions that remain unchanged upon administration.[57] In contrast, in-situ gelling systems are polymer-based solutions with a high viscosity when applied but can undergo a phase change, transitioning from a liquid to a gel state triggered by specific physicochemical factors like temperature, pH, or ionic strength. In-situ gelling systems offer distinct advantages over preformed gels. Preformed gels can be challenging to administer accurately, often causing issues such as blurred vision, eyelid crusting, and increased tearing after application. In-situ gelling systems, on the other hand, can be easily and precisely applied in liquid form and are effective at prolonging the drug's presence on the ocular surface, making them a preferred choice for ophthalmic drug delivery.[58] Preformed gels are typically composed of bioadhesive or mucoadhesive polymers that have numerous hydrophilic functional groups. These bioadhesive polymers are characterized by their high molecular weight and include examples such as polyacrylic acid (PAA) and sodium carboxymethylcellulose (CMC). Many preformed hydrogels

incorporate synthetic mucoadhesive polymers, which can be water-soluble linear chain polymers or water-insoluble cross-linked polymers that have the ability to swell. Due to their high viscosity and excellent compatibility with the eye's tear fluid, preformed hydrogels can extend the duration of drug contact with the eye, thereby increasing the drug's bioavailability.[59]

Nanosuspensions

Nanosuspensions can be described as tiny particles of insoluble drugs suspended in a liquid, with the suspension stabilized by a suitable surfactant or polymer. These nanosuspensions find applications in formulating and delivering hydrophobic drugs to the intraocular tissues in the form of aqueous dispersions. They serve to enhance the solubility of such drugs, prolong their retention within the eye, and provide sustained drug release. Consequently, they improve the overall effectiveness of poorly water-soluble drugs in ophthalmic applications.[60] In the formulation of ophthalmic nanosuspensions, various types of polymers, whether natural, synthetic, or a combination of both, are frequently employed as stabilizing agents.[61] A nanosuspension containing the anti-inflammatory drug flurbiprofen was successfully prepared using Eudragit RL 100 through the solvent displacement method. This nanosuspension demonstrated excellent stability and exhibited a sustained release profile for the drug.[62] Similarly, a cationic nanosuspension loaded with diclofenac was developed using chitosan and methoxy poly(ethylene glycol)-poly(ε-caprolactone) diblock copolymer, aiming to address ocular inflammation. In an albino rabbit model, this polymeric nanosuspension showed remarkable bioavailability, as evidenced by a higher Cmax (maximum concentration) in the aqueous humor and approximately double the area under the curve compared to commercial diclofenac eye drops.[63] Moreover, the chitosan-coated nanosuspension demonstrated enhanced corneal penetration and retention in an in vivo corneal penetration test, all without causing ocular irritation. Importantly, the nanosuspension maintained excellent stability in an aqueous humor solution even after 24 hours. These findings suggest the potential of nanosuspensions as a promising approach for improved ocular drug delivery in the treatment of inflammation.[64]

Micelles

Micelles are colloidal systems used in drug delivery that spontaneously form in a solution when the concentration of the polymer or surfactant exceeds a critical micellar concentration (CMC).[65] These amphiphilic surfactants or diblock polymers assemble themselves in solutions, creating micelles when a specific concentration or temperature is reached.[66] Micelles vary in size, typically ranging from 10 to 200 nm, and can adopt various shapes, including spherical, cylindrical, or star-shaped. Regular micelles are effective carriers for hydrophobic drugs in aqueous solutions, while reversed micelles are useful for delivering hydrophilic drugs.[67] Micelles play a crucial role in enhancing the permeability of topically applied drugs through the cornea and are promising for targeted drug delivery to ocular tissues. In the development of ocular drug delivery systems, surfactant micelles were integrated into in-situ gelling systems for the delivery of cyclosporine A. Two non-ionic surfactants, d-α-tocopherol polyethylene glycol succinate and polyoxyl-40-hydrogenated castor oil, were used to create the micellar delivery systems. These micelles were then combined with a gellan gum dispersion to form a clear and easy-to-administer aqueous solution. Upon contact with lacrimal fluid, this solution undergoes a transformation into a gel, extending its residence time on the ocular surface. Importantly, this combined approach demonstrated low toxicity to corneal cells, making it a promising strategy for eye drop formulations of hydrophobic drugs.[68]

Dendrimers

Dendrimers represent a unique polymeric nanotechnology-based delivery system characterized by a star-shaped structure with branching. These nanosystems excel in their ability to encapsulate or attach drugs and functionalize their surface groups.[69] Active pharmaceutical ingredients can be housed within the dendrimer's core or linked to its surface.[70] Different generations of dendrimers (like G1, G2, G3, G4, and G5) depend on the specific carboxylic and hydroxyl functional groups attached to the polyamidoamine dendrimer. Dendrimers offer numerous advantages, including their small size,

versatility for functionalization, targeted drug delivery capabilities, and ease of preparation. They are particularly promising for ocular drug delivery due to their ability to enhance aqueous solubility, achieve high drug encapsulation rates, and maintain uniform particle sizes. A novel dendrimer and nanofiber system, along with the glaucoma medication brimonidine tartrate, was developed to treat glaucoma.[71] It is safe, non-irritating to the eyes, and effectively reduces intraocular pressure. When used regularly over three weeks, it outperforms traditional eye drops. This system offers promise for improved glaucoma management. In a different study, a polymeric dendrimer containing a timolol analogue was developed for treating ocular hypertension.[72] This dendrimer effectively delivered the drug to the corneal tissue, resulting in a significant reduction in intraocular pressure without causing any eye irritation or toxicity. This approach holds promise for improved ocular hypertension treatment.

Contact lenses

Contact lenses are thin curved plastic disks that cover the cornea and have been used to deliver various drugs for ocular applications.[73] By loading drugs onto contact lenses, they can adhere to the corneal surface due to surface tension and provide prolonged drug release. This extended residence time in the post-lens tear film can enhance drug absorption through the cornea while reducing drainage into the nasolacrimal duct. Typically, contact lenses are soaked in drug solutions to load the drug resulting in improved drug delivery efficiency compared to traditional eye drops. This approach has been applied to deliver drugs like β-blockers, antihistamines, and antimicrobials. Kim et al.[74] have found significantly higher bioavailability of dexamethasone (DX) when using poly (hydroxyethyl methacrylate) (PHEMA) contact lenses compared to traditional eye drops. While these drug-soaked contact lenses offer better efficiency than eye drops, they face challenges such as limited drug loading capacity and short-term drug release. To address these issues, two innovative approaches have been developed. Firstly, particle-laden contact lenses have been introduced. In this method, drugs are initially trapped within vesicles like liposomes, nanoparticles, or microemulsions, and these vesicles are then dispersed within the contact lens material. This allows for improved drug loading and controlled drug release over an extended period. Gulsen et al.,[75,76] conducted research on particle-laden contact lenses for the targeted release of lidocaine. They carried out two separate studies where they developed these lenses by incorporating lidocaine-loaded microemulsion drops or liposomes into poly-2-hydroxyethyl methacrylate (p-HEMA) hydrogels. The outcomes of both studies indicated that these particle-laden contact lenses could sustain the release of lidocaine for up to 8 days. This approach holds promise for extended ocular drug delivery, although it requires storage in drug-saturated solutions to prevent drug loss during storage. To address this issue, researchers are exploring the development of stimuli-responsive "smart" particles that can release the drug only within the eye, based on factors like pH or temperature. Additionally, molecularly imprinted contact lenses have also shown potential benefits in terms of both drug loading and controlled drug release, further enhancing the prospects for innovative ocular drug delivery methods.

Various Characterization Techniques

Assessing the physicochemical characteristics is essential to assess the properties of innovative ocular preparations for efficient drug administration and to monitor their stability during storage.

Physical appearance and clarity

The formulations underwent physical examination to identify any notable changes over time. Depending on variables like size of particles, concentration of the drugs and polymers, as well as the presence of surfactants or co-surfactants, the visual appearance of the formulations ranged from clear and transparent to semi-transparent or translucent, and in some cases, milky white.[77] The transparency of the prepared nano-formulations was assessed by employing an UV-Vis spectroscopy at the specific wavelength (520nm) to measure the percentage transmittance (%T). Formulations with smaller droplet sizes allowed lighter to pass through, resulting in a transparent or translucent appearance. The

system is gelation led to a reduction in transparency by 15%. Higher percentage transmittance indicated less interference with sight.[78]

Stability studies

To establish the appropriateness of a nano formulation, it is crucial to acquire thermodynamic stability data for the prepared nano systems. Stability investigations involve subjecting the formulations to thermal cycling, centrifugation experiments, freeze-thaw cycles and storage at elevated temperatures, while carefully observing for any notable alterations.[79] Per the guidelines set by the ICH, the long-term stability of a product is evaluated by storing it at a temperature of 25°C ± 2°C with a relative humidity of 60% ± 5%. Similarly, the refrigeration stability is assessed at a temperature of 5°C ± 3°C. For accelerated stability testing, the product is subjected to conditions of 40°C ± 2°C with a relative humidity of 75% ± 5%.[80]

Particles size and polydispersity index (PDI)

The average size and polydispersity index are important parameters used to characterize the size distribution of particles in a formulation. These parameters can be determined using various techniques, including Dynamic Light Scattering or Photon Correlation Spectroscopy. Most commonly used instrument for measuring particle size and PDI is the Malvern Zetasizer or Coulter Counter Analyzers. By assessing the PDI, researchers can determine the level of uniformity in the size distribution of nanoparticles or other particles in a formulation. Values below 0.1 indicate a more desirable and homogeneous distribution, while values close to 1 indicate a lower quality or less uniform system.[81] By having small particle size and low PDI, ophthalmic formulations can enhance their efficacy, improve tissue penetration, and provide more uniform drug delivery. These factors contribute to ocular drug treatments overall effectiveness and therapeutic outcomes.[82]

Zeta potential (ZP)

The physical stability of prepared nano-formulation is influenced by the charge on the particles, which is evaluated through the measurement of zeta potential (ZP). It is determined by evaluating the particles electrophoretic mobility in the presence of an electric field.[83] There is a suggestion that maintaining a zeta potential (ZP) within the range of +20 to +40 could effectively prolong the precorneal retention time.[84]

pH determination

Precise pH measurement is of utmost importance in the development of ophthalmic formulations that demonstrate efficacy, stability, and non-irritating properties. Chemical eye injuries can occur when the eye is exposed to solutions that are highly acidic (pH<4) or strongly alkaline (pH>10), leading to potential harm and damage. Therefore, it is recommended that topical ophthalmic formulations maintain an appropriate pH range of 6.6 to 7.8 to ensure safety and compatibility.[85]

Drug Distribution

Drug diffusion within nanosystems is evaluated by assessing parameters such as Entrapment efficiency (% EE) and Drug loading (% DL). These measures provide valuable information about the amount of drug effectively encapsulated within the nanoparticles and the overall drug content in the formulation. The drug loading percentage is a measure of the amount of drug loaded within the nano-systems. On the contrary, the entrapment efficiency percentage (% EE) indicates the extent to which drugs are successfully incorporated into the nano-based system at the time of formulation procedure. It measures the efficiency of drug entrapment and provides insight into the amount of drug retained within the system. % DL is commonly influenced by the composition, physical attributes, and chemical properties of the carrier material. In contrast, % EE relies on factors such as the hydrophobicity of the drug, its molecular weight, and its structure, all of which impact the drug capability to be included within the nanosystems.

It is important to mention that obtaining a high drug loading percentage is often more challenging compared to achieving a high drug entrapment efficiency in most nanosystems.[86]

Viscosity measurement

A low viscosity nano-system offers advantages in terms of improved patient compliance by minimizing blinking pain. Alternatively, a nano-system with increased viscosity can extend the duration of contact, decrease dosing frequency, and improve the bioavailability. Nevertheless, it is crucial to acknowledge that elevated viscosity nanosystems can potentially cause discomfort to the patient. For ocular preparations, the appropriate viscosity typically falls within the range of 2 to 3 mPa.s.[87]

Index of Refraction

An Abbe refractometer is employed to measure the refractive index, which is useful in assessing potential sight issues or discomfort post-administration of eye drops. Index of refraction for tears is generally falls between 1.340 and 1.360. Therefore, it is crucial for ocular drops to have refractive index values that do not exceed 1.476. to ensure optimal compatibility.[88,89]

Morphological parameters

Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) techniques are instrumental in validating the findings obtained through PCS or DLS measurements.[90] These microscopy techniques provide direct visualization and characterization of the sample at a nanoscale level. By using TEM and AFM, researchers can observe the morphology, size, and surface characteristics of the particles, which helps validate and complement the findings obtained from PCS or DLS measurements.

Surface Tension

Tate's law states that the drop weight is closely related to the interfacial tension of the solutions. As the drop volume plays a vital role in determining the amount of API delivered to the eye, it is an essential consideration in ophthalmic formulation. The measurement of droplet volume is typically conducted using a thermostatically controlled tensiometer. For effective drug delivery in ocular formulations, a drop volume ranging from 5µL to 15µL has been established as optimal. However, commercially accessible eye droppers generally administer higher volumes, usually ranging from 25.1µL to 56.4µL, with an average drop size of 39.0µL.[91,92] To minimize droplet size and attain the intended volume, surfactants can be incorporated into ophthalmic formulations as additives that enhance permeability and act as preservatives. These surfactants help condense the droplet size and improve the effectiveness of drug delivery.[91]

Osmolarity measurements

Osmolality measurements are conducted by analyzing the colligative characteristics of tear fluid or ophthalmic nano-based systems.[93] Fluid evaporation leads to the osmolality of open-eyes falling within the range of 231 to 446mOsm/kg. Eye formulations with an osmolality below 100mOsm/kg or above 640mOsm/kg are regarded as ocular irritants. However, after the administration of a non-isotonic preparation, the osmolality is restored within 1 or 2 minutes. Maintaining appropriate osmolality in eye formulations is essential for ensuring ocular distress and to avoid irritability. Formulating eye drops with osmolality within an appropriate range is essential to ensure compatibility and minimize adverse effects.

Ophthalmic retention

For in-situ eye delivery method, the mucoadhesion force is an essential physicochemical characteristic that inhibits quick elimination and enhances the duration of the system presence on the eye surface. Various techniques are utilized to measure mucoadhesion strength, including texture analysis, the modified equilibrium method, and assessing the rheological synergy observed when the

mucoadhesive polymer is mixed. During normal blinking, the force exerted for movement of the eyelids is approximately 0.2N, while a stronger blink may require 0.8N of force.[94] Akhter et al., discovered that a finely tuned nano-emulsion solution of Chitosan-Cyclosporin A (1% w/v) displayed a mucoadhesion strength of 0.153N.[95]

Biocompatibility test

Draize test

Conventionally, the Draize test has been employed as an In-Vivo model to assess the potential irritant effects of nano-based systems in rabbit eyes. This test is widely approved for conducting safety evaluation of cosmetics and medicinal preparations.[96] Although, there are certain limitations associated with the Draize test. One of the main drawbacks of the Draize test is the species difference between rabbits and humans. In contrast, rabbit eyes differ from human eyes in several aspects including a thinner cornea, the presence of a nictitating membrane and a reduced level of tear production which should be taken into consideration when interpreting the results of the Draize test. These anatomical and physiological differences raise concerns about the extrapolation of test results to human ocular safety. Despite these limitations, the Draize test is still utilized in practice due to historical precedent and regulatory requirements.[97]

HET-CAM test

This technique is utilized to assess the potential for discomfort caused by formulated topical treatments designed for dermal or ophthalmic conditions. Researchers employ this testing to evaluate the potential irritant effects of substances and preparations, with the objective of mitigating these effects in human beings. This technique involves the use of the Chorioallantoic Membrane, which bears a resemblance to the vascularisation found in human mucosal tissue. By employing this method, researchers can investigate the potential irritant effects of formulations intended for eye or skin applications. This approach has been utilized by various researchers with the goal of ensuring their safety and minimizing any potential irritant reactions in humans.[89]

Ex-Vivo Permeation Studies

To assess the transcorneal permeability of ocular formulations, different models including In-Vivo, Ex-Vivo, and In-Vitro approaches are currently utilized. In-vivo models often involve the use of rodents such as rabbits, rats, or mice, where the formulation is administered to the eyes of the animals to evaluate its permeability. In contrast, in-vitro and ex-vivo models employ various techniques to mimic the ocular tissue barriers. This can include using cultured epithelial cell layers, reconstructed cornea models, or excised corneas.[98,99] Multiple permeation chambers exist for the evaluation of drug formulation permeability. These include the Franz diffusion cells, Perfusion cells, Ussing chamber, and Erlenmeyer flask diffusion cell.[100-103] These parameters provide insights into the formulation ability to permeate ocular barriers and aid in evaluating its potential for effective drug delivery to the target sites.

Drug-polymer compatibility study

Moreover, the physical attributes of polymeric delivery systems should be taken into account. Studies on drug-polymer compatibility are a pivotal aspect that influences the efficacy of these systems. To assess the potential interaction between the drug and polymer, various analytical techniques can be employed, including Differential Scanning Calorimetry (DSC), Fourier-transform Infrared (FTIR) Spectroscopy and X-ray Powder Diffraction (XRD).[104] By evaluating these interactions, researchers can optimize the formulation and select appropriate polymers that enhance drug stability, release, and overall efficacy.

Conclusions and Future Perspectives

Addressing anterior segment eye diseases (ASED) is challenging, but critical due to their prevalence. Research should focus on novel drug formulations that reduce dosing frequency, improve drug

penetration, release, and efficacy, and minimize side effects. Diversifying nano-based strategies is important. Future efforts should create safer nano-formulations for anterior eye delivery, accommodating small molecules and biologics, ensuring low toxicity, stability, and enhanced pharmacokinetics. Co-encapsulating drugs with enzyme inhibitors to enhance ocular absorption is promising for improving treatments for ASED. Future research in ocular drug delivery should focus on formulating nanoparticles that can release drugs effectively in various eye tissues while ensuring biodegradability and patient comfort. Vision obstruction by carriers should be carefully addressed. Ideal nanoformulations should maintain effective drug levels and high bioavailability with a single application. Loading capacity and controlled drug release are crucial factors. Nanocarriers should be capable of sustaining drug release over days or months to reduce the need for frequent administration. Viscosity and permeation enhancers should be explored for enhancing ocular bioavailability. Collaboration between formulation scientists and clinicians is essential to meet specific clinical needs. New technologies like mucus-penetrating particles and hydrogel templates should be leveraged for improved ocular drug performance. While some nanoformulations are in clinical trials or on the market, ongoing research should consider regulatory requirements for approval of ophthalmic preparations. In summary, urgent attention is needed to better understand how nanoformulations are taken up and distributed in the eye, address stability issues, and conduct comprehensive safety and toxicity studies to ensure the success of ocular drug delivery using nanotechnology.

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