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REVIEW

Breaking Barriers: Nanomedicine-Based Drug Delivery for Cataract Treatment

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Abstract: Cataract is a leading cause of blindness globally, and its surgical treatment poses a significant burden on global healthcare. Pharmacologic therapies, including antioxidants and protein aggregation reversal agents, have attracted great attention in the treatment of cataracts in recent years. Due to the anatomical and physiological barriers of the eye, the effectiveness of traditional eye drops for delivering drugs topically to the lens is hindered. The advancements in nanomedicine present novel and promising strategies for addressing challenges in drug delivery to the lens, including the development of nanoparticle formulations that can improve drug penetration into the anterior segment and enable sustained release of medications. This review introduces various cutting-edge drug delivery systems for cataract treatment, highlighting their physicochemical properties and surface engineering for optimal design, thus providing impetus for further innovative research and potential clinical applications of anti-cataract drugs.

Keywords: nanomedicine, cataract, ocular barrier, drug delivery system

Introduction

Cataract, the opacification of the normally crystalline lens in the eye, is a leading cause of global blindness, particularly in developing countries.[1] While aging serves as the primary predictor, risk factors encompass diabetes, genetics, trauma, ultraviolet radiation, smoking, and certain medications.[2] The formation is attributed to the abnormal aggregation and decreased solubility of crystalline proteins, leading to lens opacity.[3] Known cataractogenesis involves oxidative stress, osmotic pressure changes, impaired autophagy, abnormal polyol pathways, and abnormal glycosylation. Oxidative stress plays a pivotal role in cataract development, as the lens's antioxidant defenses diminish with age, making it more susceptible to oxidative damage and ultimately triggering cataract.[4] Based on the locations of the opacity, cataracts are categorized into three types: cortical, nuclear and posterior subcapsular cataracts.[2]

Currently, the only effective treatment for cataracts is the removal of the opacified lens and the implantation of an intraocular lens. However, cataract surgery is typically performed when the disease is advanced or when the patient's quality of life has been severely compromised. The surgery is invasive and risky, and some patients may experience suboptimal postoperative vision recovery.[5] As the global population ages, the incidence of cataracts is expected to increase. The demand for cataract surgery exceeds limited public health resources, particularly in low-income countries. Studies have estimated that delaying the onset of cataracts for 10 years would halve their incidence.[6] Therefore, finding alternative drug therapies is crucial to reduce the socio-economic burden and improve patients' quality of life. Early intervention is key, and augmenting antioxidant levels can reduce oxidative damage to the lens and suppress protein aggregation. This has been an area of active research for the past two decades, with a surge in studies related to pharmacological interventions for cataract.[7] For instance, lanosterol (LAN), a drug that inhibits protein aggregation, has been demonstrated to decrease cataract severity in ex vivo experiments on animals.[8]

Pharmacological treatment for cataract prevention is hindered by the complex anatomical and physiological barriers of the human eye that prevent most ophthalmic drugs from reaching the lens.[9] The traditional method of drug delivery through

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eye drops has inherent defects, such as poor permeability, uneven distribution, and inadequate bioavailability, which limit the efficacy of drugs. Furthermore, macromolecular drugs, including peptides, proteins, antibodies, and oligonucleotides, face challenges in penetrating the ocular barrier. To improve drug delivery and enhance the ability of drugs to reach the lens, researchers have focused on nano drug delivery systems. To date, numerous nanocarriers have been employed to increase drug penetration through the ocular barrier. Nanoparticles can alter the biodistribution of drugs, prolong their circulation time, reduce toxicity, and enhance drug safety. Anti-cataract nanomedicines can be designed with consideration of specific biological scenarios, such as physicochemical cues, to promote biostability and bioavailability in the lens region. Ocular nanomedicines offer a significant advantage due to their ability to penetrate complex ocular barriers, such as the cornea, with minimal side effects and adverse reactions. Additionally, certain biomaterials can trigger controlled drug release in response to exogenous physical irradiation (eg light and heat) or endogenous biological stimuli (eg redox and pH).[10] Despite crossing the ocular barrier, most drug delivery systems, including nanoparticles, have difficulty penetrating cell membranes due to a lack of cellular uptake mechanisms. To address this issue, penetrating peptides that can penetrate both the ocular barrier and cells are constantly being developed.[11] Combining cell-penetrating peptides (CPPs) with drugs can increase the cellular uptake of the drug, thereby maximizing therapeutic efficacy.[12]

This review delineates the restrictions imposed by anatomical and physiological ocular barriers and presents the utilization of diverse cutting-edge drug delivery systems in cataract treatment (Figure 1). It assesses the influence of the physicochemical characteristics of nanomaterials on their effectiveness. Additionally, it investigates approaches to achieve efficient ocular drug delivery by incorporating strategies to overcome barriers in ocular drug delivery with controlled and targeted drug release. Lastly, the prospects and challenges regarding future research and clinical translation in this field are also discussed.

The Lens: Structure and Function

The human lens is a transparent structure composed of the lens capsule, lens epithelium and lens fibers. It is avascular and has the highest protein concentration in the body. The transparency of the lens is dependent on the highly ordered cellular structure of the lens, the disappearance of organelles as the fiber cells mature, the dense accumulation of crystalline proteins, and the availability of appropriate nutrients.[13]

Lens epithelial cells (LECs) are crucial for maintaining the metabolic activity of the lens. They act as a barrier against external stimuli and have the ability to proliferate into lens fibers throughout their lifespan. At the lens equator, they transform into lens fibers and gradually compress toward the center.[14] The lens is predominantly composed of lens fiber cells, with organelles absent from the deeper fibers, which are the least metabolically active. Lens fiber cells highly express soluble lens proteins but lack organelles such as nuclei and mitochondria.[15] This characteristic maintains the transparency of the lens, but at the same time leads to an overall inactivity of the lens metabolism and repair. Exogenous damage can easily lead to abnormal aggregation and deposition of lens proteins, ultimately affecting lens transparency.

Lens proteins are essential for maintaining the transparency and refractive properties of the lens. The three main types of crystallins, α, β, and γ, make up 90% of the total protein content of the lens. While α-crystallins are present in both LECs and fibers, their synthesis is much greater in LECs than in fiber cells. Conversely, β- and γ-crystallins are exclusively found in lens fibers. The short-range ordered spatial arrangement of these proteins accounts for lens transparency. α-crystallins function as molecular chaperones, binding partially denatured proteins and maintaining their solubility, thereby preserving lens transparency.[16] β-crystallins may act as stress proteins in the lens, although their function is unknown. γ-crystallins are present in regions of low water content and high protein concentration, such as the lens nucleus, and are associated with lens stiffness. Post-translational modification of lens proteins is a crucial step in the formation of functional lens proteins and the maintenance of lens transparency.[17]

The lens is devoid of any blood supply and instead receives necessary nutrients and processes metabolites through aqueous and vitreous humor.[1,18] The leading hypothesis for maintaining the homeostasis of the mammalian lens is the microcirculatory system, which facilitates nutrient entry and waste removal.[19] Lens cells exchange energy and substances through tight junctions between them.[20] Ion channels located on the cell membrane of LECs are responsible for transporting substances within the lens. Membrane protein receptors also play a crucial role in signal transduction. Synthesized lens proteins and various cell-active enzymes contribute to maintaining lens growth and the internal environment's homeostasis.[21]

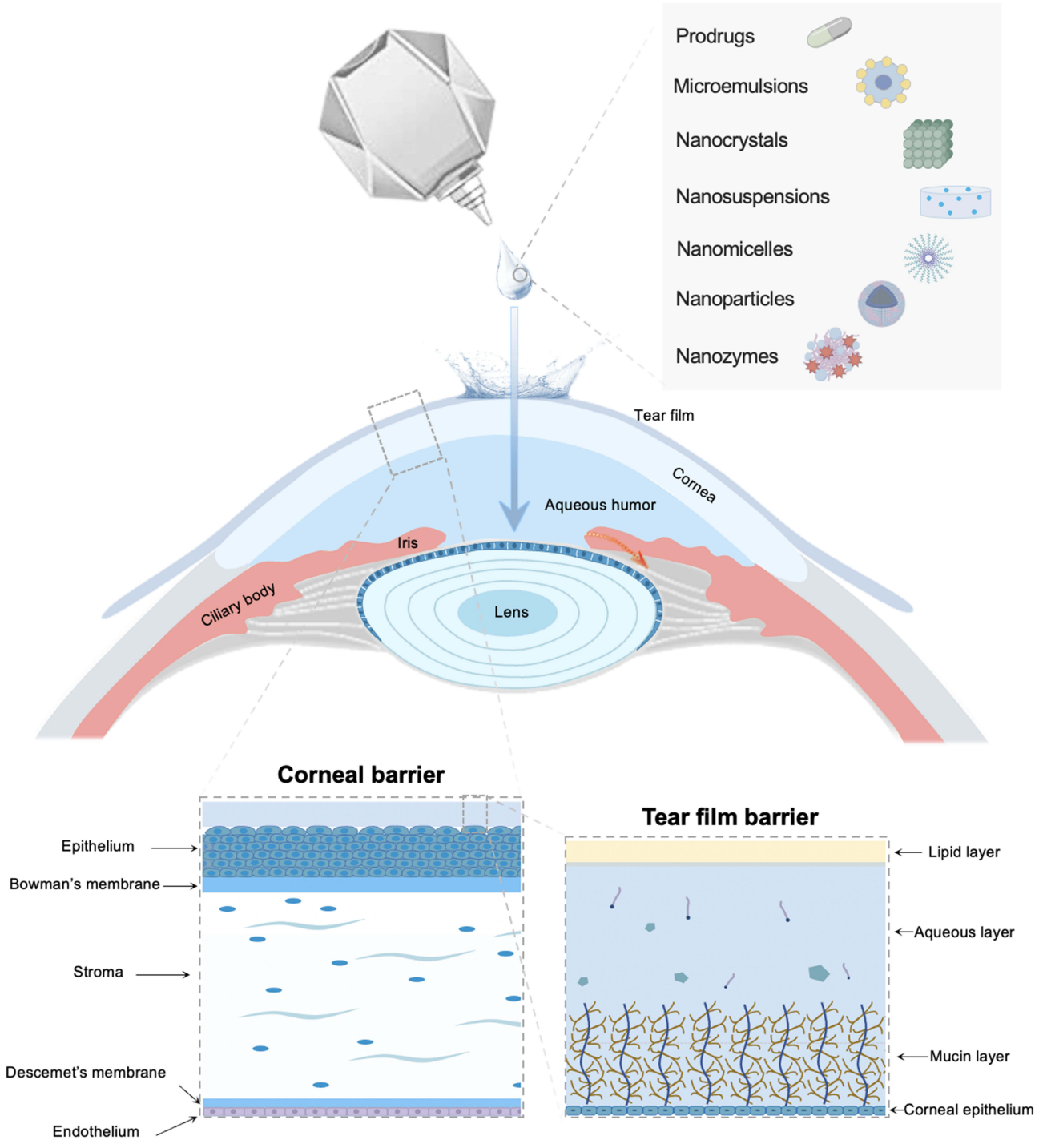

Figure 1 Schematic of drug delivery systems for delivering anti-cataract medications through ocular barriers to reach the lens.

Potential Medication Strategies for Cataracts

Anti-cataract drugs encompass a diverse range of therapeutic approaches (Figure 2). Notably, they concentrate on two pivotal areas: antioxidants and anti-crystallin aggregating agents.

The progressive accumulation of damage caused by reactive oxygen species (ROS) with aging has been identified as a contributing factor to the development of cataracts.[22] Consequently, antioxidants have been extensively investigated as a potential therapeutic strategy for cataract treatment. Thiol antioxidants, including cysteine, N-acetylcysteine, and

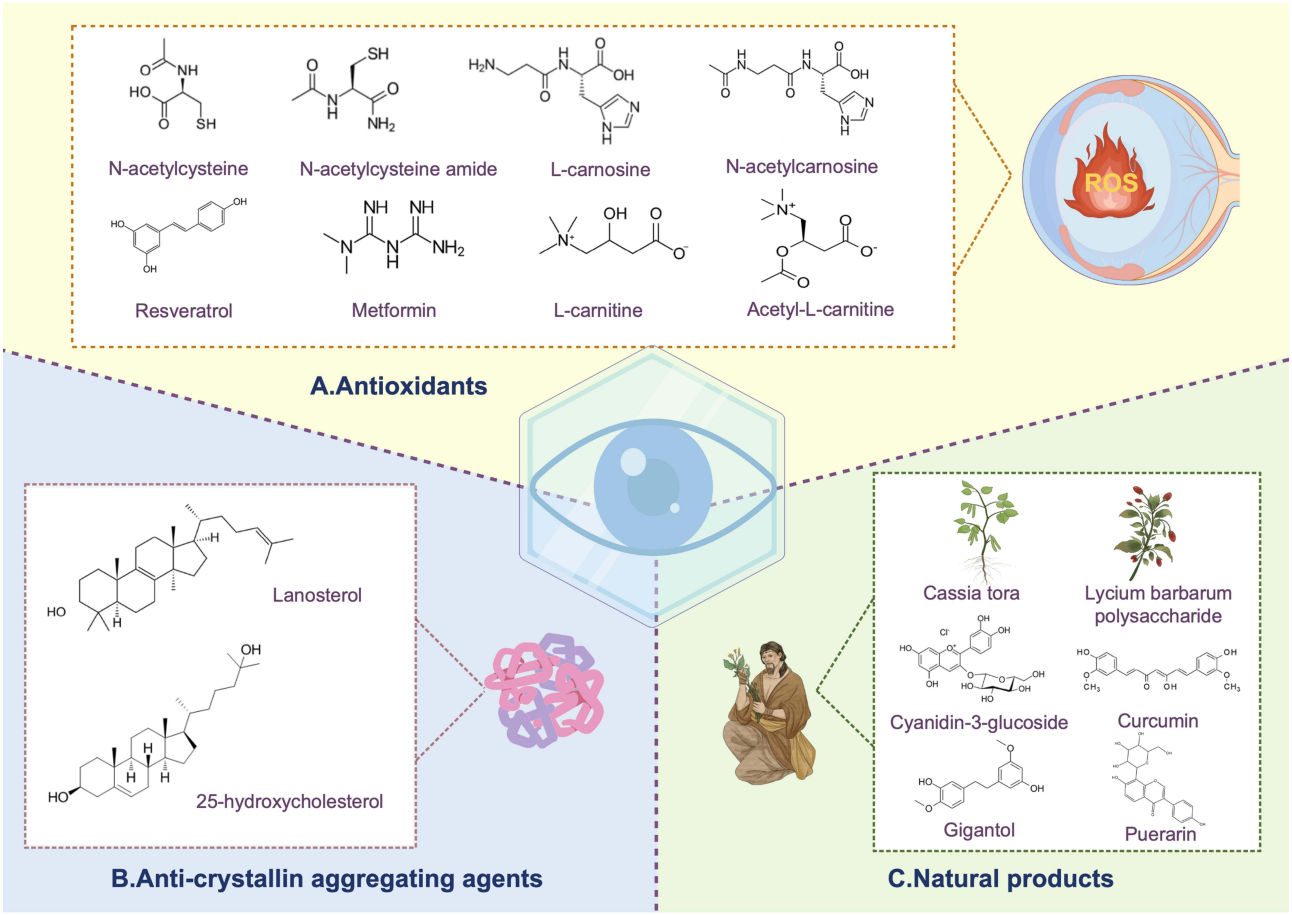

Figure 2 Schematic representation of potential medication strategies for cataracts.

N-acetylcysteine amide, have been found to possess antioxidant properties that can elevate levels of glutathione (GSH) and suppress the progression of cataracts.[23–26] Additionally, L-carnosine (LCS) and its derivative N-acetylcarnosine (NACS) have demonstrated promise in the treatment of cataracts by mitigating oxidative stress, reducing glycosylation, and inhibiting calpain-mediated proteolysis.[27,28] Resveratrol (RSV) has been shown to boost endogenous antioxidants and alleviate oxidative stress in the lens, thereby providing protection against cataract formation.[29] Metformin, a pharmaceutical agent utilized in the management of type 2 diabetes, exhibits anti-cataract properties through the reduction of oxidative stress, suppression of senescence, and stimulation of autophagy.[30,31] L-carnitine and acetyl-L-carnitine have displayed promise in the treatment of cataracts by augmenting antioxidant capacity, impeding glycosylation, and inhibiting apoptosis.[32,33]

Another therapeutic strategy approach focuses on targeting crystallin aggregation,[34] with oxysterols such as LAN and 25-hydroxycholesterol emerging as promising candidates for preventing or reversing protein aggregation in cataracts. LAN, catalyzed by LAN synthase, has exhibited the capacity to dissolve amyloid-like fibers, thereby specifically addressing and reversing crystallin aggregation in vitro and in vivo animal models.[8,35] Likewise, 25-hydroxycholesterol has demonstrated effectiveness in stabilizing the native conformations of the α-crystallin subunit and reversing crystallin aggregation in vitro, leading to improved lens opacity in animal models.[36]

A substantial number of natural products, including traditional medicine, have demonstrated potential in the treatment of cataracts. Cassia tora has been extensively studied for its therapeutic effect on cataracts, which include the regulation of ion balance, reduction of oxidative stress damage, modulation of energy metabolism and inhibition of apoptosis.[37,38] Additionally, other plant extracts such as lycium barbarum polysaccharide[39] from lycium barbarum, cyanidin-3-glucoside[40] from black rice, curcumin (CUR)[41,42] from ginger, gigantol[43,44] from orchids and puerarin[45] derived from East Asian arrow have shown promising effects in cataract treatment by regulating multiple biological processes.

Overall, these drugs have exhibited protective properties in the context of cataract therapy. To enhance the efficacy and safety, further research is imperative to optimize drug dosing within the lens and surmount obstacles associated with drug delivery.[46]

Barriers to Lens Drug Delivery

The eye can be divided into two segments: the anterior and posterior segments. The anterior segment comprises the cornea, conjunctiva, iris, ciliary body, and lens. The posterior segment comprises the vitreous, retina, choroid, sclera, and optic nerve. The complex anatomy of the eye includes multiple protective barriers that maintain visual quality at the static, dynamic and metabolic levels. However, as shown in Figure 3, these barriers also present challenges to effective drug delivery to the lens, and it is important to consider these challenges when developing drug delivery methods. Barriers that impede the penetration of anti-cataract drugs into the anterior chamber include static barriers such as the corneal and blood-aqueous fluid barriers, as well as dynamic barriers such as the conjunctival lymphatic network, tear film turnover, and nasolacrimal duct drainage. Efflux pumps expressed on the corneal surface, such as permeability glycoprotein and multidrug resistance protein, additionally restrict drug entry into the lens.[47]

Tear Film Barrier

The tear film blanketing the ocular surface acts as the primary barrier to intraocular drug delivery. It is composed of an external lipid layer, a middle aqueous layer and an internal mucin layer. Proteins and enzymes present in the tear fluid can bind and metabolize active drugs, resulting in a decrease in the concentration of free drugs. Mucins, primarily secreted by conjunctival and corneal epithelial cells, are glycoproteins with high molecular weight, hydrophilicity, and electronegativity.

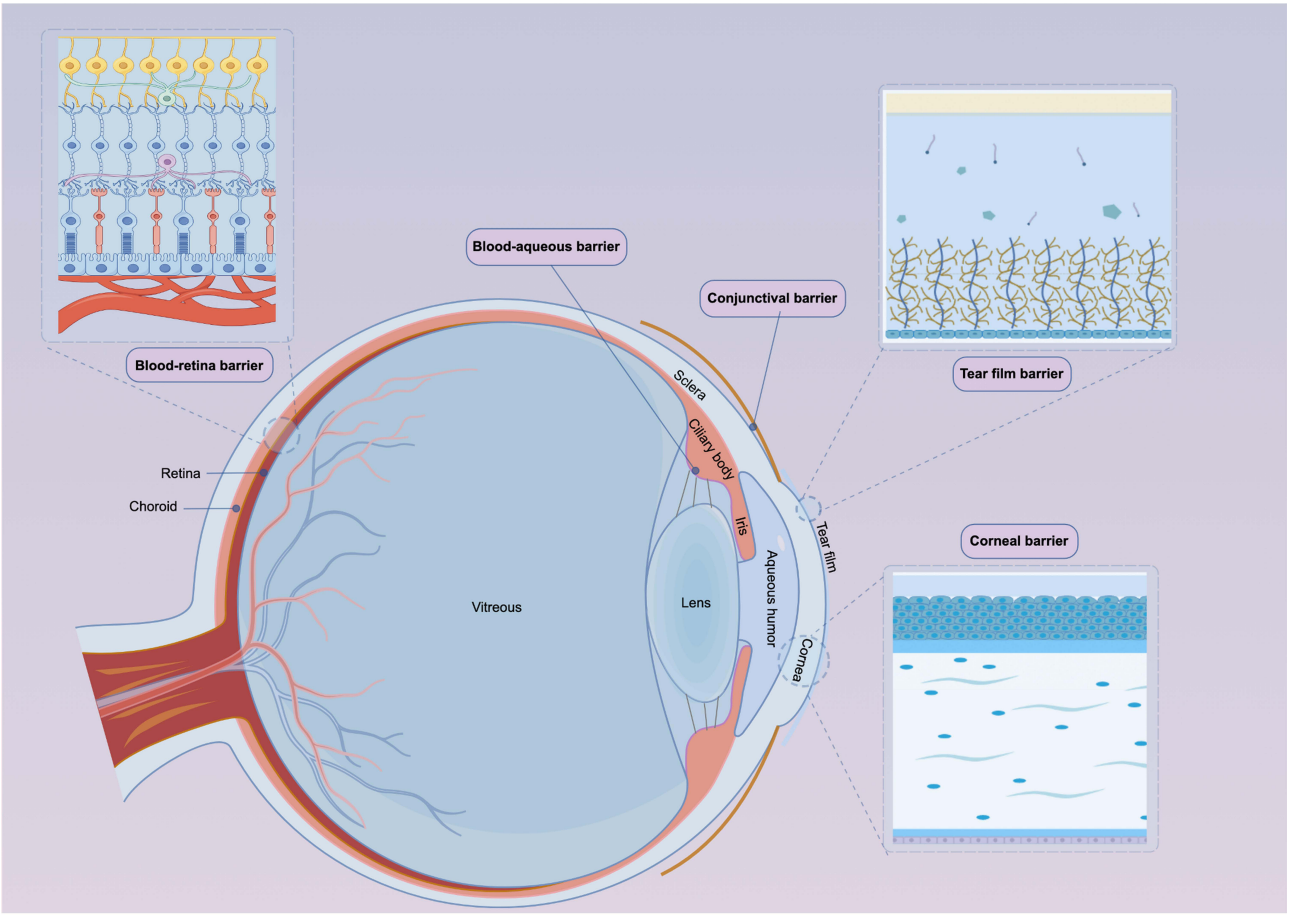

Figure 3 Schematic illustration showing the ocular barriers of drug delivery to the lens.

These distinctive attributes possess the capacity to either attract or repel drugs through non-covalent interactions such as electrostatic, ionic, and hydrogen bonding interactions.[48,49] The dynamic distribution and transition of mucins allow for their clearance from the ocular surface through reflex blinking and tear drainage, influencing the adhesion and duration of drugs.[50] Tear fluid has a similar osmolarity to blood. However, it also contains a weak buffering system of carbonate ions and weak organic acids, which can alter the extent of drug ionization and, consequently, its bioavailability.[51] The conjunctival sac can hold approximately 30 μL of tear fluid briefly, while the normal tear volume is around 7 μL. The rate of drug elimination from tears ranges from 0.5 to 2.2 μL/min, and the entire tear film is renewed within 5 minutes.[52] The recommended dosage of eye drops is 5–10 μL, but most commercially available eye drop bottles have a dosage of 50 μL per drop. After ocular administration, tear turnover and reflex blinking increase, and drugs not absorbed by the ocular tissues are physically removed.[53] Tears have a pH of approximately 7.4 and lack a robust buffering system. Therefore, the pH of the administered eyedrop will determine the current pH of the ocular surface. To maintain homeostasis, a reflex increase in tear secretion occurs to clear irritating eyedrops, which further reduces the ocular bioavailability of the drug. Hence, the ideal pH of an ophthalmic preparation should be near that of the lachrymal fluid.[54]

Conjunctival Barrier

Conjunctiva consists of the multilayered epithelium and inner stroma that comprise connective tissues with blood and lymphatic vessels. It is a more permeable structure, with a surface area approximately 17 times that of the cornea, and may therefore be a preferred route for the absorption of hydrophilic drugs with molecular weights below 20 kDa.[55] However, the high degree of vascularization results in significant drug loss into the body circulation and the posterior segment of the eye, rather than the anterior segment, further reducing the bioavailability of lens-delivered drugs.[56]

Corneal Barrier

The cornea is a multilayered structure consisting of an epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. Among these layers, the epithelium and stroma present main barriers to drug diffusion and permeation through the cornea. Hydrophilic drugs are limited by tight junctions between epithelial cells, while hydrophobic drugs are restricted by the stroma.[57] Despite the tightness of the corneal epithelial layer, which restricts paracellular drug permeation, transcorneal permeation is the primary pathway for drug penetration from the tear fluid to the aqueous humor.[58] To achieve therapeutic drug concentrations in the target tissue, drugs must successfully traverse both the lipophilic corneal epithelium and the hydrophilic corneal stroma. Lipophilic drugs generally demonstrate permeability in the cornea at least one order of magnitude higher than hydrophilic drugs.[59] However, due to the cornea's structure, drugs with high molecular weight and negative charge exhibit low permeability. Therefore, only drugs possessing specific physicochemical properties can penetrate the cornea and effectively reach their intended therapeutic target.

Blood–Aqueous Barrier

The blood-aqueous barrier is traditionally formed by tight junctions among the non-pigmented epithelium of the ciliary body, iris tissue, and iris vessels. In a broader sense, this barrier serves as a boundary separating the restrictive environment behind the iris from the permissive environment necessary for the metabolic demands of the avascular tissues facing the anterior chamber. The tight junctions within the ciliary epithelium are involved in the secretion of aqueous humor, thereby contributing to the preservation of the pristine physiological conditions established by the anatomical components of the blood-retinal barrier. The tight junctions of the posterior iris epithelium extend the blood-retinal and blood-vitreous barrier to the pupillary margin, ensuring an uninterrupted barrier. Additionally, the one-way valve mechanism of iris apposition to the lens, along with the continuous forward flow of aqueous humor, prevents retrograde flow.[60] This highly effective barrier restricts the entry of plasma albumin into the aqueous humor and also limits the bioavailability of hydrophilic medications administered systemically.[61] Intriguingly, this arrangement exposes the metabolically active epithelium on the anterior surface of the lens to the nutrients available in the anterior chamber, which is a more permissive environment.[60]

Lens Barrier

The lens, tightly packed protein-rich structure, limits drug penetration in its physiological state. The drug traverses the corneal barrier, permeates the aqueous humor, penetrates the lens basement membrane capsule, infiltrates the lens cortex, and eventually reaches the lens nucleus. The lens capsule allows for the free passage of water, ions, small molecules, and proteins.[62] Lens cells contain various channels, pumps, and transport proteins that enable the movement of drugs across the epithelium into and out of the extracellular environment. As LECs and lens fiber cells contain a large number of negatively charged crystallin proteins, positively charged drugs are more likely to enter the cells to maintain electroneutrality.[63] The lens capsule and epithelium act as barriers to drug penetration into the lens cortex, particularly for hydrophilic and macromolecular drugs, resulting in slow drug distribution in the lens. Furthermore, drug molecules are gradually eliminated from the lens as part of its storage function.[64] The lens serves as the target tissue in potential drug treatments of cataracts.[34] To elicit a pharmacological action, the drug must diffuse sufficiently deep into the lens. Despite indications of a minimum drug concentration being achieved at the target site, investigations into the actual distribution and binding of anti-cataract medications within the lens have not been thoroughly explored.[62,64]

Lens Drug Delivery System

Ocular drug delivery methods comprise topical and systemic administration. Although systemic administration via the vein and orally can be used to treat ophthalmic diseases, the blood-aqueous humor barrier limits drug penetration from the systemic circulation to the anterior segment. This limitation necessitates higher doses to achieve clinical efficacy, which may result in systemic side effects. Topical ocular administration is more advantageous than systemic administration for treating anterior segment disorders of the eye due to the lower drug clearance caused by the much lesser vascularity in the eye compared to the systemic circulatory system.[65] Intraocular injections and periocular administration may reduce systemic side effects while improving target tissue delivery. However, they are invasive, require medical personnel, and may cause intraocular hemorrhage, potential infection, and discomfort. Topical administration is commonly achieved through solutions, gels, creams, and suspensions. Unfortunately, less than 5% of the dose reaches the aqueous humor due to the ocular barrier.[66] To enhance the efficacy of topical administration, higher drug concentrations and repeated titrations may be necessary to achieve the desired therapeutic effect. However, this approach may lead to adverse effects and reduced patient adherence. Notably, children are at a higher risk of experiencing systemic side effects due to their physiological differences from adults and the lack of dosage adjustment for ophthalmic medications based on body weight.[67]

To improve the bioavailability and therapeutic effectiveness of topically administered drugs for treating cataracts, researchers are developing more bioavailable prodrugs and applying nanotechnology to protect the active molecules and maintain drug delivery.[68] These strategies aim to decrease the frequency of drug administration, minimize systemic toxicity, and enhance drug penetration into ocular tissues while improving the retention time of the anterior corneal surface. Drug delivery systems, such as prodrugs, microemulsions, nanocrystals, nanosuspensions, nanomicelles, nanoparticles, and nanozymes, have gained substantial attention owing to their better eminent functionality (Figure 4). This section reviews and discusses the application of various anti-cataract drug delivery systems with unique compositions, structures and properties based on representative research results from recent years.

Prodrugs

Prodrugs are derivatives of therapeutic drugs that have been developed to improve drug pharmacokinetics, reduce toxicity, and enhance therapeutic efficacy. They are an ingenious solution to address clinical challenges. The drug's pharmacological activity is concealed in the prodrug and is only restored in vivo after biotransformation is complete.[69] The concentration of carnosine in lenses decreased from approximately 25 μM to 5 μM during different stages of cataract development.[27] LCS, a dipeptide found naturally, has demonstrated potential in preventing and treating cataracts due to its antioxidant properties, ability to reduce glycosylation, and inhibition of protein degradation. Instead, NACS is more desirable than LCS due to its relative hydrophobicity and ability to penetrate the cornea. NACS can be metabolized to LCS in the vicinity of the lens, thus maintaining longer the active therapeutic concentration of LCS in the aqueous

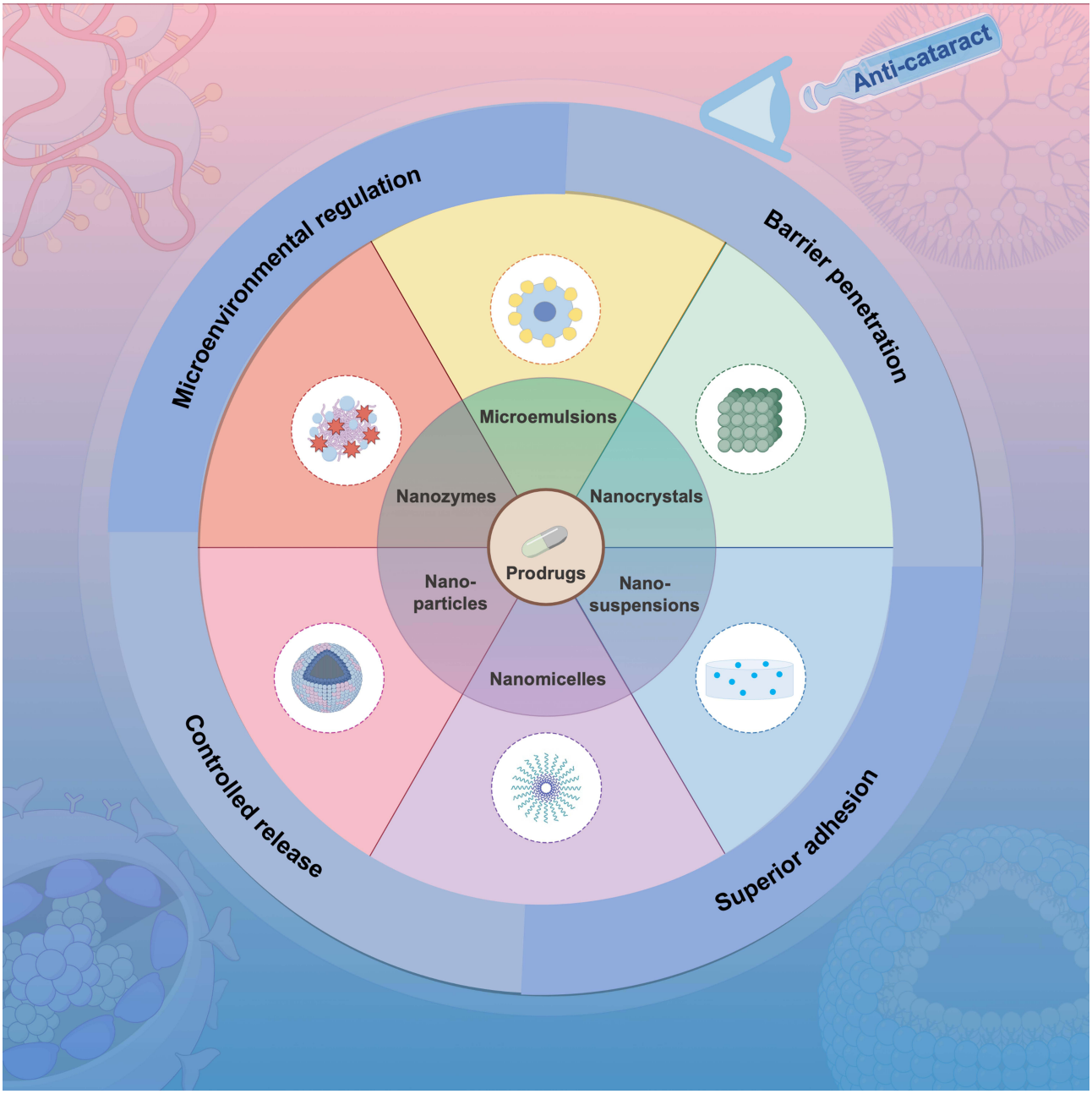

Figure 4 Schematic diagram of different nanomedicine-based drug delivery systems used to deliver anti-cataract drugs.

humor, exerting its anti-cataract effects.[28] Treatment with 1% NACS in a challenging 50,000-patient population demonstrated significant improvement in visual functions in older adult subjects and those with cataract, with reduced light scattering units in the lens.[27] However, the transformation also impedes the diffusion-dependent transportation of antioxidants to the lens center. Both LCS and NACS can also be incorporated into lipid-based carriers[70,71] and gold nanoparticles (AuNPs)[72] to enhance their efficacious corneal penetration and accumulating antioxidants in nuclear fiber cells. By carefully designing prodrugs, the release and distribution of the drug in the eye can be better controlled, resulting in prolonged intraocular retention time, increased corneal permeability and significantly improved bioavailability. This offers a promising prospect for noninvasive cataract treatment.

Microemulsions

Microemulsions are stable nanoscale colloidal systems ranging between 5 and 200 nm. Composed of oil, water, surfactant, and cosurfactant, these systems have been demonstrated to effectively incorporate hydrophilic and lipophilic drugs. In the field of ocular drug delivery, microemulsions have various beneficial effects, including facilitating drug diffusion on the anterior corneal surface, prolonging corneal contact time, enhancing drug solubility, exhibiting high corneal permeability, and enabling controlled drug release.[73] Additionally, microemulsions are optically transparent and can be sterilized through filtration to be prepared as eye drops. Notably, when tocotrienol, a water-insoluble analog of vitamin E, was topically administered in microemulsion form at concentrations of 0.01–0.05%, it exhibited significant efficacy in inhibiting the progression of cataracts in galactose-fed rats.[74] However, a major drawback of using microemulsions is the large amount of surfactant needed to form stable microemulsions. The high concentration of surfactant on the ocular surface could lead to ocular toxicity. Based on the specific circumstances, the use of a nonspontaneous preparation process in conjunction with coarse emulsions may be justified to minimize the risk of ocular toxicity. This issue can also be remedied by exploring nonionic surfactants like sugar ester surfactants and polysorbates, which have been shown to reduce both toxicity and ocular.[75,76]

Nanocrystals

Nanocrystals have the potential to enhance the pharmacokinetics, pharmacodynamics, and targeting properties of poorly water-soluble drugs. Moreover, they offer the advantage of long-term durability with biological tissues and cells.[77] The Ca^{2+} levels in cataractous lenses are higher than those in transparent lenses, and the elevated concentration of Ca^{2+} increases the activity of calpain, leading to the onset of lens opacification and cataract. Nilvadipine (NIL) plays a preventive role by reducing calcium levels and calpain activity in the lens epithelium, thus maintaining lens transparency. Conventional ophthalmic formulations have low bioavailability and are difficult to delivery sufficient drug concentration to the lens due to the tear film barrier and corneal barrier. The instillation of NIL nanocrystal dispersions with particle sizes ranging from 30 to 150 nm significantly increases NIL levels in the lens and effectively prevents lens opacification in hereditary cataractous Shumiya cataract rats, surpassing the effectiveness of NIL microcrystal-based ophthalmic formulations.[78] In addition, further studies are required to evaluate the mechanism of the ocular drug delivery system in NIL nanocrystal dispersions and to discuss the efficient strategies for maintaining drug levels in the lens and managing cataracts.

Nanosuspensions

Nanosuspensions are submicron colloidal dispersions that are utilized to stabilize low water-soluble drugs and often contain inert colloidal carriers to enhance drug solubility and bioavailability. In the field of ocular drug delivery, nanosuspensions are considered ideal vehicles for inflexible hydrophobic drugs that are restricted by factors such as high molecular weight, melting point, and dosage limitations. Unlike conventional suspensions, nanosuspension can address many issues such as poor intrinsic and saturation solubility in tear fluids, low ocular bioavailability and irritation caused by large particle size.[79] Recent studies have demonstrated that ocular nanosuspensions containing LAN and NIL can effectively counteract cataract-related factors, such as elevated Ca^{2+} and calprotectin levels. Furthermore, the combination of LAN and NIL nanosuspensions has shown significant improvement in attenuating cataract-related factors and partially restoring lens transparency in selenite-induced cataractous rats.[80] These findings highlight the potential of nanosuspensions in improving drug solubility, precorneal residence time, and bioavailability for ocular drug delivery. Additionally, nanosuspensions offer an attractive alternative to conventional eyedrops as they can avoid the high osmolarity typically associated with ophthalmic solution dosage forms. To further optimize drug release and residence time, nanosuspensions can be dispersed in selected ointment, hydrogel, or mucoadhesive bases based on the physicochemical properties of the drug.[81]

Nanomicelles

Nanomaterial-based drug delivery systems exhibit enhanced adhesion to the corneal epithelium through interactions involving hydrophilic/hydrophobic and electrostatic characteristics. Specifically, nanomicelles with strong adhesion to the corneal surface result in prolonged precorneal residence time. Nanomicelles are drug delivery nanocarriers composed of amphiphilic surfactant molecules that self-assemble into well-organized supramolecular structures. They can release drugs in response to endogenous or exogenous stimuli and are often used to deliver poorly water-soluble drugs to the eye.[82] A novel eye drop formulation in which nifedipine (NFP) is encapsulated in nanomicelles was proposed to prevent the formation and early progression of oxidative cataracts. The NFP-loaded micelles demonstrated good biocompatibility and bioavailability. They also effectively improved anti-cataract ability by inhibiting extracellular calcium ion inflow.[83] In addition, CUR, a natural compound with antioxidant properties, is widely recognized for its anti-cataract activity. However, its low water solubility and inherent corneal penetration barrier limit its routine topical application. To develop transparent ion-sensitive CUR-loaded mixed micellar in situ gels (CUR-MM-ISGs), researchers dispersed spherical and small micelles in a gellan gum solution (0.2%, w/w) at a ratio of 3:1 (v/v). The sustained release and biocompatibility of CUR-MM-ISGs as ophthalmic formulations were validated through in vitro release experiments and an irritation test. Furthermore, an ex vivo corneal penetration study demonstrated that the cumulative drug permeation of CUR-MM-ISGs was 1.32-fold higher compared to that of a CUR solution. The CUR-MM-ISGs, optimized using central composite design-response surface methodology, prolonged the ocular surface residence time and enhanced corneal permeability, leading to increased CUR bioavailability, reduced clearance and improved bioactivity.[84] The uncertain structure of micelles during the process of micellization in mixed micellar systems poses a substantial hurdle to the broader utilization of these micelles as drug carriers.[85] Most ion-sensitive carriers operate within physiological millimolar ion concentrations. However, the individual-specific ion concentrations within the physiological range may be insufficient to achieve the desired response, thus representing a significant challenge.[86] To ensure the optimal performance of these micelles, specific ionic concentrations or pH values may be necessary. Additional factors such as temperature fluctuations or exposure to light may also impact the stability of these micelles. As a result, meticulous storage and handling procedures are indispensable to maintain the stability and effectiveness of ion-sensitive mixed micelles.

Lipid Nanoparticles

Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are highly effective drug carrier systems capable of binding both hydrophilic and lipophilic drugs. They possess excellent biocompatibility and adhere well to the cornea, facilitating the permeation of drugs with low solubility, low partition coefficients, high molecular weights, and poor absorption rates. These systems can also be modified to enable targeted delivery and enhance drug absorption in particular tissues, rendering them efficient drug delivery systems. Nevertheless, liposomes possess certain stability issues, including the formation of a lipid crystal matrix, propensity for gelation, and sudden in vivo release. In contrast, SLNs represent an improvement over liposomes as they are crystallized particles composed of fatty acid chains and a drug or alternative compound. They offer several advantages, including enhanced drug loading and stability, improved regulation of release kinetics, minimal toxicity, and simplified large-scale production.[87] Magnesium taurate (MgT) has been observed to reduce the development of cataracts induced by galactose and hypertension. Its therapeutic effects may be related to the repair of ATPases, which reduce oxidative damage and balance ions in the lens.[88] Encapsulating MgT into liposomes has resulted in a more potent liposomal form of MgT, enhancing the bioactivity of Na^+-K^+-ATPase and Ca^{2+}-ATPase. These effects respectively prevent lens swelling and calcium ion overload, leading to a decrease in lens turbidity.[89] Chitosan-coated liposomes, when combined with LAN and hesperidin drugs, have also been found to delay or prevent cataracts by prolonging their intraocular residence time. These liposomes are stable, non-toxic, and up-regulate antioxidant defense systems.[77] Another study produced SLN-NAC, which has the advantages of small size, sustained release, and improved corneal permeability. The study conducted on goat cornea demonstrated that SLN-NAC has higher permeability compared to NAC eye drops and does not cause harm to corneal cells. This suggests that SLN-NAC has the potential to revolutionize cataract treatment by enhancing drug permeation, reducing toxicity, and avoiding damage to corneal tissue.[71] Penetration enhancers, such as cyclodextrins, can temporarily increase the

permeability of the cornea, allowing nanoparticles to pass through ocular tissues. They also play a crucial role in the physical stability of the nanoparticles and the permeability of drugs into ocular cells.[90] Polyphenols, such as CUR, RSV, and dibenzoylmethane, were loaded into lipid-cyclodextrin-based nanoparticles to enhance their antioxidant properties. These nanoparticles were tested on bovine lenses to assess their impact on cataract formation induced by hydrogen peroxide (H_2O_2) and exhibited excellent stability and sustained release. Treatment with these nanoparticles increased superoxide dismutase and GSH levels compared to pure polyphenols, indicating their potential therapeutic use in treating cataracts.[91] However, SLNs present certain drawbacks, particularly concerning their stability during storage. The crystallization of SLNs during the preparation phase results in the formation of higher energy modifications α and β. As time progresses, these modifications may transition into a more organized β modification, leading to the expulsion of the drug. Additionally, SLNs exhibit limitations such as low drug payload and high-water content.[92,93] To overcome the stability issues of SLNs, NLCs were developed, featuring a matrix comprising both solid and liquid lipids. The advantages of NLCs over SLNs include a better loading capacity of drugs due to their imperfect structure and improved stability as they prevent the recrystallization of the solid lipid.[94]

Albumin Nanoparticles

Albumin, a multifunctional protein widely used in the preparation of nanocarriers for drug delivery systems, offers numerous advantages such as its easy availability, chemical modifiability, excellent biocompatibility, and low immunogenicity. Researchers have shown great interest in albumin nanoparticles (BSA-NPs) due to their remarkable ability to effectively combine different drugs with minimal side effects. BSA-NPs are commonly employed to prolong the half-life of drugs, improve stability, protect against degradation and allow specific targeting of therapeutic agents in various disease states.[95] In comparison to CUR-loaded nanoparticles, the permeation rates of BSA-CUR loaded nanoparticles were found to be higher, because CUR is less likely to crystallize or aggregate more easily in BSA-CUR complex. The CUR-BSA-NPs-Gel, an ophthalmic thermoresponsive in situ gel containing CUR within BSA-NPs, has shown potential as an eye drop formulation. Upon dilution with tear fluid at the precorneal temperature of 34.5°C, this formulation transforms into a semi-solid gel. In vivo eye irritation tests have demonstrated the safety of CUR-BSA-NPs-Gel for ophthalmic use. Moreover, this gel system has the potential to enhance the bioavailability of CUR in rabbit eyes and reduce the frequency of administration compared to other suspension formulations. Therefore, this system holds promise as an ophthalmic delivery system, offering prolonged retention time of CUR in the aqueous humor and enhances ocular bioavailability.[96]

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are inorganic nanomaterials with an extensive surface area, tunable pore size, controllable morphology, and stable physicochemical properties. These characteristics make MSNs highly attractive for drug delivery applications, as they offer excellent biocompatibility, biosafety, control of biodegradation and high drug loading capacity.[97] The evidence from cellular and animal studies have confirmed the sustained release properties of MSNs for intraocular pharmacotherapy.[98] Moreover, animal experiments have demonstrated the ability of MSNs to effectively deliver drugs to the anterior chamber of the eye through the cornea. This highlights the promising role of MSNs in ocular drug delivery.[99] Cerium, particularly Ce^{3+}, known as scavenger of ROS, making it an appealing biomaterial for protecting against cataract formation.[100] Research has demonstrated the effectiveness of cerium chloride-loaded MSNs ($CeCl_3$ @$mSiO_2$) in entering the human LECs and protecting them from H_2O_2-induced oxidative stress. The administration of $CeCl_3$@$mSiO_2$ significantly antagonized oxidative stress and inhibited protein glycation in lenses of streptozotocin-induced diabetic cataract rats, thereby alleviating development and progression of diabetic cataract.[101] These studies confirmed that MSNs are suitable to use as ocular delivery carriers for cataracts and other ocular disease treatments.

Cerium Oxide Nanoparticles

Cerium oxide nanoparticles (CNPs) have gained considerable attention in the field of biomedicine as antioxidant nanoparticles with potential medical applications.[102] Although human trials have not yet been conducted, extensive preclinical research has shown the effectiveness of CNPs in various diseases.[103–106] These nanoparticles exhibit the ability to mimic superoxide dismutase (SOD) and catalase, enhance the intracellular glutathione ratio, safeguard LECs

against oxidative stress induced by H_2O_2, and effectively impede the progression of cataract formation.[107,108] Furthermore, research has been undertaken to create autologous regenerated redox cerium oxide nanoparticles, specifically CNPs coated with PEG-PLGA (PCNPs), which possess non-enzymatic or catalytic attributes and demonstrate heightened antioxidant capabilities within LECs. They not only function as antioxidants to progressively eradicate ROS but also effectively impede α-lens protein glycosylation and cross-linking, preserving lens transparency. In vivo studies have further supported these findings, as subconjunctival injection of PCNPs significantly reduced cataract formation in diabetic rats. The improved water solubility, safety, and biocompatibility conferred by PEG-PLGA likely contribute to the enhanced therapeutic effect of PCNPs.[109] However, unmodified PEG-PLGA nanoparticles tend to accumulate in the posterior than the anterior segment of the eye.[110] Therefore, further modifications of PCNPs are still needed. Despite the promising results, certain limitations exist in the understanding of the precise mechanisms underlying the penetration of CNPs into the lens and their in vivo antioxidant and antiglycation properties.

Metal Nanoparticles

AuNPs possess exceptional optical properties, chemical stability, and easy bioconjugation characteristics, making them an ideal platform for attaching therapeutic, targeting, and stabilizing agents. These properties render AuNPs highly suitable for efficient drug delivery, thus enhancing the stability, biocompatibility, and bioavailability of therapeutic biomolecules such as NACS.[111] The incorporation of NACS into AuNPs has shown promising results in improving the therapeutic effects of cataract treatment, leading to potential reductions in therapeutic doses and suppression of side effects.[72] Nevertheless, the long-term accumulation of gold in the eye raises concerns regarding potential risks, necessitating a comprehensive evaluation of the benefits of AuNP-based therapies to outweigh these risks.[112] Silver nanoparticles (AgNPs) have attracted attention for their antimicrobial properties and ability to inhibit angiogenesis, making them an intriguing alternative to AuNPs.[113] Studies have demonstrated that AgNPs in the size range of 15–50 nm exhibit a powerful antioxidant effect, which could potentially be utilized to prevent the development of cataracts. The experimental results demonstrated that AgNPs exhibited concentration-dependent antioxidant activity and potent anti-cataract effects in the selenium cataractogenesis animal model.[114] However, it is important to note that AgNPs are rather toxic.[115] Injection of 0.4 mg/L AgNPs into the eye has been found to inhibit the development of lenses in zebrafish embryos, highlighting the potential toxicity associated with the release of silver ions from the surface of the nanoparticles.[116] These findings hold significant implications for the advancement of stable and responsive metal nanoparticles in cataract treatment. To ensure comprehensive safety, further studies should be conducted to investigate the inner toxicity and ocular absorption of these nanoparticles.

Nanozymes

Nanozymes are nanomaterials with enzyme mimetic activities, which have attracted considerable interest due to their relatively higher physiochemical stability against harsh environments, higher durability, and lower costs than natural enzymes.[117] An illustration of this phenomenon can be observed in the case of Cu/Zn-superoxide dismutase nanoparticles (Nano-SOD1), which possess a multilayer poly-ionic complex encapsulation that effectively enhances the ocular penetration and retention time of enzyme activity. The findings from animal experiments reveal that the application of Nano-SOD1 eye drops through topical instillation results in a prolonged retention time and higher concentration within the eye, in comparison to the administration of SOD1 alone.[118] This substantiates the superior efficacy of drug delivery, which is of paramount importance in the treatment of ocular diseases such as cataracts, wherein the excessive production of ROS and the depletion of the antioxidant system are implicated. Nano-SOD1 emerges as a promising therapeutic approach for cataracts, as it effectively restores the antioxidant activity in the eye, leading to a reduction in the development of lens opacities. While nanozymes offer numerous benefits compared to natural enzymes, such as cost-effectiveness, ease of storage, and tunable catalytic activity, their low substrate specificity is a critical issue.[119] Furthermore, the robustness of nanozymes in a wide range of temperature and pH media is not yet satisfactory for practical applications.[120] Previous studies have demonstrated that nanozymes often experience diminished catalytic efficacy at extreme temperature and pH levels, which may be crucial for target viability.[121] Moreover, external factors like humidity and oxygen can alter the surface properties of nanozymes during storage under ambient conditions. Developing chemically and catalytically stable nanozymes with highly robust activity for practical applications remains a challenge.

Physicochemical Properties and Surface Engineering of Cataract Nanomedicines

The challenge in cataract therapy is not only to discover effective drugs, but also to develop delivery systems to ensure therapeutic drug concentrations in target tissues. The physicochemical properties and biological effects of nanomedicines have been of great interest in cataract therapy and have been critical to the study of lens nanomedicines. The characteristics of nanomedicines, such as size, surface charge, hydrophilicity and/or hydrophobicity, and biodegradability, significantly impact drug bioavailability, permeability, biodistribution, and elimination.[122] It has been observed that smaller nanoparticles possess the ability to augment the penetration of ocular physiological barriers and facilitate intracellular distribution. However, they are also more susceptible to rapid elimination and may lead to higher reactivity and toxicity due to their larger surface area.[123] The biodistribution of nanoparticles within the eye is notably influenced by their surface charge, primarily due to electrostatic interaction. Cationic nanoparticles have the potential to extend drug retention and enhance permeability by interacting with the negatively charged mucin layer of the tear film.[124,125] Additionally, they may also have the potential for non-specific targeted intracellular delivery.[126] Moreover, the hydrophilic or hydrophobic properties of drugs can influence their permeability and diffusion across biological interfaces of ocular structures. For instance, the bioavailability of drugs in the boundary of tear film and cornea can be improved by increasing the hydrophilicity of nanoparticle surfaces.[127] Nanocarriers based on amphiphilic core shells have been shown to penetrate the cornea for non-invasive drug delivery into the eye.[128] Nanosystems containing hydrophobic components that exceed those present in cellular membranes can enhance endocytosis and substrate binding.[129] The biodegradability of nanocarriers is critical for the controlled degradation of ocular nanodrugs, which leads to improved drug utilization and reduced cytotoxicity.[130] Therefore, when designing nanocarriers for ocular drug delivery, it is essential to balance stability and degradability. It is important to note that low molecular weight nanomaterials are easily degradable but unstable, which may affect therapeutic efficacy. Conversely, high molecular weight biomaterials may accumulate in normal cells and interfere with metabolic activities and transport. Additionally, ideal drug nanocarriers should be able to escape from intracellular compartments such as endosomes and lysosomes.[131] To modify drug pharmacokinetics, the initial burst of drug release can be reduced by coupling the drug to the nanocarrier.[132] Therefore, ideal drug nanocarriers should have an appropriate size, surface charge, and hydrophilic or hydrophobic properties, as well as good biocompatibility and degradability to enhance drug utilization and reduce cytotoxicity.

Cataract nanomedicines can be optimized and modified using a variety of surface engineering methods to achieve controlled and targeted drug delivery, as well as improved stability, among other benefits. One strategy involves the modification of ocular nanodrugs with specific molecules to augment drug release, prolong retention time, and enhance ocular surface permeability.[125] Another alternative method entails targeted modification with functional ligands, aiming to establish a preventive intervention for early cataract by binding to specific receptors and enabling site-specific therapy. Furthermore, a surface engineering approach can be employed, which involves encapsulating the therapeutic agent and subsequently releasing it into the designated target to achieve the desired therapeutic functions.[133] The implementation of these strategies necessitates meticulous consideration of various factors, including the appropriate selection of the conjugated chemical moiety, the preservation of functional chemistry within the ocular nanomedicine, and the on-demand release of the encapsulated substance from the ocular nanomedicine backbone to achieve the goal of personalized ophthalmic medicine.

Cell-Penetrating Peptides

Drug-loaded nanoparticles rely on the endocytosis pathway to penetrate cells, while the lipophilic nature of biological membranes restricts the entry of hydrophilic macromolecules into cells, which becomes a barrier to the therapeutic effects of drugs.[134] Polymeric nanoparticle drug-loaded systems, such as liposomes and chitosan, can enhance drug solubility and prolong the duration of action through encapsulation and sustained-release treatments, thereby increasing therapeutic efficacy and reducing toxicity. Nevertheless, these slow-release drugs are still hampered by cell membranes when penetrating cells, limiting their cellular utilization. Cell-penetrating peptides (CPPs) play a key role in enhancing the bioavailability of ocular drugs by surface modification of nanoparticles, which can improve the penetration and

delivery of drugs.[135] CPPs are capable of penetrating cell membranes with good biocompatibility and they have been explored as novel drug-delivery vehicles for carrying various bioactives intracellularly.[134] They can enter cells actively or passively through energy-dependent or non-dependent mechanisms, improve endosomal escape and cytosolic delivery efficiency, and are well-suited for the delivery of potent substances through the cytoplasm for bioactivity at low concentrations.[136,137] Therefore, CPPs have been attracting much attention and are universal in penetrating properties to the cell membranes of many animal and plant cells.

As individuals age, α-crystallin levels decline, resulting in protein aggregation and cataract formation. Previous research has demonstrated that the transportation of αB-crystallin to human lens epithelial cells can be effectively facilitated by the glycoprotein C peptide.[138] However, it is important to note that this research did not consider relevant ocular barriers. Another study discovered that the peptide for ocular delivery (POD) exhibited a strong affinity for corneal epithelial cells when administered ocularly, resulting in successful uptake and localization of POD-green fluorescent protein (GFP) fusion proteins within the lens capsule.[139] Furthermore, research has demonstrated the considerable benefits of utilizing POD nanoparticles for ocular drug delivery, encompassing reduced particle size, enhanced capture efficacy, prolonged release, and minimal in vitro toxicity.[140] Disulfiram (DSF) is a lipophilic drug that has potent antioxidant activity and can block oxidative effects by rapidly reacting with free radicals. The corneal penetration and subsequent delivery of poorly water-soluble DSF to the lens were significantly improved by utilizing lipid emulsions with nanoscale particles and incorporating octa-arginine (R8) modification. This innovative drug delivery approach has the potential to effectively disperse DSF within the anterior segment tissues, including the lens. The effectiveness of this method in preventing cataract formation was confirmed through animal experimentation.[141] These findings offer valuable perspectives for the advancement of ocular therapeutic protocols and are anticipated to facilitate the creation of more efficacious ocular therapeutic regimens in forthcoming endeavors.

Targeting Agents

One of the main limitations of CCPs is the lack of cell specificity, as they tend to enter nearly all cells. In this regard, nanomedicines offer the potential for targeted delivery to the lens through active and/or passive targeting mechanisms.[12] Various targeting agents, such as targeting ligands, can be attached to the surface of nanocarriers, enabling them to be directed toward specific cells or tissues based on the identification of molecular targets.[142] Active targeting strategies involve binding to specific biomarkers, facilitating high levels of cellular internalization, whereas passive targeting strategies are directly related to the intrinsic physicochemical properties of the nanocarriers, such as size and charge.[143] The identification of peptides with specific affinity for cataract-associated target molecules offers the possibility of developing cataract-targeted therapeutic approaches. Notably, the free cyclic peptide (CKQFKDTTC) was found to selectively bind to βB2-crystallin, thereby establishing a crucial foundation for the development of targeted therapies aimed at lens proteins.[5] Targeting agents hold potential for the formulation of locally administered drugs or nanoparticles through non-invasive methodologies, while also offering novel insights into drug-targeted approaches for cataract treatment.

Sustained-Release Hydrogel Systems

Nanocarriers have demonstrated enhanced lens bioavailability in comparison to traditional dosage forms, yet they are constrained by factors such as limited drug loading and drug burst release. In situ gel systems are regarded as promising sustained-release systems for ocular drug delivery, as they have the capability to extend ocular surface contact time and modify drug release kinetics.[144] Hydrogels can be developed as independent systems or in conjunction with other technologies. Nanoparticle-incorporated in situ gel systems exhibit heightened therapeutic effectiveness when compared to nanoparticles or gels utilized individually. For instance, drug-loaded nanoparticles may be suspended in an in-situ gel, and this combined technology can enhance drug permeability into the aqueous humor and lens. Stimulus-responsive hydrogels, which change from a sol to a gel in response to specific stimuli such as pH, temperature, light and ions, are a promising approach and have been applied to the design of smart drug delivery systems.[145] Nanoparticles typically display a biphasic release pattern, consisting of an initial burst followed by a sustained phase. Incorporation of nanoparticles into thermal hydrogels or corneal contact lenses has been observed to completely eliminate the initial burst release of ophthalmic pharmaceuticals.[146,147]

Several studies have sought to optimize the efficacy of LAN through the integration of pharmaceutical interventions and the investigation of efficient delivery systems. In one study, researchers designed LAN nanoparticles in situ gel (LAN-NPs/ISG) that underwent gelation at 37°C and effectively penetrated the cornea through energy-dependent endocytosis. This increased the LAN content in the lens, mitigated spatial and structural collapse of the lens, and delayed the onset of cataracts in rats. LA-NPs/ISG has the potential to mitigate alterations in cataract-related factors and uphold the equilibrium of the lens' internal milieu.[148] The implementation of sustained-release platforms is anticipated to address the issue of rapid drug dissipation and extend the duration of drug release. Furthermore, hydrogels characterized by high water content could prove advantageous in preserving the stability of peptides and proteins.[149]

Conclusions and Outlook

The pharmacotherapy of cataracts presents a multifaceted challenge that encompasses the development of efficacious pharmaceutical agents and the creation of drug-delivery systems that guarantee the targeted delivery of therapeutic substances at appropriate concentrations. The unique structure of the human eye offers an ideal platform for ocular nanomedicine-based drug delivery systems, which can circumvent systemic distribution and introduce novel opportunities for pharmacologically treating cataracts. The integration of nanotechnology in the formulation of anti-cataract medications has the potential to effectively mitigate the limitations of traditional drug delivery methods and exhibit diverse therapeutic applications. Nanomedicine presents numerous advantages to optimize drug delivery to the lens, including leveraging inherent therapeutic properties, precise and controlled drug release, reduced risk of toxicity and adverse effects, enhanced bioavailability, and simultaneous delivery of multiple therapeutic agents with diverse physicochemical properties.

Although considerable progress has been made, no registered clinical trial is yet evaluating the potential translation of nanomedicines to treat human cataracts, highlighting the need for further research. Cellular and animal studies have provided insights into the therapeutic potential of nanomedicines, but understanding the underlying mechanisms of their action on the lens and in vivo response kinetics remains a challenge. Furthermore, many existing models cannot fully elucidate human disease mechanisms, as demonstrated by the high failure rate of drug candidates that showed efficacy in animal or cellular models but did not translate to success in human clinical trials.[150] It is essential to conduct continuous research in clinical studies to ensure the safety and efficacy of ocular nanomedicines, with particular attention to biocompatibility and toxicity.[115]

Evaluation of preparation and preservation techniques for nanomedicines should consider factors such as sterility, simplicity, reproducibility of fabrication techniques, ease of storage, and stability maintenance.[151] Developing nanomedicine with desired characteristics to overcome barriers is a challenging task, which historically relied on a trial-and-error approach. However, a thorough understanding of underlying mechanisms is crucial to facilitate the creation of nanomedicines with specific properties. Exploring the incorporation of artificial intelligence techniques could further optimize nanomedicine formulations.

Companion diagnostics play a crucial role in identifying patients who can benefit from specific nanomedicine treatments.[152] Further research and development efforts are necessary to address the individual needs of patients and enhance the effectiveness of lens drug delivery strategies. Altogether, we believe that nanomedicine will run more smartly in cataract treatment for the foreseeable future, which depends on sophisticated designs, chemical and physical strategies, and a deep understanding of the underlying mechanisms.

Abbreviations

AgNPs, Silver nanoparticles; AuNPs, Gold nanoparticles; BSA-NPs, Albumin nanoparticles; $CeCl_3$@$mSiO_2$, Cerium chloride-loaded mesoporous silica nanoparticles; CNPs, Cerium oxide nanoparticles; CPPs, Cell-penetrating peptides; CUR, Curcumin; DSF, Disulfiram; GFP, Green fluorescent protein; GSH, Glutathione; LAN, Lanosterol; LAN-NPs/ISG, Lanosterol nanoparticles in situ gel; LCS, L-carnosine; LECs, Lens epithelial cells; MgT, Magnesium taurate; MSNs, Mesoporous silica nanoparticles; NACS, N-acetylcarnosine; Nano-SOD1, Cu/Zn-superoxide dismutase nanoparticles; NFP, Nifedipine; NIL, Nilvadipine; NLCs, nanostructured lipid carriers; PCNPs, Cerium oxide nanoparticles coated with PEG-PLGA; POD, Peptide for ocular delivery; R8, Octa-arginine; ROS, Reactive oxygen species; RSV, Resveratrol; SLNs, Solid lipid nanoparticles; SOD, Superoxide dismutase.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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