German J Pharm Biomaterials 2024; 3(3): 34-58
https://doi.org/10.5530/gjpb.2024.3.10

GJPB

Review Article

# Ophthalmology: Navigating ocular barriers with advanced nanocarriers

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Received: 01 June 2024; Revised: 14 July 2024; Accepted: 24 July 2024

**Abstract**

The unique anatomy and physiology of the eye present significant challenges for effective drug delivery, necessitating innovative approaches to manage ocular diseases. This review examines the intricate structure of the eye and the barriers that impede drug penetration, including the corneal epithelium, conjunctival tissue, and blood-retinal barriers. Traditional ocular administration routes-topical, periocular, and intraocular-often face limitations in drug bioavailability and patient compliance. Recent advancements in nanotechnology offer promising solutions to these challenges. Nanocarriers such as nanoparticles, liposomes, nanosuspension, nanoemulsion, micelles, and dendrimers enhance drug delivery by improving bioavailability, controlling release rates, and minimizing systemic side effects. Factors influencing the efficacy of these nanocarriers include their size, surface charge, and hydrophilic-lipophilic balance. This review highlights the potential of these novel drug delivery systems in treating chronic ocular conditions such as glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy. These advanced technologies are poised to significantly enhance the therapeutic management of ocular diseases by overcoming the inherent ocular barriers and optimizing drug delivery.

**Keywords:** Ophthalmology; ocular barriers/ ocular drug delivery; glaucoma; age-related macular degeneration; diabetic retinopathy; ocular diseases; nanocarriers

## Introduction

Modern ocular illnesses have a devastating impact on patients' ability to see and ways of living in the modern day. According to the data in Figure 1, an estimated 1.1 billion individuals worldwide were visually impaired in 2020. There were 510 million people who lost near eyesight, 258 million who lost mild vision, 295 who lost moderate to severe vision, and 43 million who were blind. These figures add up to a significant amount. We may expect the total to have risen to over 1.8 billion by 2050, with 866 million people with near vision loss, 360 million with mild vision loss, 474 with moderate to severe vision loss, and 61 million cases of blindness [1].

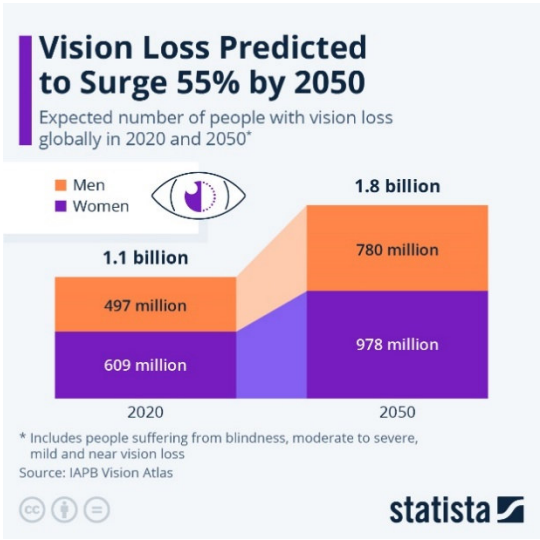


**Figure 1.** Chart shows the expected number of people with vision loss globally in 2020 and 2050. Reprinted under the terms of the Creative Commons Attribution 3.0 International (CC BY) license [1].

Drug delivery to the eye can be broadly classified into two main parts: anterior and posterior segments (Figure 2) [2]. The front part of the eye, about a third of the total, contains the ciliary body, cornea, iris, conjunctiva, aqueous humour, and crystalline lens [3]. In contrast, the back half of the eye

comprises the choroid, neural retina, sclera, optic nerve, vitreous humour, and retinal pigment epithelium (RPE) [4-6]. Both parts of the eye are vulnerable to various disorders that can cause permanent vision loss. The following conditions can affect the eye: uveitis, cataracts, choroiditis, retinitis, retinopathies, optic neuritis, retinal dystrophies, ectasia of the cornea, keratopathy, keratoconjunctivitis, scleritis, glaucoma, choroiditis, or retinopathy [7-11].

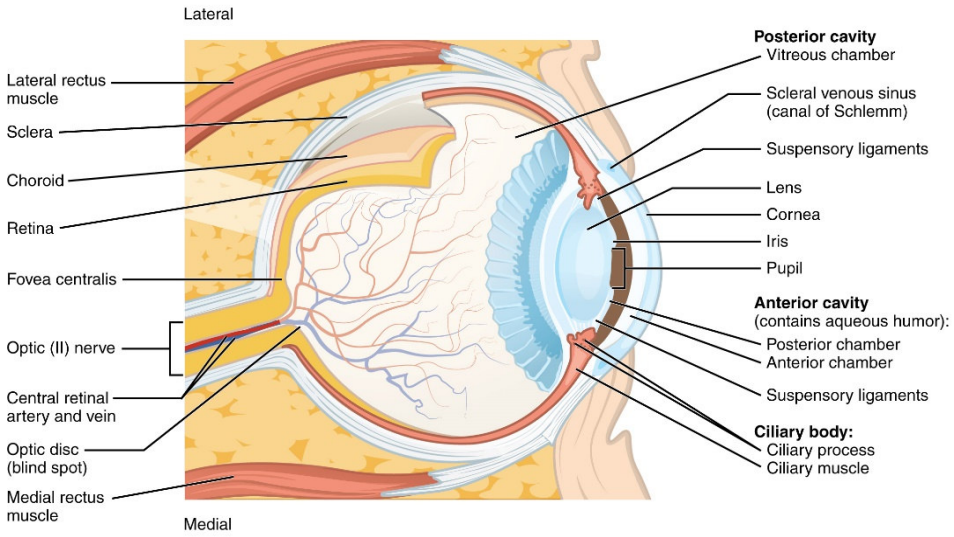


**Figure 2.** Structure of the eye. Reprinted under the terms of the Creative Commons Attribution 3.0 International (CC BY) license [2].

Even though the eyes are one of the body's most accessible organs, it is pretty challenging to administer medication to their tissues. Like the brain, the eye is considered "immune privileged" since it is part of the central nervous system protected from blood flow. An organ that is highly isolated from systemic circulation is the eye due to its complex ocular barriers and precise design. Thus, many obstacles can be overcome when treating eye illnesses, particularly those affecting the posterior region [12]. A non-invasive method widely used for administering drugs to the anterior portion of the eye is known as local instillation [13,14]. This method is popular since it is simple to use and patient-friendly. Following the administration of the drug, it quickly comes into contact with the mucus found on the eye's surface [15]. Lacrimal drainage, which travels through the upper and lower canaliculus and eventually reaches the lacrimal sac, which opens into the nasolacrimal duct, is responsible for quickly removing the dosage [16].

Additionally, the ocular bioavailability of topical eye drops could be improved. Several anatomical and physiological restrictions present hurdles and make it challenging to penetrate deeper ocular tissues. These limits include tear turnover, lacrimal drainage, blink reflex, and dynamic and static ocular barriers [17].

**Barriers affecting ocular drug delivery**

*Tear film barrier*

The initial permeability barrier that inhibits the transport of ocular drugs is tear film, a thin lipid layer covering the outside of the eye, a middle layer of aqueous fluid, and an innermost layer of mucous [12,18]. From an anatomical standpoint, the outer oil layer both keeps water from evaporating and decreases drug absorption into the sclera and cornea [19]. Reduced bioavailability can occur when specific endogenous proteins in the middle aqueous layer bind and metabolize the administered medicine. These proteins include lactoferrin, globulin, and albumin [20]. The mucus layer, located inside, is an intricate combination of many substances, such as water, lipids, salts, enzymes, and mucins [21]. The mucus layer is the most dense at the epithelial apex because of its pore structure, which contains negatively charged glycans and hydrophobic regions. It becomes more diluted as it extends outward into the tear fluid. It plays a significant role as a barrier in drug delivery because it can trap

and adhere to foreign particulates. Then, it is washed away by mucus turnover before it reaches the corneal surface [22,23]. After topical treatment, the average tear volume increases to 30 μL from 7 μL. This leads to the rapid drainage of excess fluid through the nasolacrimal duct and the loss of more than 85% of the drug dose before it reaches the corneal surface. The fast turnover of tears further dilutes the retained drugs, reducing the concentration gradient and diffusion rate. As a result, intraocular medicines often have limited bioavailability in aqueous humor, typically between 0.1% and 5% [24,25].

Regarding drug distribution, the most recommended and patient-friendly strategy is the topical administration of eye drops, instilled explicitly into the lower precorneal pocket. The blink reflex, however, renders this approach mostly ineffective since it causes the majority of the topical doses to be lost. Surprisingly, only approximately 20% of the amounts that are injected stay in the pocket long enough to have the desired impact [26]. For passive diffusion to occur across the corneal layers, the concentration of the medication in this lower precorneal area is a crucial factor. Nevertheless, the complicated task of achieving therapeutic medication concentrations for the posterior eye tissues persists. Topical drug use may be more effective in the conjunctiva and sclera due to their more excellent permeability than in the cornea; nevertheless, these posterior tissues have very poor drug absorption due to the fast circulation, making this treatment even more difficult [27]. Both static and dynamic barriers, such as the sclera, choroid, and RPE, and the passage of lymphatic and blood through the episcleral and conjunctiva, respectively, hamper the delivery of drugs to the eye [28,29]. Topical delivery requires a permeable cornea and prolonged corneal contact time, although other routes of administration, like intravitreal and periocular injections or systemic administration, have also been investigated. Because of the eye's tiny volume and the presence of the retinal blood barrier, which limits systemic administration, intravitreal injection is especially notable for its success in treating deep-seated ocular illnesses [30-32]. The transscleral route refers to the method of delivering therapeutic agents to the eye by passing them through the sclera, the tough, fibrous outer layer of the eye. This route is considered for delivering drugs directly to the posterior segment of the eye, such as the retina and choroid, which are otherwise challenging to reach via traditional topical or systemic routes [33].

*Vitreal barrier*

The anatomical and physiological features of the vitreous humor that restrict the penetration and diffusion of substances from the anterior segment (such as the aqueous humor) into the posterior segment (such as the retina and choroid) are collectively referred to as the vitreal barrier, which is also called the vitreoretinal barrier. This barrier is essential to stabilize the eye's internal environment and shield the retina from damaging substances. The vitreal barrier poses significant challenges to drug delivery to the posterior segment of the eye. The dense, gel-like nature of the vitreous humor impedes the free movement of substances. Large molecules and particles have difficulty diffusing through this matrix. The network of collagen fibers can trap and hinder the movement of therapeutic agents. Similar to the blood-brain barrier, the Blood-Retinal Barrier (BRB) is a physiological barrier that restricts the entry of substances from the bloodstream into the retinal tissue. It consists of tight junctions between retinal capillary endothelial cells and the RPE. Enzymes within the vitreous can degrade certain drugs before they reach their target. Larger molecules and those with specific charge properties may diffuse more slowly through the vitreous. Lipophilic (fat-soluble) substances often have better diffusion rates compared to hydrophilic (water-soluble) ones [34-36]. Specifically, negatively charged particles diffuse freely, while positively charged particles get trapped in the vitreous body [37]. As a result, the drug's vitreous dispersion and retinal bioavailability are significantly affected by its molecular weight and charge.

*Blood-ocular barrier (BOB)*

The eye is a highly specialized organ requiring precise regulation of its internal environment to maintain optimal function and protect delicate structures from potentially harmful substances. The BOB is a critical component in this regulatory system, comprising two main barriers: the blood-aqueous barrier (BAB) and the BRB. These barriers work in concert to control the exchange of substances between

the bloodstream and the ocular tissues, ensuring a stable environment for visual processes. The BAB primarily regulates the passage of substances into the anterior segment of the eye, particularly the aqueous humor. It consists of several anatomical components: Non-pigmented Ciliary Epithelium, Iris Vasculature, and Endothelial Cells of the Schlemm's Canal. However, The BRB is essential for protecting the neural retina and maintaining a controlled environment for photoreceptor function. It has two main components: the Inner Blood-Retinal Barrier and the Outer Blood-Retinal Barrier. Tight junctions between endothelial cells of retinal capillaries form the inner Blood-Retinal Barrier. These junctions restrict the passage of large molecules and ions from the bloodstream into the retinal tissue, ensuring the retina remains free from blood-borne toxins and pathogens. The outer blood-retinal barrier comprises the RPE, which forms tight junctions with adjacent RPE cells. The RPE regulates nutrient and waste exchange between the retina and the choroid, maintaining the subretinal space's homeostasis [5,18,38-43].

Furthermore, Ocular drug delivery presents unique challenges due to the eye's complex anatomy and protective barriers, which limit the bioavailability of therapeutic agents. Various advanced drug delivery systems have been developed to overcome these obstacles and enhance drug bioavailability, as shown in Figure 3 [44]. Nanotechnology has enabled rapid advancements in the ocular delivery of drugs, leading to novel therapeutic approaches for ocular disorders [45,46]. In comparison to conventional drug delivery methods, nanocarriers have many benefits, such as the ability to cross the ocular barrier, increase transcorneal permeability, decrease drug degradation, decrease dosage frequency, boost patient compliance, accomplish controlled release, target specific drugs, and deliver genes [47,48]. These systems aim to provide targeted, controlled, and sustained release of drugs to improve therapeutic outcomes while minimizing side effects.

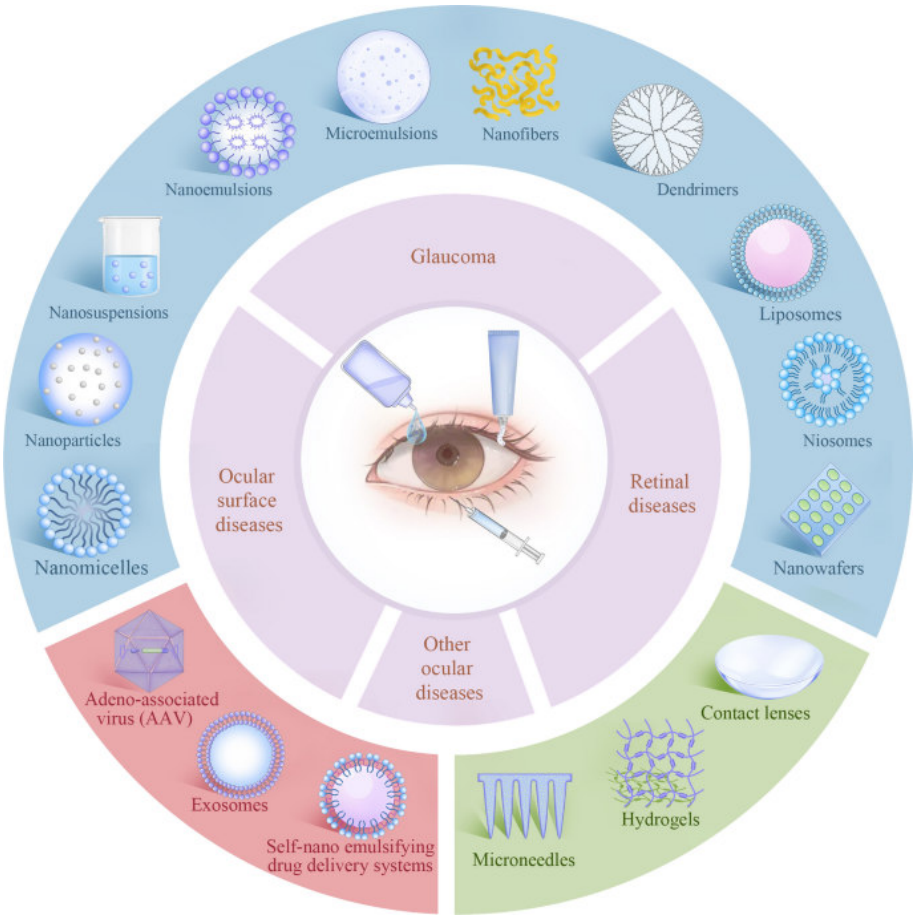


**Figure 3.** Advanced Ocular drug delivery systems. Reprinted under the terms of the Creative Commons Attribution 4.0 International (CC BY) license [44].

**Ocular diseases**

Ocular diseases encompass many conditions that affect the eyes, potentially leading to vision impairment or blindness if not properly managed. These diseases can affect different eye parts, including the cornea, lens, retina, optic nerve, and surrounding tissues. Understanding these conditions, their causes, symptoms, and treatment options is crucial for preserving eye health and preventing vision loss.

*Glaucoma*

Glaucoma is a group of eye conditions that cause damage to the optic nerve, which is vital for good vision. This damage is often caused by abnormally high pressure in the eye (intraocular pressure or IOP). Glaucoma is one of the leading causes of blindness for people over the age of 60, but it can occur at any age [49]. The presence of high IOP is an indication of glaucoma [50]. Corneal endothelial cells can be damaged due to increased intraocular pressure [51]. A further consequence of elevated IOP is the compression of the retinal blood vessels, which can harm the optic nerve and retinal ganglion cells [52].

The treatment of glaucoma focuses on lowering IOP to prevent damage to the optic nerve and preserve vision. Various treatment modalities are employed, tailored to the type and severity of glaucoma. The primary approach involves pharmacological therapy with eye drops, which aim to either decrease the production of aqueous humor or enhance its outflow. Common medications include prostaglandin analogs, beta-blockers, alpha agonists, and carbonic anhydrase inhibitors [49,53]. When medications fail to adequately control IOP or cause significant side effects, laser therapy or surgical interventions may be considered. Laser trabeculoplasty is a widely used procedure for open-angle glaucoma, improving the outflow of aqueous humor through the trabecular meshwork. For more severe cases or when laser therapy is ineffective, surgical options such as trabeculectomy or drainage implants are performed to create new pathways for fluid drainage, thereby lowering IOP [54,55]. Additionally, minimally invasive glaucoma surgeries (MIGS) have emerged as less invasive alternatives with fewer complications and quicker recovery times. Treatment choice depends on individual patient factors, disease progression, and response to initial therapies, underscoring the importance of personalized care in managing glaucoma effectively [56].

*Age-related macular degeneration (AMD)*

AMD is a leading cause of vision loss in older adults, characterized by the progressive deterioration of the macula, the central part of the retina responsible for sharp, detailed vision. AMD is classified into two main types: dry (atrophic) and wet (neovascular or exudative). Dry AMD, the more common form, involves the thinning of the macula and the accumulation of drusen, yellow deposits beneath the retina. Wet AMD, though less common, is more severe and occurs when abnormal blood vessels grow under the retina and leak fluid or blood, leading to rapid vision loss [57]. The pathogenesis of AMD is complex and involves a combination of genetic, environmental, and lifestyle factors. Key risk factors include advanced age, smoking, family history of AMD, and specific genetic variants, such as those in the complement factor H (CFH) gene [58]. Oxidative stress and chronic inflammation also play critical roles in disease [59]. Current treatments for dry AMD are limited, focusing primarily on nutritional supplements (AREDS2 formula) that may slow progression in intermediate stages.

In contrast, wet AMD is treated with anti-vascular endothelial growth factor (anti-VEGF) injections, which help reduce the growth of abnormal blood vessels and fluid leakage. Recent advances include the development of long-acting anti-VEGF agents and gene therapies aimed at providing sustained treatment effects with fewer injections [60]. Intravitreal injection (IVT) with anti-VEGF (including bevacizumab (Bev) and aflibercept, amongst others) is a successful treatment for neovascular age-related macular degeneration (AMD). However, it is still considered invasive [61]. Consequently, developing drug delivery technologies to achieve tailored drug delivery is of utmost significance.

*Diabetic retinopathy*

Diabetic retinopathy (DR) is a common complication of diabetes mellitus and a leading cause of vision impairment and blindness among working-age adults. It is characterized by damage to the retinal blood vessels due to chronic hyperglycemia. The disease progresses through two main stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). In NPDR, early changes include microaneurysms, retinal hemorrhages, lipid exudates, capillary occlusion, and leakage. As the condition advances to PDR, there is an abnormal growth of new blood vessels (neovascularization) on the retina and vitreous humor, which can lead to severe complications such as vitreous hemorrhage and tractional retinal detachment [62]. Chronic hyperglycemia in diabetes leads to metabolic changes contributing to retinal vascular dysfunction, including oxidative stress, inflammation, and activating the protein kinase C pathway. These changes compromise the blood-retinal barrier, leading to vascular leakage and edema. Diabetic macular edema (DME) can occur at any stage and is a significant cause of vision loss in DR, characterized by fluid accumulation in the macula, the central part of the retina responsible for sharp vision [63].

Management of diabetic retinopathy involves tight glycemic control to slow disease progression and regular retinal screening to detect early changes. Treatment strategies for advanced stages include intravitreal injections of anti-VEGF agents, which inhibit abnormal blood vessel growth and reduce macular edema. Additionally, corticosteroids may be used to reduce inflammation and macular edema. Laser photocoagulation remains a cornerstone treatment for PDR, preventing further neovascularization and sealing leaking blood vessels. In severe cases, vitrectomy surgery removes vitreous hemorrhage or scar tissue that can cause retinal detachment [64]. Because drugs have a low bioavailability, the possibility of unwanted effects, and the inherent dangers associated with major surgery, it is necessary to develop new drug delivery systems to bring about new ideas for the treatment of DR.

*Dry eye disease*

Dry eye disease (DED) is a multifactorial condition characterized by a loss of homeostasis of the tear film, leading to ocular discomfort, visual disturbances, and potential damage to the ocular surface. It is associated with increased osmolarity of the tear film and inflammation of the ocular surface. DED can be broadly classified into two main types: aqueous-deficient dry eye, where the lacrimal glands fail to produce sufficient tear volume and evaporative dry eye, often due to meibomian gland dysfunction (MGD) leading to increased tear evaporation [65]. The pathophysiology of DED involves complex interactions between the tear film, ocular surface, and neural pathways. Inflammation plays a central role, with pro-inflammatory cytokines and matrix metalloproteinases contributing to ocular surface damage and a cycle of inflammation exacerbating the disease.

Additionally, environmental factors, systemic medications, and systemic diseases such as Sjögren's syndrome and rheumatoid arthritis can contribute to the development and severity of DED [66]. Management of DED focuses on a personalized approach tailored to the underlying cause and severity of the condition. Treatment strategies include artificial tears and lubricants to provide symptomatic relief and improve tear film stability. Anti-inflammatory therapies, such as cyclosporine A, lifitegrast, and corticosteroids, reduce ocular surface inflammation. For evaporative dry eye, warm compresses, lid hygiene, and medications like doxycycline or azithromycin are recommended to manage MGD. Advanced treatments include autologous serum eye drops and scleral contact lenses for severe cases. Lifestyle modifications, such as optimizing screen time, increasing ambient humidity, and ensuring adequate hydration, also play an essential role in managing DED [67]. Artificial tears, local secretagogues, corticosteroids, and immunosuppressants are standard drug therapies; nevertheless, they have adverse effects like glaucoma, raised intraocular pressure, ocular pain, and poor patient

compliance [68]. Employing novel drug delivery strategies is of the utmost importance to increase drug bioavailability and circumvent ocular barriers.

**Traditional routes of ocular drug administration**

Traditional routes of ocular drug administration aim to deliver therapeutic agents effectively to treat various ocular conditions. The most common methods include topical, periocular, intraocular, and systemic administration.

*Topical administration*

Topical administration of drugs to the eye is the most common method for treating various ocular conditions affecting the anterior segment, such as infections, inflammations, and glaucoma. This route is favored due to its ease of use, non-invasiveness, and patient compliance. The primary formulations used include eye drops and ointments, which offer localized treatment with minimal systemic side effects compared to systemic administration methods. Despite its advantages, topical administration faces significant challenges due to the eye's complex anatomical and physiological barriers. The cornea, tear film, and nasolacrimal drainage system are significant obstacles that limit drug absorption and retention on the ocular surface, often resulting in less than 5% of the administered dose reaching the target tissue [17,69,70]. When an eye drop is instilled, a substantial portion of the drug is rapidly drained through the nasolacrimal duct, leading to reduced drug availability at the target site. Additionally, the corneal epithelium's low permeability further restricts drug penetration into deeper ocular tissues [70,71].

Advancements in drug delivery systems have been explored to improve the efficacy of topical ocular therapies. Nanotechnology-based formulations, including nano micelles, nanoparticles, and liposomes, have shown promise in enhancing drug bioavailability. These nanocarrier systems increase the retention time of the drug on the ocular surface and enable controlled and sustained drug release, potentially overcoming the eye's natural barriers [70]. Despite these advances, achieving consistent and effective drug delivery remains challenging, necessitating ongoing research and development to optimize these innovative systems for clinical use [70,72].

*Periocular administration*

Periocular administration involves injections or depot systems around the eye, including subconjunctival, sub-Tenon, and peribulbar injections. This route provides higher drug concentrations to the posterior segment, making it suitable for treating posterior segment diseases like uveitis and macular edema. Despite its advantages, periocular administration can be invasive and cause discomfort or complications such as hemorrhage or infection [73]. This method includes several injection techniques: subconjunctival, sub-Tenon's, peribulbar, retrobulbar, and posterior juxta scleral routes. These approaches aim to circumvent the ocular barriers that impede drug delivery to the posterior eye, such as the corneal epithelium, conjunctival tissue, and blood-retinal barrier. Subconjunctival injection involves administering drugs beneath the conjunctiva, which allows for a slow release of medication over time and can be particularly effective for treating anterior segment diseases. However, its effectiveness in reaching the posterior segment is limited due to the multiple barriers the drug must traverse. Sub-Tenon's injection places the drug into the Tenon's capsule, a thin membrane surrounding the eyeball, offering a more direct route to the posterior segment but still facing significant diffusion barriers [74]. Peribulbar and retrobulbar injections target the space around and behind the eyeball. These techniques are often used for anesthesia in ophthalmic surgeries but have also been explored for drug delivery. Peribulbar injections deposit the drug in the adipose tissue surrounding the eyeball, allowing for slower systemic absorption and sustained local drug release. Retrobulbar injections place the drug closer to the optic nerve, potentially increasing the drug concentration in the posterior segment but posing risks such as optic nerve injury and hemorrhage [75]. Posterior juxta scleral injection delivers the drug near the sclera at the back of the eye, aiming for closer proximity to the retina and choroid.

This method can enhance drug penetration to the posterior segment but is technically challenging and can cause patient discomfort [74,76].

Despite these techniques, achieving therapeutic drug levels in the posterior segment remains challenging due to the eye's protective barriers. The drug's molecular size, lipophilicity, and formulation can significantly impact its ability to reach the posterior segment effectively. Research into advanced drug delivery systems aims to improve periocular administration's bioavailability and therapeutic efficacy. These systems can enhance drug retention, control release rates, and facilitate penetration through ocular barriers. For instance, nanoparticle-based delivery systems can encapsulate drugs, protecting them from degradation and enhancing their penetration through the ocular tissues [70].

*Intraocular administration*

Among the several intraocular delivery routes, the most common ones are intracameral, intravitreal, subretinal, intrastromal, suprachoroidal, and intrastromal. The intracameral injection approach is typically utilized after cataract surgery to treat anterior segment diseases such as bacterial and fungal keratitis. This technique includes the direct injection of the drugs into the anterior chamber. However, because the drug cannot penetrate the aqueous humor flow in the eye, this approach is not successful in delivering drugs to the posterior portion of the eye [77]. Because of this, intravitreal injection is utilized to achieve medication concentrations in the posterior region of the eye. Direct intravitreal injection and intravitreal implanted devices are the two components of this procedure, which has emerged as the most popular approach to treating vitreoretinal disorders in the past few decades [78]. Intravitreal injections of anti-VEGF agents [79], steroids [80], and genes [81] increase the drug concentration in the vitreous and retina. However, repeated injections can lead to complications like retinal toxicity, optic nerve damage, endophthalmitis, secondary glaucoma, cataracts, vitreous hemorrhage, excessive intraocular pressure, and bleeding [82,83]. Recent advancements in drug delivery systems aim to enhance the safety and efficacy of intraocular administration. For instance, liposomes and poly lactic-co-glycolic acid (PLGA) nanoparticles have been extensively studied for their potential to enhance drug retention and penetration within ocular tissues, offering promising avenues for long-term treatment of chronic eye diseases [84].

*Systemic administration*

Systemic administration of drugs, which reach the eye through the bloodstream, is vital for treating various ocular conditions, especially when localized administration is insufficient. Systemic delivery involves introducing a drug into the circulatory system via oral ingestion, intravenous injection, or other parenteral routes. Once in the bloodstream, the drug can traverse the blood-ocular barriers, including the blood-aqueous and blood-retinal barriers, to reach ocular tissues. The blood-ocular barriers, however, pose significant challenges for drug delivery. These barriers protect the eye from toxins and pathogens and limit therapeutic agent penetration. For example, the blood-aqueous barrier consists of tight junctions between endothelial cells of the iris and ciliary body capillaries, preventing many substances in the blood from entering the aqueous humor.

Similarly, the blood-retinal barrier restricts drug access to the retina and vitreous body, necessitating higher systemic drug concentrations to achieve therapeutic levels within the eye [85,86]. Systemically administered drugs can be crucial in managing conditions like uveitis, diabetic retinopathy, and age-related macular degeneration. For example, corticosteroids, commonly used for their anti-inflammatory properties, can be administered orally or intravenously to treat severe intraocular inflammation. Oral acetazolamide is used to lower intraocular pressure in glaucoma by decreasing aqueous humor production [85]. The systemic route is also beneficial when rapid and uniform drug distribution is required, as in the case of acute ocular infections. Intravenous antibiotics can quickly achieve therapeutic concentrations in ocular tissues, providing a more effective treatment than topical applications alone [87]. However, systemic drug administration is not without risks. High doses required to overcome the blood-ocular barriers can lead to systemic side effects, including gastrointestinal disturbances, cardiovascular issues, and potential toxicity.

Moreover, drugs eliminated via systemic circulation can cause unwanted effects in non-target tissues, emphasizing the need for careful dosing and monitoring [85,86]. While traditional routes of ocular drug administration have been essential in managing various eye conditions, each route has its own set of challenges and limitations. Ongoing research and development aim to enhance drug efficiency and patient outcomes through improved formulations and novel delivery systems.

**Ocular drug kinetics**

Ocular drug kinetics involves the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs administered to the eye, as illustrated in Figure 4. Drug penetration tactics can be categorized into several routes: topical delivery through trans-corneal and non-corneal penetration (Routes 1 and 2), systemic administration via the blood-aqueous barrier (Route 3) and the blood-retinal barrier (Route 4), and direct injection through vitreous administration (Route 7). The main drug elimination strategies entail the movement of the drug through the trabecular meshwork and Schelemm's canal (Route 5), the drug entering the systemic circulation through the blood-aqueous barrier (Route 6), the drug crossing the blood-retinal barrier (Route 8), and the drug passing from the front to the back of the eye through the anterior route to the posterior chamber (Route 9) [12]. The eye's unique anatomical and physiological characteristics significantly influence these processes, presenting challenges and opportunities for effective therapeutic interventions.

*Absorption*

The primary routes for ocular drug delivery include topical, periocular, and intraocular methods. Topical administration is the most common due to its ease of use and non-invasiveness. However, it faces significant barriers, such as the corneal epithelium, which limits drug penetration. The cornea, comprising five layers, including the lipophilic epithelium and hydrophilic stroma, acts as a barrier to many drugs, restricting their bioavailability [88]. The tear film and nasolacrimal drainage further complicate absorption by rapidly diluting and removing the drug from the ocular surface [89].

*Distribution*

Once absorbed, the distribution of drugs within the eye is influenced by various factors, including molecular size, lipophilicity, and the presence of ocular barriers such as the BAB and the BRB. These barriers protect the eye from systemic toxins but also impede drug delivery. For example, the BAB limits the penetration of drugs from the systemic circulation into the aqueous humor, while the BRB restricts access to the retina and vitreous humor [90].

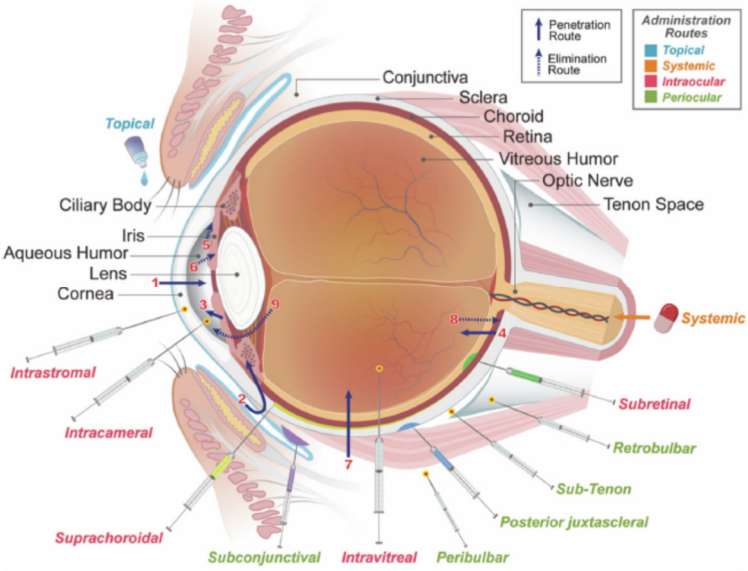


**Figure 4.** Approach of ocular administrations with different delivery routes. Reprinted under the terms of the Creative Commons Attribution 4.0 International (CC BY) license [12].

*Factors influencing ocular drug kinetics*

Several aspects, including drug formulation, delivery vehicle, and administration technique, influence the efficacy of ocular drug delivery systems. For instance, nanoparticles and liposomes can enhance drug penetration and retention in ocular tissues, providing sustained release and improved bioavailability [91]. Hydrogels and in situ gelling systems offer prolonged contact time on the ocular surface, enhancing drug absorption and therapeutic effects [92]. Understanding ocular drug kinetics is crucial for developing effective treatments for ocular diseases. Optimizing drug delivery systems to overcome ocular barriers and enhance drug absorption, distribution, and retention can improve therapeutic outcomes [93].

**Nanocarrier-based ocular drug delivery systems**

Nanotechnology-based ocular drug delivery systems are at the forefront of addressing the unique challenges of ocular drug delivery. Traditional methods often need better bioavailability and rapid clearance, but nanotechnology offers innovative solutions.

*Enhanced penetration and retention*

Nanoparticles, liposomes, dendrimers, and micelles are designed to improve drug penetration and retention in ocular tissues. Due to their small size and surface characteristics, nanoparticles can traverse the corneal barrier more effectively. For instance, chitosan-coated nanoparticles have shown enhanced mucoadhesive properties, prolonging the corneal surface's residence time and improving drug absorption [94]. PLGA nanoparticles have been extensively studied for their ability to provide sustained drug release, reducing the frequency of administration and improving patient compliance [95].

*Targeted delivery*

Nanocarriers can be engineered for targeted delivery, minimizing systemic side effects and enhancing therapeutic efficacy. Functionalizing nanocarriers with ligands, such as antibodies, peptides, or small molecules, enables specific targeting of ocular tissues or cells. Nanoparticles functionalized with transferrin have targeted the retina, providing localized treatment for retinal diseases [96]. This targeted approach allows for higher drug concentrations at the site of action, improving efficacy while reducing systemic exposure.

*Overcoming ocular barriers*

Nanotechnology helps overcome the physiological barriers of the eye, such as the BRB. With their highly branched structure, Dendrimers provide multiple sites for drug attachment and can penetrate the BRB effectively. This capability is particularly beneficial for treating posterior segment diseases like AMD and DR [97]. Moreover, micelles can solubilize poorly water-soluble drugs, enhancing their delivery across the ocular barriers [98].

*Biocompatibility and Safety*

The biocompatibility and safety of nanocarriers are paramount for their use in ocular applications. Materials like PLGA, chitosan, and polyethylene glycol (PEG) are commonly used due to their biocompatibility and biodegradability. These materials degrade into non-toxic byproducts, making them safe for ocular use. Additionally, surface modification of nanocarriers with PEG can reduce immunogenicity and prolong circulation time, further enhancing their efficacy [99].

**Factors influences nanocarriers for ocular**

Several factors influence the efficacy of nanocarriers in managing ocular diseases, including size, surface properties, drug loading capacity, release mechanisms, and biocompatibility.

*Size of nanocarriers*

The size of nanocarriers significantly impacts their distribution, penetration, and retention in ocular tissues. Nanocarriers typically range from 10 nm to 1 μm [100]. To ensure that medication is delivered

effectively, drug carriers must be sufficiently minuscule to pass through the ocular barriers and be well tolerated by the human eye when administered [101]. Nanoparticles that are smaller in size have the potential to provide improved stability and biodistribution, respectively. Smaller nanoparticles can penetrate deeper ocular tissues, including the retina, while larger particles may be more suitable for prolonged release in the anterior segment. Optimal size selection helps overcome barriers such as the corneal epithelium and BRB. Studies suggest that nanoparticles around 200 nm enhance permeation and retention in ocular tissues [100].

*Surface properties*

Surface charge and hydrophilicity/hydrophobicity balance are crucial in determining the interaction of nanocarriers with ocular tissues. Positively charged particles have higher mucoadhesion due to electrostatic interactions with the negatively charged mucin layer on the ocular surface, facilitating prolonged residence time [102]. Additionally, surface modification with hydrophilic polymers like PEG can enhance stability and reduce opsonization, prolonging systemic circulation time and improving ocular bioavailability [103].

*Drug loading capacity and encapsulation efficiency*

The drug loading capacity of nanocarriers determines the therapeutic dose that can be delivered. High encapsulation efficiency ensures that sufficient drug reaches the target site. For example, PLGA nanoparticles are well-known for their high encapsulation efficiency and controlled release properties [95].

*Release mechanisms*

Controlled and sustained drug release from nanocarriers is vital for maintaining therapeutic levels over extended periods, reducing dosing frequency, and improving patient compliance. Nanocarriers can be designed to release drugs through diffusion and degradation or are responsive to environmental stimuli such as pH and temperature. For instance, thermosensitive in situ gels that solidify at body temperature sustain drug release to the ocular surface [99].

*Biocompatibility and Toxicity*

The materials used in nanocarriers must be biocompatible and non-toxic to ocular tissues. Biodegradable polymers like PLGA, polycaprolactone (PCL), and chitosan are frequently used for their safety profiles and ability to degrade into non-toxic byproducts [104]. Additionally, the potential immunogenicity of nanocarriers must be considered, as ocular tissues are sensitive to inflammatory responses.

*Specific targeting*

Nanocarriers can be engineered to target specific ocular tissues or cells by modifying their surface with ligands such as antibodies, peptides, or small molecules. Targeted delivery enhances drug concentration at the disease site, minimizing systemic exposure and side effects. For example, nanoparticles functionalized with antibodies targeting vascular endothelial growth factor (VEGF) can provide targeted therapy for AMD [105].

*Stability and Storage*

The stability of nanocarriers during storage and upon administration is critical for maintaining their efficacy. Factors such as aggregation, degradation, and drug leakage can compromise their performance. Techniques like lyophilization and incorporation of stabilizing agents are employed to enhance the shelf-life of nanocarrier formulations [70,90,106,107].

**Nanocarrier platforms**

*Nanoparticles*

Nanoparticles are tiny particles that range in size from 1 to 1000 nm. Due to their small size and large surface area-to-volume ratio, nanoparticles possess unique physical and chemical properties that make them highly effective in various applications, including drug delivery, imaging, and diagnostics. In ocular drug delivery, nanoparticles offer several advantages over traditional drug delivery systems. They can enhance the solubility and stability of drugs, facilitate sustained and controlled release, and improve drug penetration across ocular barriers such as the cornea and BRB [88,90]. These nanoparticles can encapsulate hydrophilic and hydrophobic drugs, protecting them from degradation and enhancing their therapeutic efficacy. The targeting capability allows nanoparticles to deliver drugs directly to specific ocular tissues or cells, thereby increasing therapeutic efficacy and minimizing systemic side effects [96].

Yu et al. synthesized dexamethasone-glycol chitosan (Dex-GCS) conjugates with 277-289 nm particle sizes and a positive charge of approximately +15 mV. Dex-GCS nanoparticles caused slight cytotoxicity against L929, HCEC, and RAW 264.7 cells after 24 h incubation. They displayed a nearly identical anti-inflammatory efficacy to dexamethasone sodium phosphate (Dexp) in lipopolysaccharide (LPS)--activated RAW 264.7 macrophages. Overall, the results suggest that the Dex-GCS nanoparticles showed good ocular tolerance and provided a relatively longer precorneal duration compared with that of the aqueous solution formulation, which suggested that the self-assembled Dex-GCS nanoparticle might be a promising candidate for ophthalmic drug delivery [108]. Zein and PLGA nanoparticles embedded in bio-adhesive thermosensitive gel for the delivery of lutein via topical application were developed by Bodoki et al. Cataracts were induced in rats via selenite injection at 13 days post-partum, followed by 7 days of treatment with free lutein or lutein-loaded nanoparticles administered orally or topically. The authors concluded that Cataract severity was significantly reduced in rats treated with topical applications of lutein-loaded nanoparticles compared to the positive control [109]. Xing et al. formulated Triamcinolone acetonide (TA) in PLGA-chitosan (PLC) nanoparticles to treat ocular inflammatory diseases. When tested against human corneal epithelial (HCE) cells, TA-loaded polylactide nanoparticles (PLC NPs) showed remarkable anti-inflammatory properties. Furthermore, these nanoparticles dramatically decreased the release of interleukin (IL)-6 in cells stimulated by tumor necrosis factor (TNF)—$\alpha$. Pharmacokinetic analysis of rabbit eyes revealed that TA-loaded PLC nanoparticles peaked at 6 h. Substantial concentrations of TA were observed until 24 h, indicating the superiority of this PLC-based nanocarrier system [110].

*Liposomes*

It was not until 1965 that liposomes were used for the first time as drug delivery vehicles. Liposomes have emerged as a significant advancement in ocular drug delivery due to their unique structural and functional characteristics, which enable efficient encapsulation and delivery of therapeutic agents to the eye. Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate hydrophilic and hydrophobic drugs, thus protecting them from degradation and enhancing their bioavailability. This is particularly advantageous in ocular drug delivery, where the eye's complex anatomy and physiology pose significant challenges to conventional drug delivery systems. The ocular surface is protected by multiple barriers, including the tear film, corneal epithelium, and blood-ocular barriers, which limit drug penetration and absorption. Traditional methods like eye drops and ointments often suffer from low bioavailability and rapid drug clearance. Liposomes, however, can enhance drug retention time on the ocular surface and facilitate controlled and sustained release of the therapeutic agents, thus improving the efficacy of the treatment [111]. One of the critical advantages of liposomes in ocular drug delivery is their ability to improve drug penetration through the corneal and conjunctival epithelia. The lipid bilayer of liposomes can merge with the lipid layers of the ocular surface, facilitating drug release directly into the ocular tissues [112].

Additionally, liposome size and surface charge can be modified to optimize their interaction with ocular tissues and enhance drug absorption. Studies have demonstrated that positively charged liposomes show better adhesion to the negatively charged ocular surface, enhancing drug delivery efficiency [113]. Liposomes have also shown promise in delivering a wide range of drugs, including

anti-inflammatory agents, antibiotics, and anti-glaucoma medications. For instance, liposomal formulations of corticosteroids have been developed to treat inflammatory conditions of the eye, providing prolonged anti-inflammatory effects with reduced dosing frequency [114]. Similarly, liposomal antibiotics have been utilized to treat bacterial infections, achieving higher local drug concentrations and minimizing systemic side effects [115].

Moreover, liposomes can be engineered to deliver targeted drugs, further enhancing their therapeutic potential. Surface modification with ligands, such as antibodies or peptides, allows liposomes to specifically target diseased ocular tissues or cells, thereby increasing drug efficacy and reducing off-target effects [116]. This targeted approach is particularly beneficial in treating retinal diseases, where precise delivery of drugs to the retina is crucial. Despite the promising attributes of liposomes, some challenges need to be addressed for their widespread clinical application. The stability of liposomal formulations during storage, potential immunogenicity, and large-scale manufacturing are significant concerns. However, ongoing research and technological advancements are focused on overcoming these hurdles, making liposomes a viable option for ocular drug delivery shortly [117]. Zang et al. investigated the effects of the molecular weight (MW) and concentration of trimethyl chitosan (TMC) on the characteristics of Coenzyme Q10-loaded liposomes coated with trimethyl chitosan and the efficacy of the antioxidant Coenzyme Q10 in delaying selenite-induced cataract was assessed. Compared to the control group, the presence of TMC with a larger Mw increased in the precorneal residence period, which was nearly 4.8 times more than anticipated. Coenzyme Q10 demonstrated a significant anti-cataract effect, as evidenced by the fact that the percentage of lens opacity was approximately 53% after the study. It was concluded that the physical properties and precorneal retention time of liposomes could be modified with TMC, and ophthalmic instillation of Coenzyme Q10 can retard selenite-induced cataract formation [118]. Moiseev et al. developed Maleimide-Decorated PEGylated mucoadhesive liposomes for ocular drug delivery conventional, PEGylated, and maleimide-decorated PEGylated liposomes. The fluorescent flow-through approach was utilized to investigate the retention of these liposomes in the cornea and conjunctiva beyond the confines of the animals. Liposomes that were adorned with maleimide demonstrated superior retention performance on bovine conjunctiva when compared to other types of liposomes that were utilized in the research. On the bovine cornea, it was noted that all liposomal formulations retained themselves poorly [119].

*Nanoemulsions*

Nanoemulsions have gained considerable attention in the field of ocular drug delivery due to their unique properties that address the limitations of conventional ocular formulations. Nanoemulsions are submicron-sized emulsions with droplet sizes typically ranging from 20 to 200 nm. These systems consist of an oil phase, water phase, surfactant, and co-surfactant, creating a stable dispersion of oil droplets in water (O/W) or water droplets in oil (W/O). The small droplet size and high surface area of nanoemulsions enable enhanced drug solubilization, stability, and bioavailability, which are crucial for effective ocular drug delivery [120]. One of the significant advantages of nanoemulsions in ocular drug delivery is their ability to improve drug penetration and retention in ocular tissues. The tiny droplet size facilitates the interaction of the nanoemulsion with the corneal and conjunctival epithelium, promoting better drug absorption. Additionally, the surfactants in nanoemulsions can act as penetration enhancers, temporarily disrupting the tight junctions of the epithelial cells and thereby increasing drug permeability [121]. This property is particularly beneficial for delivering hydrophobic drugs with poor solubility in aqueous ocular environments. Nanoemulsions also offer the advantage of prolonged drug release, which can reduce the frequency of administration. The oil phase of the nanoemulsion acts as a reservoir for the drug, allowing a controlled and sustained release over time. This is particularly important in treating chronic ocular conditions, such as glaucoma and dry eye syndrome, where consistent therapeutic levels are required [122].

Furthermore, nanoemulsions can be easily sterilized and are generally well-tolerated, making them suitable for ocular applications. They are also versatile regarding the types of drugs that can be incorporated, ranging from anti-inflammatory agents and antibiotics to antifungal and antiviral drugs.

For example, a nanoemulsion formulation of cyclosporine A has been developed to treat dry eye disease, showing improved bioavailability and therapeutic efficacy compared to traditional formulations [123]. In addition to improving drug delivery to the anterior segment of the eye, nanoemulsions hold the potential for delivering drugs to the posterior segment, such as the retina. Due to their small size and ability to enhance drug permeability, nanoemulsions can potentially penetrate deeper into ocular tissues and reach the posterior segment, which is a significant challenge with conventional delivery systems [124]. The stability of nanoemulsions during storage is a critical issue, as phase separation and drug degradation can occur. Formulation strategies, such as using appropriate surfactants and co-surfactants, are essential to ensure the long-term stability of nanoemulsions.

Additionally, the potential toxicity of surfactants and other formulation components must be thoroughly evaluated to ensure safety for ocular use [125]. Nanoemulsions containing besifloxacin for ocular drug delivery were formulated by Kassaee and Mahboobian. In the ex vivo transcorneal permeation studies, the Nanoemulsions loaded with besifloxacin exhibited a sustained release pattern and 1.7-fold greater penetration than the solution that served as the control. According to the results of the HET-CAM test, there was no irritation, and the HL% test showed no damage to the tissue; hence, the eye tolerates the optimal Nanoemulsion well. In conclusion, besifloxacin-loaded Nanoemulsions have the potential to be considered an appropriate alternative to the suspension currently on the market for the treatment of bacterial eye infections [126]. Tang et al. fabricated stearoyl L-carnitine-modified nanoemulsions (SC-NEs). An improved corneal penetration, ocular surface retention ability, and ocular bioavailability were achieved as a result of the modified SC-NEs' capacity to target the new organic cation/carnitine transporter 2 (OCTN2) and amino acid transporter B (0+) (ATB0,+) on the corneal epithelium. Additionally, in a rabbit model of endotoxin-induced uveitis, SC-NEs demonstrated extremely high levels of anti-inflammatory activity in vivo. Based on the results of the ocular safety test, it was determined that the SC-NEs were biocompatible. According to the findings, OCTN2 and ATB0,+ -targeted nanoemulsions, were promising ophthalmologic drug delivery systems [127].

*Nanosuspensions*

Nanosuspensions have emerged as a promising formulation strategy in ocular drug delivery. A nanosuspension is a submicron colloidal dispersion of pure drug particles stabilized by surfactants or polymers [4,128]. One of the primary benefits of nanosuspensions in ocular drug delivery is their ability to enhance drug solubility and bioavailability. Poor water solubility is a common challenge with many ocular drugs, leading to inadequate therapeutic levels at the target site. Nanosuspensions address this issue by reducing the drug particle size, thereby increasing the surface area and improving the dissolution rate. This increases drug concentrations in the aqueous humor, enhancing the therapeutic efficacy [129]. Nanosuspensions also offer the advantage of prolonged drug retention on the ocular surface. The small particle size allows the drug to remain in the precorneal area for extended periods, crucial for maintaining therapeutic drug levels in the eye. Additionally, nanosuspensions can provide a controlled release of the drug, allowing for steady therapeutic effects over time [130]. The formulation flexibility of nanosuspensions is another significant advantage. They can be formulated with various stabilizers, including surfactants, polymers, and biopolymers, to enhance their stability and bioavailability. For instance, hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and Pluronic F68 are commonly used stabilizers that improve the stability and ocular tolerability of nanosuspensions [131]. These stabilizers also help prevent particle aggregation, ensuring uniform distribution of drug particles.

Further, this system is particularly beneficial for delivering drugs to both the anterior and posterior segments of the eye. Drugs intended for the posterior segment, such as those for treating age-related macular degeneration or diabetic retinopathy, face significant delivery challenges due to the eye's anatomical barriers. Nanosuspensions, with their small particle size and enhanced penetration capabilities, can effectively traverse these barriers and deliver therapeutic concentrations of drugs to the posterior segment [132]. One primary concern is nanosuspension stability during storage, as particle aggregation and Ostwald ripening can occur, leading to a loss of efficacy. Formulation strategies, such

as using appropriate stabilizers and manufacturing techniques like high-pressure homogenization and media milling, are essential to ensure nanosuspension's long-term stability [133]. Using the quasi-emulsion solvent evaporation procedure, Qin et al. developed a voriconazole-loaded ophthalmic nanosuspension based on Eudragit RS 100 and Pharmasolve®. This nanosuspension was investigated for its potential ability to augment corneal permeability. The nanoparticle, which was well-discrete and had a size of 138 ± 1.3 nm, was created with a high entrapment efficiency of 98.6 ± 2.5%. Additionally, the nanoparticle exhibited a positive zeta potential in the 22.5-31.2 mV range, indicating its excellent physical stability. The nanosuspension that was loaded with voriconazole and contained the penetration enhancer demonstrated a high level of permeability in both in vitro and in vivo conditions. Furthermore, it demonstrated a high level of antifungal activity, significantly suppressing the growth of Candida albicans at a lower concentration of voriconazole (2.5μg/ml, $p < 0.05$) [134].

*Micelles*

Micelles have emerged as a highly promising platform for ocular drug delivery due to their unique structural characteristics and versatile functionality. Micelles are colloidal aggregates formed from amphiphilic molecules, typically surfactants or block copolymers, that self-assemble in aqueous environments. These structures have a hydrophobic core and a hydrophilic shell, which allows them to encapsulate hydrophobic drugs and enhance their solubility and stability in aqueous media [135]. One of the primary advantages of micelles in ocular drug delivery is their ability to improve the bioavailability of poorly water-soluble drugs. Many ocular therapeutics suffer low solubility, leading to inadequate drug levels at the target site. Micelles can encapsulate these hydrophobic drugs within their core, protecting them from the aqueous environment and enhancing their solubility. This encapsulation prevents premature degradation and extends the drug's half-life, improving therapeutic efficacy [136]. The small size of micelles, typically in the range of 10 to 100 nm, facilitates their penetration through the ocular barriers. The cornea and conjunctiva are significant barriers to drug delivery, but the nanoscale size of micelles enables them to traverse these barriers more effectively than larger particles. Furthermore, the hydrophilic shell of micelles can interact favorably with the tear film and mucosal surfaces, enhancing retention time on the ocular surface and improving drug absorption [137]. Micelles can also be functionalized to achieve targeted drug delivery. Modifying the micelles' surface with ligands such as antibodies, peptides, or small molecules can be directed to specific cells or tissues within the eye. This targeted approach ensures that higher drug concentrations reach the desired site of action, minimizing systemic exposure and potential side effects. For instance, micelles functionalized with hyaluronic acid have shown enhanced targeting of the ocular surface, providing more efficient treatment for dry eye disease [138].

Moreover, micelles exhibit excellent biocompatibility and safety profiles, essential for ocular applications. The materials used to form micelles, such as Pluronic block copolymers and phospholipids, are generally considered safe and have been extensively studied for their biocompatibility. These materials do not elicit significant inflammatory or immune responses, making them suitable for prolonged use in sensitive ocular tissues [135]. One of the primary challenges is the stability of micelles in the dynamic ocular environment. The presence of tears, blinking, and tear turnover can lead to the rapid clearance of micelles from the ocular surface. Formulation strategies, such as incorporating mucoadhesive polymers or developing in situ gelling systems, can enhance the retention and stability of micelles in the eye [139]. The formulation of Posaconazole (PSC) micelles for ocular delivery was carried out by Durgun et al., and in vitro permeability, ocular irritation, and anti-fungal activity investigations were evaluated. According to the findings, the micellar carrier system improved the permeability of PSC to the eye's tissues. Further, PSC-loaded micellar formulations' effectiveness against Candida albicans strains was confirmed through in vitro anti-fungal activity data. It was determined that micellar systems have the potential to be an effective and safe method of delivering PSC for the treatment of ocular fungal infections [140].

*Dendrimers*

Dendrimers, highly branched synthetic macromolecules, have shown significant promise in ocular drug delivery due to their unique architecture and versatile functionalization capabilities. These nanoscale structures comprise a central core, interior branching units, and peripheral functional groups, creating a globular, tree-like structure. Dendrimers' size, shape, surface functionality, and internal cavities can be precisely controlled during synthesis, making them highly customizable for drug delivery applications [141]. The hydrophobic core of dendrimers can encapsulate these drugs, increasing their solubility in aqueous environments. This encapsulation protects the drugs from enzymatic degradation, improving their stability and therapeutic efficacy. For instance, polyamidoamine (PAMAM) dendrimers have significantly enhanced the solubility and ocular bioavailability of various drugs, including anti-inflammatory and anti-glaucoma agents [142]. Dendrimers offer controlled and sustained drug release, crucial for treating chronic ocular diseases requiring prolonged medication. The release profile can be modulated by adjusting the generation and surface functionality of the dendrimers. High-generation dendrimers, with more branching and surface groups, tend to release drugs more slowly, providing a sustained therapeutic effect. This property is particularly beneficial for conditions such as glaucoma, where continuous drug administration is necessary to maintain intraocular pressure [143]. Dendrimers also enhance drug penetration through ocular barriers. The corneal epithelium is a significant barrier to drug delivery, but dendrimers can improve drug penetration through various mechanisms. For instance, surface modification with hydrophilic groups or targeting ligands can enhance interaction with the corneal surface and facilitate drug transport.

Additionally, the nanoscale size of dendrimers allows them to traverse the tight junctions of the corneal epithelium more effectively than larger particles [144]. Biocompatibility is another critical factor for ocular applications, and dendrimers have demonstrated favorable biocompatibility profiles. The surface chemistry of dendrimers can be tailored to reduce toxicity and enhance compatibility with ocular tissues. For example, dendrimers' PEGylation (attachment of polyethylene glycol chains) can reduce surface charge and decrease cytotoxicity, making them safer for ocular use. Studies have shown that PEGylated dendrimers exhibit minimal irritation and inflammation when applied to the eye, making them suitable for long-term use [145,146]. To determine the ocular cytotoxicity and biosafety of Poly(amidoamine) PAMAM dendrimers, Qin et al. researched ocular systems both in vitro and in vivo. According to the findings, the quantity of PAMAM below 50 μg/ml had a negligible effect on the ocular tissue. However, the concentration above 50 μg/ml severely damaged the ocular tissue in the evaluated circumstance. Furthermore, the results obtained from in vivo experiments indicated that a higher concentration of dendrimer, namely 100 μg/mL, was linked to functional impairment, as displayed by the utilization of optical coherence tomography and electroretinogram studies. Overall, it was determined that a higher concentration of PAMAM, precisely above 50 μg/ml, has the potential to cause harm to the functional aspects of the eye. On the other hand, PAMAM at concentrations lower than 50 μg/ml demonstrated a high level of biocompatibility and biosafety in human ocular cells and tissues [147].

**Stability of nanocarriers in ocular drug delivery**

The stability of nanocarriers in ocular drug delivery is a critical factor in determining their efficacy and safety in treating various eye diseases. Nanocarriers are designed to enhance drug solubility, bioavailability, and targeted delivery. However, their stability is influenced by several factors, including physicochemical properties, formulation composition, storage conditions, and biological environment interactions [148]. Physicochemical stability is a significant concern for nanocarriers in ocular drug delivery. Particle size, surface charge, and encapsulation efficiency are vital in maintaining stability. Nanocarriers must maintain a consistent particle size distribution to ensure uniform drug delivery and prevent aggregation or sedimentation. Surface charge, typically imparted by surfactants or polymers, affects the colloidal stability of nanocarriers by preventing particle agglomeration through electrostatic

repulsion. Encapsulation efficiency, the amount of drug encapsulated within the nanocarrier, must remain high to ensure therapeutic efficacy [149].

The choice of stabilizers and excipients in the formulation significantly impacts the stability of nanocarriers. Surfactants and polymers, such as polysorbates, Pluronic F68, and polyvinyl alcohol (PVA), are commonly used to stabilize nanocarriers. These stabilizers help to maintain particle size and prevent aggregation during storage and application. Additionally, using antioxidants and preservatives can enhance the stability of nanocarriers by preventing oxidative degradation and microbial contamination [150]. In addition, Storage conditions, such as temperature, light exposure, and humidity, also affect the stability of nanocarriers. Elevated temperatures can accelerate degradation processes, such as hydrolysis and oxidation, reducing drug potency and efficacy. Light exposure can cause photodegradation of both the nanocarrier and the encapsulated drug, while high humidity levels can lead to hydrolytic degradation. Therefore, proper storage conditions, such as refrigeration and protection from light and moisture, are essential to maintain the stability of nanocarriers [151].

Biological environment interactions pose another challenge to the stability of nanocarriers in ocular drug delivery. The ocular surface and internal eye structures present a dynamic and complex environment, with barriers such as the tear film, corneal epithelium, and BOB. Enzymatic degradation and interaction with tear proteins can destabilize nanocarriers, affecting drug release and bioavailability. Mucoadhesive polymers, such as chitosan and hyaluronic acid, can be incorporated into nanocarrier formulations to enhance retention time on the ocular surface and protect against enzymatic degradation [152]. Further, various strategies are employed to address stability challenges in designing and formulating nanocarriers. For example, using cross-linking agents in polymeric nanoparticles can improve structural integrity and resistance to degradation. Surface modification with polyethylene glycol (PEGylation) can enhance stability by providing a steric barrier against protein adsorption and enzymatic degradation. Additionally, advanced manufacturing techniques, such as high-pressure homogenization and freeze-drying, can enhance the stability and shelf-life of nanocarrier formulations [153].

**Future prospects**

Nanocarriers are revolutionizing ocular drug delivery, offering new strategies to overcome the anatomical and physiological barriers that limit the efficacy of conventional treatments. The prospects of nanocarriers in this field are promising, driven by advancements in nanotechnology, materials science, and biomedical engineering. These prospects include enhanced drug delivery efficiency, targeted therapy, sustained release, improved patient compliance, and innovative treatment modalities. Nanocarriers have shown potential in enhancing the bioavailability of ocular drugs. Their small size allows better penetration through ocular barriers like the corneal epithelium and the blood-retinal barrier. Future developments will optimize these nanocarriers' size, surface charge, and hydrophobicity to enhance further their penetration and retention in ocular tissues [154]. One of the most exciting prospects for nanocarriers is the ability to achieve targeted drug delivery. The precise targeting of diseased tissues can be accomplished by functionalizing nanocarriers with ligands, antibodies, or peptides that recognize specific cell types or receptors in the eye. This targeted approach increases therapeutic efficacy while minimizing systemic side effects and reducing the required dosage. For example, targeted nanocarriers could deliver drugs directly to the retina in AMD or the trabecular meshwork in glaucoma, enhancing treatment outcomes [155]. Nanocarriers can be engineered to provide sustained and controlled drug release, which is crucial for treating chronic ocular diseases that require prolonged medication. The release profile can be modulated by adjusting the generation and surface functionality of the nanocarriers. High-generation dendrimers, for instance, release drugs more slowly, providing a sustained therapeutic effect. This property is particularly beneficial for conditions such as glaucoma, where continuous drug administration is necessary to maintain intraocular pressure [143]. Moreover, improving patient compliance is critical in ocular drug delivery, particularly for

conditions like glaucoma, which require regular medication. Nanocarriers can be formulated into user-friendly delivery systems such as eye drops, contact lenses, or in situ gels that provide sustained drug release with fewer applications. Future advancements include the development of smart contact lenses or ocular inserts that can continuously monitor ocular conditions and release drugs as needed [156].

Further, Nanocarriers are opening up new possibilities for innovative treatment modalities. Gene therapy and RNA interference (RNAi) are promising approaches that nanocarriers can facilitate to deliver genetic material or siRNA directly to target cells. These therapies can potentially treat genetic ocular diseases or conditions like DR and AMD at the molecular level [157]. The development of multifunctional nanocarriers that can perform multiple roles, such as imaging, diagnosis, and therapy, is a promising area of research. These theranostic nanocarriers can deliver drugs while simultaneously allowing for real-time monitoring of treatment progress through imaging modalities. This dual functionality could lead to more personalized and effective treatment strategies [158]. Despite their advantages, overcoming biological barriers remains a challenge for nanocarriers. The research will focus on designing nanocarriers that can navigate the ocular environment more effectively. This includes developing strategies to prevent rapid clearance by tear turnover, blinking, and ocular surface mucins. Advances in surface engineering and bioadhesive materials will play a crucial role in addressing these challenges [36]. As research progresses, nanocarriers are expected to play an increasingly pivotal role in treating ocular diseases, offering improved therapeutic outcomes and better quality of life for patients.

**Conclusions**

The field of ophthalmology is witnessing a transformative shift with the advent of advanced nanocarriers, which offer unprecedented potential for navigating ocular barriers and enhancing drug delivery. Traditional ocular therapies have long struggled with the eye's complex anatomy and physiology, formidable barriers to effective drug absorption and retention. The cornea, conjunctiva, BRB, and tear turnover are just a few of the many obstacles that reduce the efficacy of conventional treatments. Nanocarriers represent a groundbreaking development in ophthalmology, offering solutions to the longstanding challenges of ocular drug delivery. However, advanced nanocarriers are overcoming these challenges, ushering in a new era of targeted and efficient ocular drug delivery. These nanocarriers can encapsulate such drugs, protecting them from enzymatic degradation and facilitating sustained release, crucial for treating chronic conditions like glaucoma and AMD. Researchers can precisely target diseased ocular tissues by functionalizing nanocarriers with specific ligands, antibodies, or peptides. This targeted approach increases the efficacy of the treatment by concentrating the drug where it is needed most. It also minimizes systemic side effects and reduces the overall dosage required. For instance, targeting the retina in AMD or the trabecular meshwork in glaucoma can significantly enhance therapeutic outcomes. Despite the significant progress, challenges remain in the clinical translation of nanocarrier-based therapies. Issues such as long-term safety, potential toxicity, and the complexity of large-scale manufacturing need to be addressed. Nonetheless, ongoing research and technological advancements are likely to overcome these hurdles, making nanocarriers an integral part of future ocular therapies. The future of ocular drug delivery lies in the continued exploration and optimization of these innovative nanotechnologies, heralding a new era in the management and treatment of ocular diseases.

**Acknowledgements**

I am grateful for the support extended by Vivekananda College of Pharmacy, which provided me with the opportunity to conduct this study within their state-of-the-art facilities.

**Declaration of interest**

The authors declare no conflict of interest.

**Financial support**

This study received no specific grant from any funding agency in the public, commercial, or not-for profit sectors.

**References**

1. URL: https://www.statista.com/chart/31502/expected-number-of-people-with-vision-loss-globally/. [cited 2024 April 26].
2. URL: https://commons.wikimedia.org/wiki/File:1413_Structure_of_the_Eye.jpg#filelinks. [cited 2024 April 28].
3. Stjernschant, J, Astin M. Anatomy and physiology of the eye. Physiological aspects of ocular drug therapy. Biopharmaceutics of ocular drug delivery. CRC Press; 2019. p. 1-25.
4. Fathi-Karkan S, Ramsheh NA, Arkaban H, Narooie-Noori F, Sargazi S, Mirinejad S, et al. Nanosuspensions in ophthalmology: Overcoming challenges and enhancing drug delivery for eye diseases. Int J Pharm. 2024;12:658:124226.
5. Cholkar K, Dasari SR, Pal D, Mitra AK. Eye: Anatomy, physiology and barriers to drug delivery. Ocular transporters and receptors: Their Role in Drug Delivery Elsevier, 2013. pp. 1-36.
6. Fangueiro J F, Veiga F, M Silva A, B Souto E. Ocular drug delivery-new strategies for targeting anterior and posterior segments of the eye. Curr Pharm Des. 2016;22(9):1135-46.
7. Yamada M, Hiratsuka Y, Nakano T, Kita Y, Watanabe T, Tamura H. Detection of glaucoma and other vision-threatening ocular diseases in the population recruited at specific health checkups in Japan. Clin Epidemiol. 2020;12:1381-8.
8. Chomicz L, Szaflik JP, Padzik M, Izdebska J. Acanthamoeba keratitis: The emerging vision–threatening corneal disease. Advances in Common Eye Infections. InTech. 2016.
9. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. Autoimmune Dis. 2012:2012:290898.
10. Threatt J, Williamson JF, Huynh K, Davis RM, Hermayer K. Ocular disease, knowledge and technology applications in patients with diabetes. Am J Med Sci. 2013;345(4):266-70.
11. Chaerkady R, Shao H, Scott S-G, Pandey A, Jun AS, Chakravarti S. The keratoconus corneal proteome: loss of epithelial integrity and stromal degeneration. J Proteomics. 2013;87:122-31.
12. Han H, Li S, Xu M, Zhong Y, Fan W, Xu J, et al. Polymer- and lipid-based nanocarriers for ocular drug delivery: Current status and future perspectives. Adv Drug Deliv Rev. 2023;196:114770.
13. Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems-recent advances. Prog Retin Eye Res. 1998;17(1):33-58.
14. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci. 2004;45(7): 2342-7.
15. Detorakis ET, Zissimopoulos A, Ioannakis K, Kozoboli, VP. Lacrimal outflow mechanisms and the role of scintigraphy: Current trends. World J Nucl Med. 2014;13(1):16-21.
16. Scruggs J, Wallace T, Hanna C. Route of absorption of drug and ointment after application to the eye. Ann Ophthalmol. 1978;10(3):267-71.
17. Gaudana R, Jwala J, Boddu SSH, Mitra AK. Recent perspectives in ocular drug delivery. Pharm Res. 2009;26(5): 1197-216.
18. Cunha-Vaz J, Bernardes R, Lobo C. Blood-Retinal Barrier. Eur J Ophthalmol. 2011;21 Suppl 6:S3-9.
19. Mandal A, Bisht R, Rupenthal ID, Mitra AK. Polymeric micelles for ocular drug delivery: from structural frameworks to recent preclinical studies. J Control Release. 2017;248:96-116.
20. Gachon AM, Richard J, Dastugue B. Human tears: normal protein pattern and individual protein determinations in adults. Curr Eye Res. 1982;2(5):301-8.
21. Cone RA. Barrier properties of mucus. Adv Drug Deliv.Rev. 2009;61(2):75-85.
22. Lai SK, Wang YY, Hanes J. Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues. Adv Drug Deliv Rev. 2009;61(2):158-71.
23. Zierden HC, Josyula A, Shapiro RL, Hsueh HT, Hanes J, Ensign LM. Avoiding a sticky situation: bypassing the mucus barrier for improved local drug delivery. Trends Mol Med. 2021;27(5):436-50.
24. Alshaikh RA, Waeber C, Ryan KB. Polymer based sustained drug delivery to the ocular posterior segment: barriers and future opportunities for the treatment of neovascular pathologies. Adv Drug Deli Rev. 2022; 187:114342.

25. Subrizi A, M del Amo E, Korzhikov-Vlakh V, Tennikova T, Ruponen M, Urtti A. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug Discov Today. 2019;24(8):1446-57.
26. Schoenwald RD. Ocular drug delivery: Pharmacokinetic considerations. Clin Pharmacokinet. 1990;18(4):255-69.
27. Harikumar SL, Sonia A. Nanotechnological approaches in Ophthalmic delivery systems. Int J Drug Dev & Res. 2011;3(4):9-19.
28. Kim SH, Lutz RJ, Wang NS, Robinson MR. Transport barriers in transscleral drug delivery for retinal diseases. Ophthalmic Res. 2007;39(5):244-54.
29. Lee SJ, He W, Robinson SB, Robinson MR, Csaky KG, Kim H. Evaluation of clearance mechanisms with transscleral drug delivery. Invest Ophthalmol Vis Sci. 2010;51(10):5205-12.
30. Bochot A, Fattal E. Liposomes for intravitreal drug delivery: a state of the art. J Control Release. 2012;161(2):628-34.
31. Hogan M J, Alvarado JA, Weddell JE. Histology of the Human Eye: An Atlas and Textbook. Philadelphia: Saunders; 1971.
32. Forrester JV, Dick AD., McMenamin PG, Roberts F, Pearlman E. The Eye: Basic sciences in practice. Elsevier Health Sciences. 2016.
33. Ambati J, Adamis AP. Transscleral drug delivery to the retina and choroid. Prog Retin Eye Res. 2002;21(2):145-51.
34. Wilson CG, Tan LE, Mains J. Principles of Retinal Drug Delivery from Within the Vitreous. In: Kompella U, Edelhauser H, editors. Drug product development for the back of the eye. AAPS Advances in the Pharmaceutical Sciences Series. Springer, Boston, MA. 2011.
35. Berkowitz BA, Wilson CA, Tofts PS, Peshock RM. Effect of vitreous fluidity on the measurement of blood-retinal barrier permeability using contrast-enhanced MRI. Magn Reson Med. 1994;31(1):61-6.
36. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010;12(3), 348-60.
37. Xu Q, Boylan NJ, Suk JS, Wang YY, Nance EA, Yang JC, et al. Nanoparticle diffusion in, and microrheology of, the bovine vitreous ex vivo. J Control Release. 2013;167(1):76-84.
38. Cunha-Vaz J. The blood-ocular barriers. Surv Ophthalmol. 1979;23(5):279-96.
39. Campbell M, Humphries P. The blood-retina barrier: Tight junctions and barrier modulation. dv Exp Med Biol. 2012;763:70-84.
40. Coca-Prados M. The Blood-Aqueous barrier in health and disease. J Glaucoma. 2014;23(8 Suppl 1):S36-8.
41. Lee J, Pelis RM. Drug transport by the blood-aqueous humor barrier of the eye. Drug Metab Dispos. 2016;44(10): 1675-81.
42. Huang D, Chen YS, Rupenthal ID. Overcoming ocular drug delivery barriers through the use of physical forces. Adv Drug Deliv Rev. 2018;126:96-112.
43. O'Leary F, Campbell M. The blood-retina barrier in health and disease. FEBS J. 2023;290(4):878-91.
44. Li S, Chen L, Fu Y. Nanotechnology-based ocular drug delivery systems: recent advances and future prospects. J Nanobiotechnol. 2023;21(1):232.
45. Akhter Md H, Ahmad I, Alshahrani MY, Al-Harbi AI, Khalilullah H, Afzal O, et al. Drug delivery challenges and current progress in nanocarrier-based ocular therapeutic system. Gels. 2022;8(2):82.
46. Gorantla S, Rapalli VK, Waghule T, Singh PP, Dubey SK, Saha RN, et al. Nanocarriers for ocular drug delivery: current status and translational opportunity. RSC Adv. 2020;10(46):27835-55.
47. Onugwu AL, Nwagwu CS, Onugwu OS, Echezona AC, Agbo CP, Ihim SA, et al. Nanotechnology based drug delivery systems for the treatment of anterior segment eye diseases. J Control Release. 2023;354:465-88.
48. Kang-Mieler JJ, Rudeen KM, Liu W, Mieler WF. Advances in ocular drug delivery systems. Eye (Lond). 2020;34(8):1371-9.
49. Weinreb RN, Khaw P T. Primary open-angle glaucoma. Lancet. 2004;363(9422):1711-20.
50. Gagnon MM, Boisjoly HM, Brunette I, Charest M, Amyot M. Corneal endothelial cell density in glaucoma. Cornea. 1997;16(3):314-8.
51. Li X, Zhang Z, Ye L, Meng J, Zhao Z, Liu Z, et al. Acute ocular hypertension disrupts barrier integrity and pump function in rat corneal endothelial cells. Sci Rep. 2017;7(1):6951.
52. Renner M, Stute G, Alzureiqi M, Reinhard J, Wiemann S, Schmid H, et al. Optic nerve degeneration after retinal ischemia/reperfusion in a rodent model. Front Cell Neurosci. 2017;11:254.

53. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. Br J Ophthalmol. 2021 Jun;105(Suppl 1):1-169.
54. Friedman DS, Wilson MR, Liebmann JM, Fechtner RD, Weinreb R N. An evidence-based assessment of risk factors for the progression of ocular hypertension and glaucoma. Am J Ophthalmol. 2004;138(3 Suppl):S19-31.
55. Quigley H A. Glaucoma. Lancet. 2011;377(9774):1367-77.
56. Bagnis A, Papadia M, Scotto R, E Traverso C. Current and emerging medical therapies in glaucoma. Expert Opin Emerg Drugs. 2011;16(2):293-307.
57. Wong W L, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106-16.
58. Fritsche LG, Igl W, Bailey JNC, Grassmann F, Sengupta S, Bragg-Gresham JL, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet. 2016;48(2):134-43.
59. Ambati J, Atkinson JP, Gelfand BD. Immunology of age-related macular degeneration. Nat Rev Immunol. 2013;13(6):438-451.
60. Gillies MC, Campain A, Barthelmes D, Simpson JM, Arnold JJ, Guymer RH, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. Ophthalmology. 2015;122(9):1837-45.
61. Bakri SJ, Thorne JE, Ho AC, Ehlers JP, Schoenberger SD, Yeh S, et al. Safety and efficacy of anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration: a report by the american academy of ophthalmology. Ophthalmology. 2019;126(1):55-63.
62. Wong TY, Cheung CMG, Larsen M, Sharma S, Simo R. Diabetic retinopathy. Nat Rev Dis Primers. 2016;17:2:16012.
63. Aiello LP, Odia I, Glassman AR, Melia M, Jampol LM, Bressler N M, et al. Comparison of Early Treatment Diabetic Retinopathy Study Standard 7-Field Imaging With Ultrawide-Field Imaging for Determining Severity of Diabetic Retinopathy. JAMA Ophthalmol. 2019;137(1):65-73.
64. Tan TE, Wong TY. Diabetic retinopathy: Looking forward to 2030. Front Endocrinol (Lausanne). 2023;13:1077669.
65. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15(3):276-83.
66. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15(3):438-510.
67. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15(3):334-65.
68. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. Ocul Surf. 2017;15(3):575-628.
69. Mostafa M, Al Fatease A, G. Alany R, Abdelkader H. Recent Advances of Ocular Drug Delivery Systems: Prominence of Ocular Implants for Chronic Eye Diseases. Pharmaceutics 2023, 15(6), 1746.
70. Liu LC, Chen YH, Lu DW. Overview of recent advances in nano-based ocular drug delivery. Int J Mol Sci. 2023;24(20):15352.
71. Urtti A, Salminen L. Minimizing systemic absorption of topically administered ophthalmic drugs. Surv Ophthalmol. 1993;37(6):435-56.
72. M. del Amo E. Topical ophthalmic administration: Can a drug instilled onto the ocular surface exert an effect at the back of the eye? Front Drug Deliv. 2022;2:954771.
73. Hartman RR, Kompella UB. Intravitreal, Subretinal, and Suprachoroidal Injections: Evolution of Microneedles for Drug Delivery. J Ocul Pharmacol Ther. 2018;34(1-2):141-153.
74. Varela-Fernández R, Díaz-Tomé V, Luaces-Rodríguez A, Conde-Penedo A, García-Otero X, Luzardo-Álvarez A. et al. Drug Delivery to the Posterior Segment of the Eye: Biopharmaceutic and Pharmacokinetic Considerations. Pharmaceutics. 2020;12(3):269.
75. M. del Amo E, Rimpelä AK, Heikkinen E, Kari OK, Ramsay E, Lajunen T, et al. Pharmacokinetic aspects of retinal drug delivery. Prog Retin Eye Res. 2017;57:134-85.

76. Burhan AM, Klahan B, Cummins W, Andrés-Guerrero V, Byrne ME, J O'Reilly N, et al. Posterior Segment Ophthalmic Drug Delivery: Role of Muco-Adhesion with a Special Focus on Chitosan. Pharmaceutics. 2021;13(10):1685.
77. Raghava S, Hammond M, Kompella UB. Periocular routes for retinal drug delivery. Expert Opin Drug Deliv. 2004;1(1):99-114.
78. Choonara YE, Pillay V, Danckwerts MP, Carmichael TR, du Toit LC. A review of implantable intravitreal drug delivery technologies for the treatment of posterior segment eye disease. J Pharm Sci. 2010;99(5):2219-39.
79. Jiang P, Chaparro FJ, Cuddington CT, Palmer AF, Ohr MP, Lannutti JJ, et al. Injectable biodegradable bi-layered capsule for sustained delivery of bevacizumab in treating wet age-related macular degeneration. J Control Release. 2020;320:442-456.
80. Ryu M, Nakazawa T, Akagi T, Tanaka T, Watanabe R, Yasuda M, et al. Suppression of phagocytic cells in retinal disorders using amphiphilic poly (c-glutamic acid) nanoparticles containing dexamethasone. J Control Release. 2011;151:65-73.
81. Tan G, Liu D, Zhu R, Pan H, Li J, Pan W. A core-shell nanoplatform as a nonviral vector for targeted delivery of genes to the retina. Acta Biomater. 2021;134:605-20.
82. Bisht R, Jaiswal JK, Chen YS, Jin J, Rupenthal ID. Light-responsive in situ forming injectable implants for effective drug delivery to the posterior segment of the eye. Expert Opin Drug Deliv. 2016;13(7):953-62.
83. Meredith TA, Ulrich JN. Infectious Endophthalmitis. In: Ryan SJ, Sadda SR, Hinton DR, Schachat AP, Sadda SR, Wilkinson CP, et al. (editors). Retina (Fifth Edition), W.B. Saunders; 2013. p. 2019-39.
84. Tsai CH, Wang PY, Lin IC, Huang H, Liu GS, Tseng CL. Ocular Drug Delivery: Role of Degradable Polymeric Nanocarriers for Ophthalmic Application. Int J Mol Sci. 2018;19(9):2830.
85. Url: https://www.cd-bioparticles.net/blog/the-route-and-process-of-ocular-administration/. [cited 2024 May 09].
86. Url: https://www.msdmanuals.com/home/drugs/administration-and-kinetics-of-drugs/drug-administration. [cited 2024 May 09].
87. Shah SS, Denham LV, Elison JR, Bhattacharjee PS, Clement C, Huq T, et al. Drug delivery to the posterior segment of the eye for pharmacologic therapy. Expert Rev Ophthalmol. 2010;5(1):75-93.
88. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: An overview. World J Pharmacol. 2013;2(2):47-64.
89. Schoenwald RD. Ocular drug delivery: Pharmacokinetic considerations. Clin Pharmacokinet. 1990;18(4):255-69.
90. Del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discov Today. 2008;13(3-4):135-43.
91. Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacol Rep. 2012;64(5):1020-37.
92. Sultana Y, Jain R, Aqil M, Ali A. Review of ocular drug delivery. Curr Drug Deliv. 2006;3(2):207-17.
93. Barar J, Aghanejad A, Fathi M, Omidi Y. Advanced drug delivery and targeting technologies for the ocular diseases. Bioimpacts. 2016;6(1):49-67.
94. Vandervoort J, Ludwig A. Preparation and evaluation of drug-loaded gelatin nanoparticles for topical ophthalmic use. Eur J Pharm Biopharm. 2004;57(2):251-61.
95. Preeti, Sambhakar S, Malik R, Bhatia S, Harrasi AA, Rani C. Nanoemulsion: An Emerging Novel Technology for Improving the Bioavailability of Drugs. Scientifica (Cairo). 2023;2023:6640103.
96. Farjo KM, Ma JX. The potential of nanomedicine therapies to treat neovascular disease in the retina. Angiogenes Res. 2010;2:21.
97. Kannan RM, Nance E, Kannan S, Tomalia DA. Emerging concepts in dendrimer-based nanomedicine: From design principles to clinical applications. J Intern Med. 2014;276:(6):579-617.
98. Durgun ME, Güngör S, Özsoy Y. Micelles: Promising ocular drug carriers for anterior and posterior segment diseases. J Ocul Pharmacol Ther. 2020;36(6):323-341.
99. Gupta H, Jain S, Mathur R, Mishra P, Mishra AK, Velpandian T. Sustained ocular drug delivery from a temperature and pH triggered novel in situ gel system. Drug Deliv. 2007;14(8):507-15.
100. Ammar HO, Salama HA, Ghorab M, Mahmoud AA. Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride. AAPS PharmSciTech. 2009;10(3):808-19.
101. Liu S, Jones L, Gu FX. Nanomaterials for ocular drug delivery. Macromol Biosci. 2012;12(5):608-20.

102. Calvo P, Vila-Jato JL, Alonso MJ. Comparative in vitro evaluation of several colloidal systems, nanoparticles, nanocapsules, and nanoemulsions, as ocular drug carriers. J Pharm Sci. 1996;85(5):530-6.
103. Bucolo C, Drago F, Salomone S. Ocular drug delivery: a clue from nanotechnology. Front Pharmacol. 2012;3: 188.
104. Yuan X, Marcano DC, Shin CS, Hua X, Isenhart LC, Pflugfelder SC. Ocular drug delivery nanowafer with enhanced therapeutic efficacy. ACS Nano. 2015;9(2):1749-58.
105. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina. 2006;26(8);859-70.
106. Kaushal U, Kaur M, Nagpal M, Bhuyan M, Gounder KP. Nanocarriers based ocular therapeutics: updates, challenges and future prospectives. Curr Drug Res Rev. 2023;15(1):15-28.
107. Zhang J, Jiao J , Niu M, Gao X, Zhang G , Yu H, et al. Ten Years of Knowledge of Nano-Carrier Based Drug Delivery Systems in Ophthalmology: Current Evidence, Challenges, and Future Prospective. Int J Nanomedicine. 2021;16:6497-530.
108. Yu A, Shi H, Liu H, Bao Z, Dai M, Lin D, et al. Mucoadhesive dexamethasone- glycol chitosan nanoparticles for ophthalmic drug delivery. Int J Pharm. 2020;575:118943.
109. Bodoki E, Vostinaru O, Samoila O, Dinte E, Bodoki AE, Swetledge S, et al. Topical nanodelivery system of lutein for the prevention of selenite-induced cataract. Nanomedicine. 2019;15(1):188-97.
110. Xing Y, Zhu L, Zhang K, Li T, Huang S. Nanodelivery of triamcinolone acetonide with PLGA-chitosan nanoparticles for the treatment of ocular inflammation. Artif Cells Nanomed Biotechnol. 2021;49(1):308-16.
111. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. Drug Dev Ind Pharm. 2013;39(11):1599-617.
112. Das B, Nayak AK, Mallick S. Lipid-based nanocarriers for ocular drug delivery: An updated review. J Drug Deliv Sci Technol. 2022;76:103780.
113. Tasharrofi N, Nourozi M, Marzban A. How liposomes pave the way for ocular drug delivery after topical administration. J Drug Deliv Sci Technol. 2022;67:103045.
114. Mishra GP, Bagui M, Tamboli V, Mitra AK. Recent Applications of Liposomes in Ophthalmic Drug Delivery. J Drug Deliv. 2011;2011:863734.
115. Pérez-Santonja JJ, Güell JL, Gris O, Vázquez Dorrego XM, Pellicer E, Benítez-Del-Castillo JM. Liposomal Ozonated Oil in Ocular Infections: A Review of Preclinical and Clinical Studies, Focusing on Its Antiseptic and Regenerative Properties. Clin Ophthalmol. 2022;16:1953-62.
116. Chatin B, Mével M, Devallière J, Dallet L, Haudebourg T, Peuziat P, et al. Liposome-based Formulation for Intracellular Delivery of Functional Proteins. Mol Ther Nucleic Acids. 2015;4:e244.
117. Tian Bo, Bilsbury E, Doherty S, Teebagy S, Wood E, Su W, et al. Ocular Drug Delivery: Advancements and Innovations. Pharmaceutics. 2022;14(9):1931.
118. Zhang J, Wang S. Topical use of coenzyme Q10-loaded liposomes coated with trimethyl chitosan: tolerance, precorneal retention and anti-cataract effect. Int J Pharm. 2009;372(1-2):66-75.
119. Moiseev RV, Kaldybekov DB, Filippov SK, Radulescu A, Khutoryanskiy VV. Maleimide-Decorated PEGylated Mucoadhesive Liposomes for Ocular Drug Delivery. Langmuir. 2022;38(45):13870-9.
120. Wilson RJ, Li Y, Yang G, Zhao CX. Nanoemulsions for drug delivery. Particuology. 2022;64:85-97.
121. Gawin-Mikołajewicz A, Nartowski KP, Dyba AJ, Gołkowska AM, Malec K, et al. Ophthalmic nanoemulsions: from composition to technological processes and quality control. Mol. Pharmaceutics. 2021;18(10):3719-40.
122. Chime SA, Kenechukwu FC, Attama AA. Nanoemulsions - Advances in formulation, characterization and applications in drug delivery. Application of Nanotechnology in Drug Delivery. InTech; 2014.
123. Labetoulle M, Leonardi A, Pisella PJ, Baudouin C. Ciclosporin A Cationic emulsion 0.1% for the management of dry eye disease: facts that matter for eye-care providers. Ocul Immunol Inflamm. 2023;31(8): 1707-15.
124. Dhahir RK, Al-Nima AM, Al-Bazzaz F. Nanoemulsions as ophthalmic drug delivery systems. Turk J Pharm Sci. 2021;18(5):652-64.
125. Fernandes AR, Sanchez-Lopez E, dos Santos T, Garcia ML, Silva AM, Souto EB. Development and Characterization of Nanoemulsions for Ophthalmic Applications: Role of Cationic Surfactants. Materials (Basel). 2021;14(24):7541.
126. Kassaee SN, Mahboobian MM. Besifloxacin-loaded ocular nanoemulsions: design, formulation and efficacy evaluation. Drug Deliv Transl Res. 2022;12(1):229-39.

127. Tang B, Wang Q, Zhang G, Zhang A, Zhu L, Zhao R, et al. OCTN2$^{-}$ and ATB$^{0,+}$ -targeted nanoemulsions for improving ocular drug delivery. J Nanobiotechnology. 2024;22(1):130.
128. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: Rationale for development and what we can expect for the future. Adv Drug Deliv Rev. 2001;47(1):3-19.
129. Sharma Y, Patel P, Kurmi BD. A Mini-review on New Developments in nanocarriers and polymers for ophthalmic drug delivery strategies. Curr Drug Deliv. 2024;21(4):488-508.
130. Araújo J, Gonzalez E, Antonia Egea M, Luisa Garcia M, Souto EB. Nanomedicines for ocular NSAIDs: safety on drug delivery. Nanomedicine. 2009;5(4):394-401.
131. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020;24:3.
132. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. J Pharm Pharmacol. 2004;56(7):827-40.
133. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm. 2006 Jan;62(1):3-16.
134. Qin T, Dai Z, Xu X, Zhang Z, You X, Sun H, et al. Nanosuspension as an Efficient Carrier for Improved Ocular Permeation of Voriconazole. Curr Pharm Biotechnol. 2021;22(2):245-53.
135. Torchilin VP. Micellar nanocarriers: pharmaceutical perspectives. Pharm Res. 2006;24(1):1-16.
136. Gao Y, Xie J, Chen H, Gu S, Zhao R, Shao J. Nanotechnology-based intelligent drug design for cancer metastasis treatment. Biotechnol Adv. 2014;32(4):761-77.
137. Negut I, Bita B. Polymeric Micellar Systems-A Special Emphasis on "Smart" Drug Delivery. Pharmaceutics. 2023 Mar; 15(3): 976.
138. Cai R, Zhang L, Chi H. Recent development of polymer nanomicelles in the treatment of eye diseases. Front Bioeng Biotechnol. 2023;11:1246974.
139. Liu Y, Liu J, Zhang X, Zhang R, Huang Y, Wu C. In Situ gelling gelrite/alginate formulations as vehicles for ophthalmic drug delivery. AAPS PharmSciTech. 2010; 11(2):610-20.
140. Durgun ME, Kahraman E, Hacıoğlu M, Güngör S, Özsoy Y. Posaconazole micelles for ocular delivery: in vitro permeation, ocular irritation and antifungal activity studies. Drug Deliv Transl Res. 2022;12(3):662-75.
141. Kesharwani P, Gothwal A, Iyer AK, Jain K, Chourasia MK, Gupta U. Dendrimer nanohybrid carrier systems: an expanding horizon for targeted drug and gene delivery. Drug Discov Today. 2018;23(2):300-14.
142. Holden CA, Tyagi P, Thakur A, Kadam R, Jadhav G, Kompella UB, et al. Polyamidoamine dendrimer hydrogel for enhanced delivery of antiglaucoma drugs. Nanomedicine. 2012;8(5):776-83.
143. Yavuz B, Pehlivan SB, Ünlü N. Dendrimeric systems and their applications in ocular drug delivery. ScientificWorldJournal. 2013;2013:732340.
144. Wei D, Pu N, Li SY, Zhao N, Song ZM, Tao Y. Application of Hydrogels in the Device of Ophthalmic Iontophoresis: Theory, Developments and Perspectives. Gels. 2023;9(7):519.
145. Lopez AI, Reins RY, McDermott AM, Trautnerc BW, Cai C. Antibacterial activity and cytotoxicity of PEGylated poly(amidoamine) dendrimers. Mol BioSyst. 2009;5:1148-56.
146. Dhull A, Yu C, Hunter WA, Chen M, Sharma A, Yiu S. Dendrimers in corneal drug delivery: recent developments and translational opportunities. Pharmaceutics. 2023;15(6):1591.
147. Qin C, Wen S, Zhu S, Liu D, Chen S, Qie J, et al. Are Poly(amidoamine) Dendrimers safe for ocular applications? toxicological evaluation in ocular cells and tissues. J Ocul Pharmacol Ther. 2020;36(10):715-24.
148. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh DF, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018;10(2): 57.
149. Alshawwa SZ, Kassem AA, Farid RM, Khamis MS, Labib GS. Nanocarrier Drug Delivery Systems: Characterization, Limitations, Future Perspectives and Implementation of Artificial Intelligence. Pharmaceutics. 2022;14(4):883.
150. Joseph A, Motchoffo SG, Gao T, Alhindi N, Xu N, Graham DJ, et al. Surfactants influence polymer nanoparticle fate within the brain. Biomaterials. 2024;277:121086.
151. Pınar SG, Oktay AN, Karaküçük AE, Çelebi N. Formulation strategies of nanosuspensions for various administration routes. Pharmaceutics. 2023;15(5):1520.
152. Zhao K, Xie Y, Lin X, Xu W. The Mucoadhesive Nanoparticle-Based Delivery System in the Development of Mucosal Vaccines. Int J Nanomedicine. 2022;17:4579-4598.
153. Sarangi Mk. Parenteral lipid based drug delivery system. Inventi Rapid: NDDS. 2013;(4):1-5.

154. Tayeb Oucif Khaled M, Zaater A, Ben Amor I, Zeghoud S, Ben Amor A, Hemmami H, et al. Drug delivery methods based on nanotechnology for the treatment of eye diseases. Ann Med Surg (Lond). 2023;85(12):6029-40.
155. Yang C, Yang J, Lu A, Gong J, Yang Y, Lin X, et al. Nanoparticles in ocular applications and their potential toxicity. Front Mol Biosci. 2022;9:931759.
156. Ciolino JB, Stefanescu CF, Ross AE, Salvador-Culla B , Cortez P , Ford EM, et al. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials. 2014;35(1):432-9.
157. Ylä-Herttuala S. Endgame: glybera finally recommended for approval as the first gene therapy drug in the European Union. Mol Ther. 2012;20(10):1831-1832.
158. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev. 2002;54(5):631-51.

**How to cite this article:**
Mustafa S. Ophthalmology: Navigating ocular barriers with advanced nanocarriers. German J Pharm Biomaterials. 2024;3(3):34-58.