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Innovative ocular drug delivery systems: A comprehensive review of nano formulations and future directions

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Abstract

The eye's intricate structure and blood-ocular barriers pose significant challenges to effective ocular drug delivery. The blood-retinal barrier and blood-aqueous barrier restrict drug penetration, leading to poor bioavailability and limited treatment options for ocular diseases. Various administration routes, including systemic, topical, intravitreal, subconjunctival, and intracameral, have been explored to overcome these barriers. Nanotechnology-based platforms, such as liposomes, nanoemulsions, nanomicelles, nanosuspensions, and niosomes, have shown promise in enhancing ocular drug delivery. These platforms offer improved solubility, stability, and targeted release, increasing the efficacy of treatments for conditions like age-related macular degeneration, cataracts, diabetic retinopathy, fungal keratitis, and retinoblastoma. Future perspectives focus on developing minimally invasive, sustained-release systems that maintain intraocular efficacy. Nanofibers and stimuli-responsive drug delivery systems also hold potential for overcoming ocular delivery challenges.

Keyword: Ocular drug delivery; Blood-ocular barriers; Nanotechnology; Nano-emulsions; Diabetic retinopathy; Cataract

1. Introduction

The eye, which is comprised of anterior and posterior portions, is one of the body's most constrained yet intricate organs. The cornea, conjunctiva, aqueous humor, iris, cilliary body, and crystalline lens make up the anterior segment, whereas the sclera, choroid, and retinal pigment epithelium make up the posterior section [1]. The delivery of therapeutic medicines is complicated by the construction of the eye. The eye is protected against exposure to external chemicals and pharmacological agents that attempt to enter the targeted ocular tissues because of the blood-retinal barrier (BRB) [2]. Delivering drugs to the human eye is an important part of medical care. A major challenge for formulators is bypassing the eye's protective barrier without causing permanent tissue damage. Newer, more sensitive diagnostic techniques and the development of novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy [3]. By avoiding the hepatic first pass effect, the medicine penetrates the systemic circulation and can be used to treat ocular illnesses. All of the drawbacks of traditional dosage forms, such as ophthalmic solutions that irritate the eyes and result in lacrimation, are addressed by this approach. Most medications used in ophthalmology, such as atropine, pilocarpine, epinephrine, and local anesthetics, are weak bases that are often prepared at an acidic pH to improve stability [4]. Several intracranial nerves, blood arteries, orbital adipose tissue, and extra ocular muscles that regulate eye movement surround the orbit, a protective and supporting bone structure in the skull, where the eye is situated [5]. The typical dimensions of the human eye are roughly 69 to 85 mm in circumference and 22 to 27 mm in anteroposterior diameter [6]. Depending on the lens, the anterior and posterior parts of the eyeball's anatomical anatomy can be separated. Depicts the structure of the human eye. The cornea, conjunctiva, iris, cilliary

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body, aqueous humor, and lens are all part of the anterior segment, whereas the sclera, choroid, retina, and vitreous body are part of the posterior segment [7].

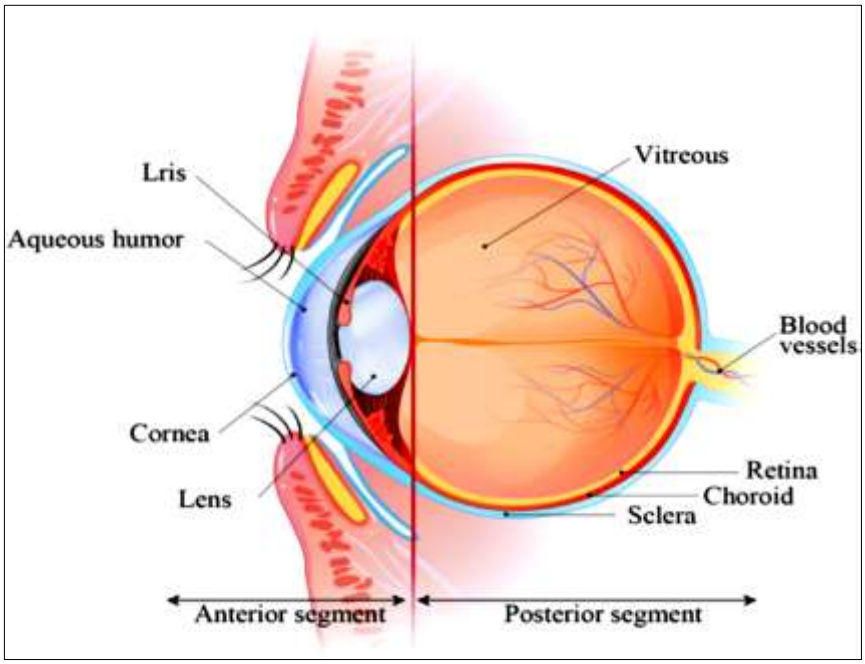

Figure 1 The anatomy of the eye[7]

1.1. Anatomy of the Eye

- **Cornea:** The outer layer of the eyeball is made up of the cornea and sclera. This coat's primary function is to shield inside ocular structures [8].
- **Sclera:** The outer layer of the eye ball is made up of the sclera, which is the white portion of the eye that looks as an opaque, hard white coating [9].
- **Conjunctiva:** Through the production of mucus and tears, the conjunctiva of the eye protects and lubricates the eye. It contributes to immune surveillance and stops microbes from entering the eye. It covers the sclera and lines the interior of the eyelids. It has many lymphatic vessels and is highly vascularized [10].
- **Iris:** The iris is a round, contractile muscle structure that faces the cornea and the lens. The iris's diaphragm, which comes in different diameters, helps to align the pupil and control the amount of light that enters the eye [9].
- **vitreous humor:** A transparent, jelly-like substance known as vitreous humor fills the biggest of the three chambers, the vitreous chamber [11].

1.2. Advantages of ocular drug delivery systems [12]

The following is the benefits of ocular medication delivery systems:

- They give the dosage rate precision and consistency. It is possible to prevent pulsed dosing of traditional systems.
- Drugs can be released in a controlled and sustained manner.
- They improve the ocular bioavailability of medications by lengthening the corneal contact time, which is accomplished by the drug's efficient adhesion to the corneal surface.
- Targeting within the ocular globe is necessary to prevent the loss of ocular tissues.

1.3. Disadvantages of ocular drug delivery system [12]

The following are the main disadvantages of ocular medication delivery systems:

- Little period of time the medication solution and ocular surface are in touch.
- Inadequate bioavailability.
- Instability of medications that have dissolved.

- Preservative use [12].

2. Ocular diseases

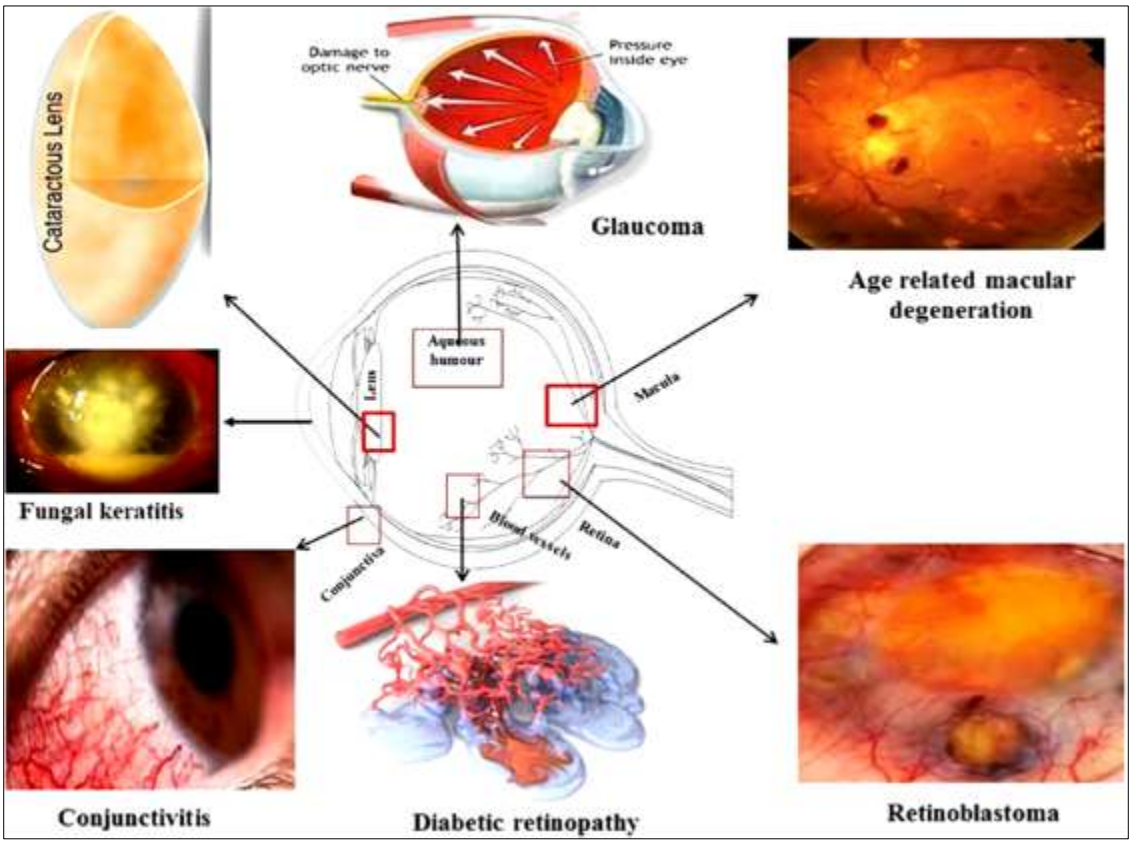

Figure 2 Various ocular diseases affecting the two segments of the eye [13]

2.1. Age-related macular degeneration (AMD):

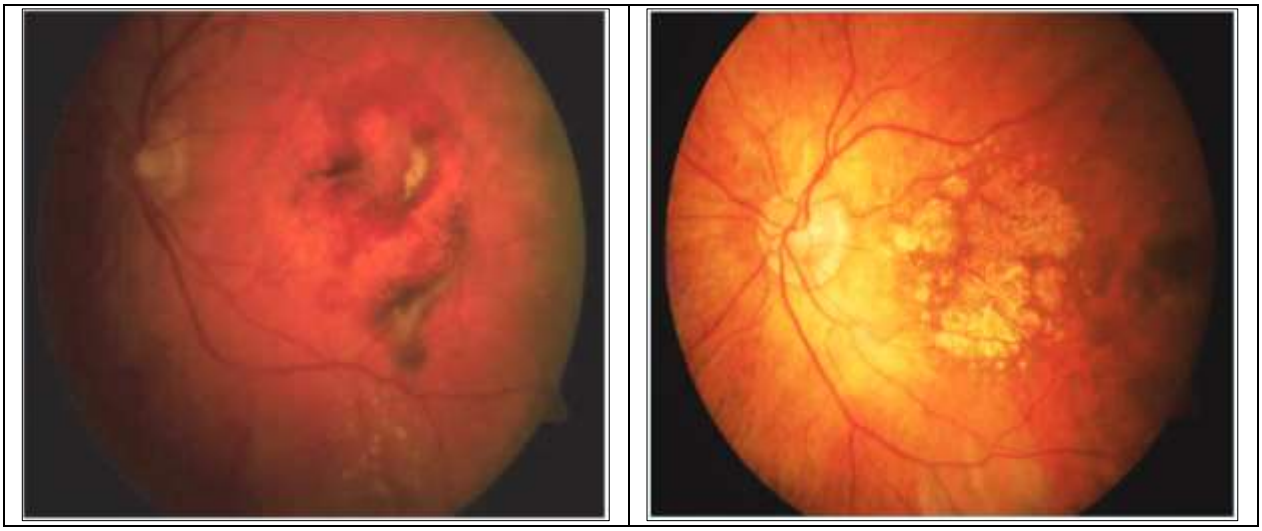

Figure 3 Wet AMD and Dry AMD [14]

This condition impairs visual acuity by affecting the macula, a particular structure in the central retina [14]. A dangerous condition known as age-related macular degeneration (AMD) results in an irreversible loss of central vision. AMD is the leading cause of adult blindness in developed nations, and it usually affects those over the age of 55 [15]. Although only around 10% of AMD patients have the exudative form, up to 80% to 90% of cases result in blindness and significant

vision impairment [16]. Age-related maculopathy, or drusen in the macular, is the initial symptom of dry AMD and can progress to geographic atrophy. Dry AMD does not currently have a cure. Aberrant blood vessel growth is the source of wet AMD [17]. The wet form of AMD is more common in women than in males, while the longer life duration and more health-care consumption by women confound the issue [18]. Increasing age, ethnicity, and heredity are some of the multifactorial risk factors for the development of severe AMD [19]. The pathophysiology of AMD is largely influenced by the immune system and inflammation [20]. There are two types of late-stage AMD: the atrophic form, which develops more slowly, and the neovascular form, which advances quickly [21]. Reading ability is lost in people with late-stage AMD due to decreased visual acuity [22].

2.2. Cataract

51% of blindness worldwide is caused by cataracts, making them the most common cause of blindness [23]. One of the most common eye conditions in older persons, cataracts are linked to both worsening visual acuity and more extensive psychosocial effects [24]. Most of the time, cataracts develop gradually and painfully [25]. Blindness can have a negative impact on societies by lowering the quality of life and productivity of the blind and those who care for them, and cataracts have been linked to depression [26]. Congenital cataract incidence is estimated to be between 12 and 136 per 100,000 births, with most nations reporting an incidence of about 72 per 100,000 children [27]. Weight increases with cataract maturity in both diabetic and senile cataracts [28]. Cataracts can be divided into three categories based on their cause: age-related cataracts, cataracts in children, and cataracts secondary to other reasons [29]. For many years, attempts have been made to prevent, treat, or delay cataracts through medical means. Poor pharmacological agent penetration into the lens has proven to be a significant barrier to effective treatments, despite the fact that the majority of medications have addressed antioxidant effects [30]. Since cataract grades can give patients intelligible information on the diagnosis, course, and significance of treatment for their cataracts, they might promote communication between the patient and the doctor [31].

2.3. Diabetic retinopathy

Diabetes mellitus is a common problem that has led to a significant number of fatalities worldwide [32]. The primary cause of vision loss in the elderly is diabetic retinopathy (DR), a typical microvascular consequence of diabetes mellitus [33]. Approximately one-third of diabetics develop diabetic retinopathy [34]. One of the main causes of blindness and visual impairments is diabetic retinopathy (DR), and its prevalence is rising worldwide [35]. It has long been acknowledged that DR is a micro vascular condition [36]. DR falls into one of two categories: proliferative diabetic retinopathy or nonproliferative diabetic retinopathy (NPDR) [37]. Individuals who acquire diabetic retinopathy are also at a higher risk of cardiovascular disease and diabetic nephropathy, among other vascular problems [38]. Patients with type 1 diabetes do not exhibit diabetic retinopathy at the time of diagnosis [39]. The presence of hypertension, poor glycemic management, and the length of the disease are the most significant risk factors for the development of DR [40]. Patients with type II diabetes have been the subject of the majority of research on asymmetric DR; nevertheless, the age range of these studies varies from 21 to 84 years [41]. Prevention, early identification, and ophthalmological treatments to lower the risk of vision loss in eyes with sight-threatening problems are the three main categories of management concepts [42]. Fortunately, a large portion of DR-related vision loss may be avoided, and over the past few decades, the incidence of both DR and diabetes-related vision loss have gradually decreased [43].

2.4. Fungal keratitis

Also referred to as mycotic keratitis (MK), fungal keratitis (FK) is one of the main causes of microbial keratitis that can result in corneal blindness [44]. FK is an ocular emergency [45] that happens when fungal spores and/or hyphal fragments get past the protective epithelium and reach the stroma [46]. Fungal ulcers are more prevalent in remote and rural areas [47]. FK is a serious and urgent infection that is more prevalent in tropical developing nations, where it may account for as much as 67% of all cases of infectious keratitis [48]. Generally speaking, FK is caused by the following fungal species: Candida albicans, Fusarium, Aspergillus, etc [49]. In tropical and subtropical countries, filamentous fungi are the most common cause of corneal infections, but yeasts are more common in temperate environments [50]. Topical antifungal agents are typically used to treat filamentous fungal keratitis (FK) [51]. The most widely used medications include azoles like fluconazole and voriconazole, as well as polyenes like natamycin and amphotericin B [52]. Severe cases may worsen quickly and necessitate corneal transplantation due to irreversible visual loss [53]. Due to the difficulties of early identification, the restricted selection of antifungal drugs, and the development of antifungal drug resistance and tolerance, treating fungal keratitis is still difficult [54]. Confocal microscopy has recently shown great promise as a noninvasive adjuvant diagnostic method for microbial keratitis [55]. The following are risk factors for fungal keratitis: eye traumas from 26% to 39% of cases; surgical interventions on cornea 37.6%; wearing contact lenses-from 24.5% to 42%; corneal diseases from 28% to 51.3%; systemic and local immunosuppression 35.9% [56].

2.5. Retinoblastoma

In 1597, Petrus Pawius made the first mention of retinoblastoma [57]. A tiny, spherical, blue-cell tumor is called retinoblastoma [58]. When treated promptly, retinoblastoma is a cancer that can be cured and can save the eye, but if treatment is not received, it is always deadly [59]. Leukocoria is the most prevalent symptom [60]. If detected early enough, retinoblastoma is a malignancy that can be treated [61]. Early diagnosis and appropriate treatment are critical to survival and prognosis [62]. Since newborns and young toddlers are the age group most affected by RB, vision testing techniques must be modified for them [63]. Chemotherapy, especially intravascular chemotherapy and chemo reduction, has emerged as a key treatment option for RB malignancies among the several clinical treatment choices available [64]. It is best to monitor a retinoblastoma survivor for the rest of their lives [65]. If left untreated, RB can cause death within a year or two, however in affluent nations, survival rates are above 95% when therapy is adequate [66].

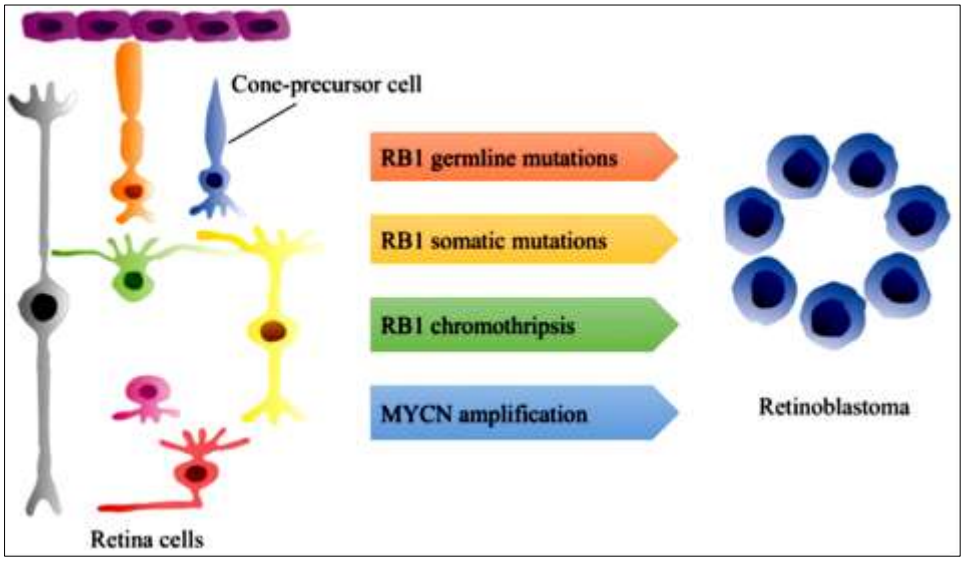

Figure 4 Pathogenesis of RB [64]

3. Barriers to ocular drug delivery

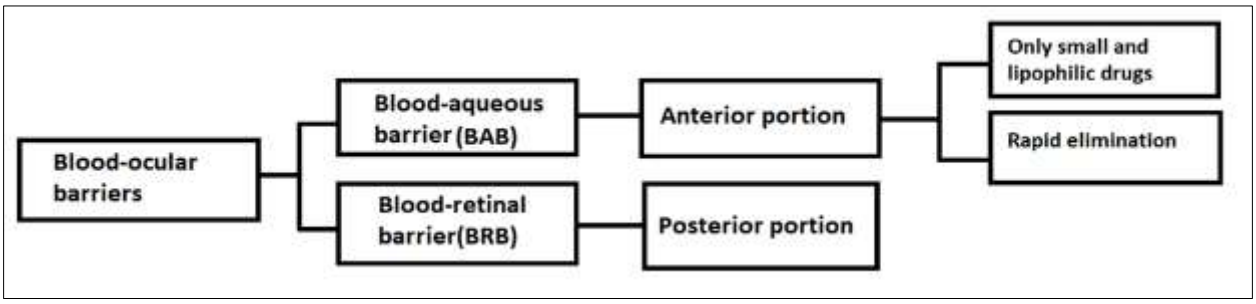

Figure 5 Schematic diagram of Blood ocular barriers [13]

3.1. Blood ocular barrier

The blood-ocular barrier is made up of the blood-aqueous barrier (BAB) and the blood-retinal barrier (BRB), both of which are important obstacles to topical medication administration in the anterior and posterior chambers of the eye [9]. These physical barriers between the blood and the eye play a key role in the penetration, removal, and preservation of homeostatic control of medications used via ophthalmic routes [67].

3.1.1. Blood retinal barrier

The BRB regulates the flow of water, proteins, and ions into and out of the retina and is very selective [68]. The most crucial barrier in the back of the eye is the blood-retinal barrier, which has both internal and exterior components [7]. A number of blinding eye illnesses are caused by dysfunctions in the blood–retinal barrier (BRB), which serves to maintain the ideal retinal environment for vision [69]. The RPE layer, Bruch's membrane, and chorio capillaries comprise the outside barrier of the BRB, whereas retinal endothelial cells create the inner barrier [70]. However, age-related macular degeneration, a leading cause of vision loss in the elderly, is associated with poor BRB [71].

3.1.2. Blood aqueous barrier

The blood-aqueous barrier, consisting of the non-pigmented cilliary body of the iris vasculature and the epithelial tissue of the endothelial cells, is the main barrier in the anterior segment of the eye, which prevents the nonspecific entry of various solutes in the intraocular environment [8]. The BAB is not completely impermeable; instead, it serves as a specialized gateway for controlled molecule movement [7].

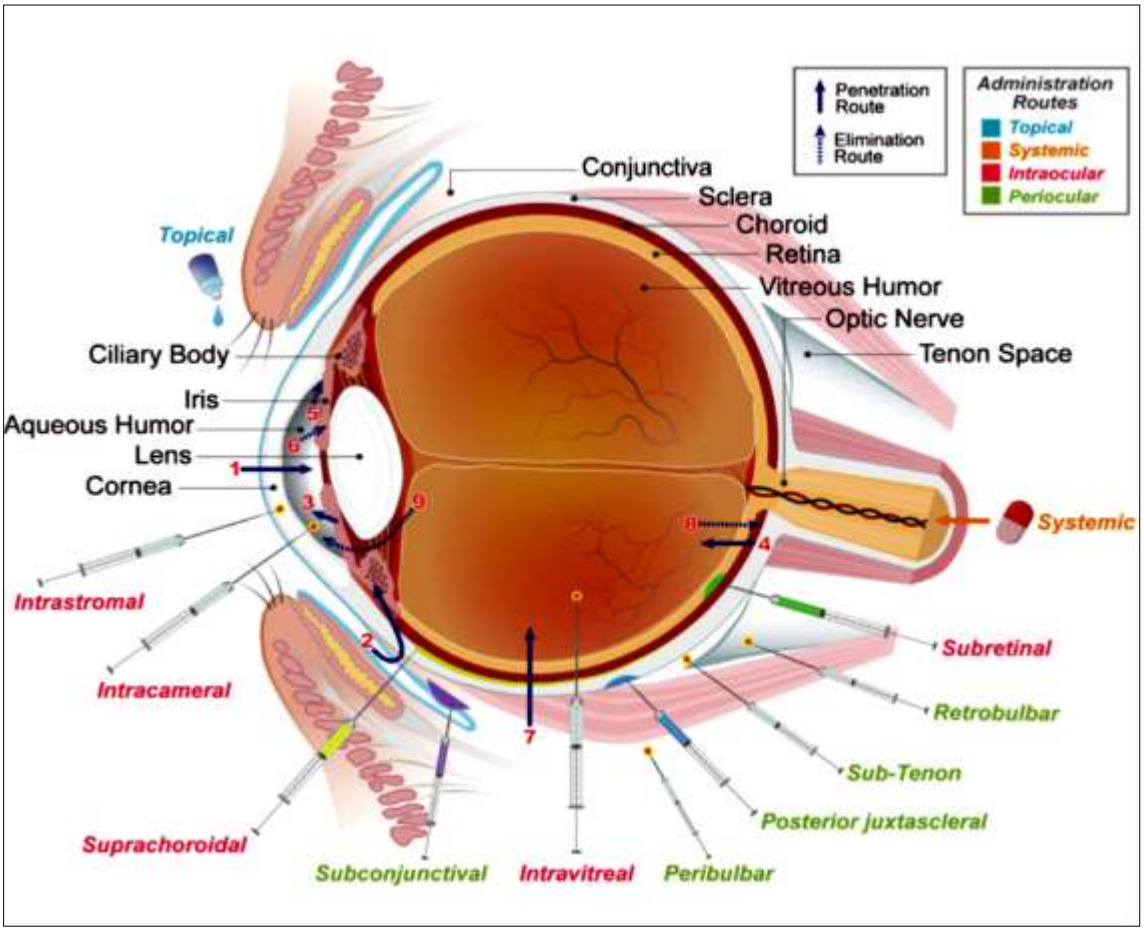

Figure 6 Routes of Drug Administration for Ocular Drug Delivery System [72]

4. Routes for ocular drug delivery

4.1. Systemic administration

Systemic administration techniques for ocular medication delivery include parenteral and oral dosage. Due to the eye's poor blood supply in comparison to the rest of the body and the retinal pigment epithelium cells tight connections, only 1% to 2% of a medicine supplied can reach the retina and vitreous region. This means that frequent drug delivery is necessary to achieve the intended therapeutic effect [73]. Frequent administration of greater doses increases the risk of systemic toxicity. Because P-Glycoprotein is less readily available in the blood–brain barrier in infants and children, they are primarily impacted by systemic side effects [74]. The blood-aqueous barrier and blood-retinal barrier serve as the major barriers for ocular drug delivery in the anterior and posterior segments, respectively. The blood-aqueous

barrier comprises two distinct cellular layers situated in the anterior part of the eye: the endothelium of the iris and ciliary blood vessels, and the nonpigmented ciliary epithelium. Both cellular layers exhibit tight junction complexes that inhibit the ingress of solutes into the intraocular milieu, including the aqueous humor [75]. Blood ocular barriers, poor cardiac output to the eye, and the requirement for a high dose and frequent dosing because of drug dilution in the blood are some disadvantages of the systemic route. When a medicine is taken systemically, less of it reaches the vitreous humor because of liver metabolism and kidney clearance [76].

4.2. Topical administration

The recommended method of treating ocular conditions is topical treatment. Due to high patient compliance, traditional formulations such eye drops, suspensions, and ointments are applied topically [73]. The most popular and patient-friendly ocular drug delivery technique for treating a variety of anterior segment problems is topical administration [74]. For the treatment of anterior segment disorders, the topical route is a very effective delivery method. However, it is thought to be highly ineffective for posterior segment disorders due to the presence of several ocular barriers, including the cornea, conjunctiva, tear drainage, and blood-aqueous barrier [77]. Compared to ointments, gels, and emulsions, which are used to treat conditions affecting the anterior segment of the eye, eye drops are the greatest examples of ophthalmic dosage forms used for topical administration of medications in the eye [78]. Nevertheless, the topical route has a number of drawbacks, including a shorter contact duration, limited permeability, and a quicker drug clearance rate [33]. Elderly and disabled people should not use topical routes [13].

4.3. Intravitreal injection

This method involves administering the drug by injections into the eye's vitreous fluid. Numerous eye conditions are treated with this administration method; it is delivered through the ocular channel [78]. The most popular method for administering 20–100 ml of solution or suspension into the vitreous cavity is intravitreal injection, which uses a 27 or 30 gauge needle [73]. This route, in contrast to others, provides the interior eye tissue, such as the retina and choroid, with large concentrations of the medication locally [74]. A single intravitreal injection of vitamin E/polylactic-co-glycolic acid microspheres containing cell line-derived neurotrophic factor is one novel method of treating glaucoma [13].

4.4. Subconjunctival Routes

This method involves administering the medication to the mucous membrane, which includes the inner surface of the eyelids and the open area of the eyeball [78]. A minimally invasive method of delivering medication to the posterior region of the eye is the subconjunctival route. Bypassing the conjunctival and corneal barriers, drug injections or implants in the subconjunctival space exhibit greater permeability through the retinal region [77]. However, because of the conjunctiva's lymphatic and blood outflow, the subconjunctival route may cause medication loss [7].

4.5. Intracameral administration

When a medicine is administered this way, it acts on the anterior or posterior chambers of the eye. Anesthetic injections into the anterior chamber of the eye, typically performed during surgery, can be used to illustrate it [78]. Drugs are injected directly into the anterior chamber of the eye during intracameral administration. The negative effects and first-pass metabolism of certain systemic medicines are circumvented by this local delivery method. However, it also stays away from the BAB, cornea, and conjunctiva [7]. In intracameral injections, an antibiotic is injected directly into the vitreous cavity or the anterior part of the eyeball. In order to prevent endophthalmitis caused by an eye infection that may arise during cataract surgery, it is typically performed after the procedure [13].

4.6. Retro bulbar Injection

In order to administer medication to the retro bulbar space, needles are injected via the orbital fascia and eyelid [7]. Compared to intravenous administration, retrobulbar injection of amphotericin B had greater antifungal activity [13].

5. Advanced ocular drug delivery formulations

5.1. Liposome

A liposome is a tiny vesicle, with a membrane composed of a phospholipid bilayer. Phospholipids are amphiphilic with its polar head as hydrophilic and hydrocarbon tail as hydrophobic [79]. Their spherical structures, which range in size from 0.02 to 10 μm, are composed of phospholipid bilayers encircling an inner aqueous space. Liposomes are beneficial for drug delivery because they can hold both water-loving and water-hating medicines, as well as being biocompatible

and biodegradable [80-82]. Because of its many benefits, including a longer residence time for drug absorption, liposome-nanocarrier made of a lipid bilayer that resembles a biological membrane and envelops an aqueous phase represent a viable option for ocular drug administration [83]. The ability of the liposome to load and release drugs determines how effective liposomal medication therapy is [84]. Drug-loaded liposome have been used to treat a number of anterior and posterior segment ocular problems throughout the past ten years [85]. It was discovered that the liposomal formulation was uniform and stable [86].

5.2. Nanoemulsion

Water in oil or oil in water are two immiscible liquid phases that combine to form colloidal systems called nanoemulsion [87]. They are primarily made up of the dispersion medium or the internal, dispersed, and exterior phases [88]. Lyotropic phases produced via spontaneous self-assembly rather than mechanical shear are known as microemulsions, and they produce a system that is thermodynamically stable [89]. Nanoemulsions, which range in size from 20 to 500 nm, are transparent or translucent systems that are kinetically stable but thermodynamically unstable [90]. A transparent, nano-sized device called a nanoemulsion (NE) has been developed to provide high patient adherence, longer ocular medication delivery, and decreased drug administration and side effects [91]. By increasing their water solubility, nanoemulsions are effective devices for enhancing the administration of lipophilic medications, per earlier research [92]. Nanoemulsion can be prepared using a variety of high- or low-energy processes [93]. An aqueous phase, an oily phase, a primary surfactant acting as an emulsifying agent, a cosurfactant—typically an intermediate-chain-length alkanol—and an electrolyte are often present in nanoemulsion, which are thermodynamically stable and optically transparent fine dispersions of multi-component fluids [94]. A noncorneal route is one potential medication delivery method for the created nanoemulsion [95]. Nanoemulsions (NEs), which are highly developed lipid-based colloidal dispersions, are one of these diverse drug delivery technologies that have been widely used to treat a variety of ocular illnesses [96]. In order to ease corneal drug delivery, NEs have special physicochemical qualities, such as a strong solubilizing capacity for a variety of medicines and the ability to enhance penetration [97].

5.3. Nanomicelles

In comparison to distilled water, the nanomicelles produced by the direct dissolving and thin-film hydration methods were off-white, translucent, clear, and slightly opalescent in color [98]. These nanoparticles' amphiphilic monomers, hydrophobic heads, and hydrophilic tails provide for excellent solubility, stability, and hydrophobic drug loading [99]. To improve the ocular bioavailability and effectiveness of poorly soluble medications, micellar solubilization has been extensively studied [100]. These NPs were able to enter the retina and remain close to the optic nerve for over three months after injection because these polymersomes demonstrated a longer retention period in the vitreous environment for several months [101]. Frequent dosing into ocular tissues may be limited by the long-term, sluggish drug release from these polymeric nanomicelles [102]. Colloidal dispersions of surfactants or aggregates of polymeric surfactant molecules with a relatively limited size distribution of spherically shaped particles are known as nanomicelles [103]. Depending on their form, nanoparticles can be 0D, 1D, 2D, or 3D [104]. The medication is sequestered in the lipophilic core of the nanomicelles, favoring solubilization processes [105]. Because of their superior bioavailability, biodegradable polymeric micelles have been widely used in medical therapies among the many varieties of nanocarrier-based drug delivery systems [106]. With hydrophilic shells and hydrophobic cores, nanomicelles may self-assemble [107]. Improved residence duration in the precorneal ocular pocket, improved aqueous solubility of hydrophobic drugs, and improved tissue penetration and absorption are all possible with nanomicelles [108]. Because of its obvious benefits, including their tiny size for transcorneal penetration, high drug-loading potency, and ease of manufacture, nanomicelles have garnered interest in ocular applications among these many delivery systems [109].

5.4. Nanosuspension

Nanosuspension consists of pure drug particles dispersed in water. These are colloidal dispersions of nanoscale drug particles stabilized by surfactants [110]. The most popular approach to treating both internal and external ocular disorders is topical ocular drug administration [111]. Heterogeneous, nanoscale aqueous dispersions of insoluble drug particles stabilized by surfactants are known as pharmaceutical nanosuspensions [112].The most popular approach to treating both internal and external ocular diseases is topical ocular drug administration [113]. An increase in the sedimentation rate of dispersed nanoparticles during storage may cause physical instability in nanosuspension [114].

5.5. Niosomes

In terms of stability, large-scale production, and sterilization, niosomes are superior than liposomes [115]. By assembling a range of hydrophilic moieties and molecules with a hydrophobic alkyl group, a niosomal formulation can also be defined as a self-assembly system that traps hydrophilic and/or hydrophobic active components in these vesicles [116]. Numerous researchers and pharmaceutical companies are investigating niosomes, which are bi/multi-

layer nanoparticles, for a variety of purposes [117]. Niosomes acts as prospective drug carriers as these are able to avoid the restrictions associated with liposomes, because these contain surfactants which are easily derivatized and gives higher adaptability to the vesicular structure [118].

Future perspectives

The field of ocular drug discovery has seen a lot of research in the past decade [119]. Other avenues have recently been investigated to improve the treatment of ocular cystitis [120]. Reducing intraocular pressure (IOP) and protecting the optic nerve are the main goals of treatment plans. Topical drugs such prostaglandin analogs, beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors are frequently used in first-line therapy [121]. It has been shown that the use of nanotechnology and/or stimuli responsive drug delivery can produce better drug delivery outcomes in the treatment of numerous eye diseases [122]. Due to their characteristics, including the ability to modify porosity and fiber diameters, the use of biocompatible materials, flexibility, and functionalization with various materials for specific applications. [123]. Up until now, a number of commercial polymeric subconjunctival implants have been made available on the market to treat a variety of ocular conditions. These implants include Xen Gel and Ologen [124]. Furthermore, the process and expense of future nano-commodities must be carefully taken into account in order to produce them on a big scale and manage glaucoma on a daily basis [125].

6. Conclusion

Innovative ocular drug delivery systems have transformed the treatment of various eye diseases. Despite the challenges posed by the blood-ocular barrier, researchers have made significant progress in designing novel drug delivery systems. Nanotechnology-based formulations, including liposomes, nanoemulsions, nanosuspensions, and noisome, have shown promising results in enhancing ocular bioavailability and reducing side effects. Further research is needed to overcome existing barriers and develop more efficient ocular drug delivery systems for better treatment outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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