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REVIEW ARTICLE

Ocular Drug Delivery Routes: Diseases Overview and Advanced Administration Methods

Ceren YETGIN[*], Fatma Nur TUĞCU-DEMİRÖZ[**], Sevgi TAKKA[***°]

Ocular Drug Delivery Routes: Diseases Overview and Advanced Administration Methods

SUMMARY

The eye, which is essential for vision, is susceptible to diseases such as diabetic retinopathy, age-related macular degeneration, glaucoma, and dry eye syndrome. These conditions can significantly impair quality of life and lead to blindness. Traditional treatments for eye diseases, especially eye drops, have low bioavailability and short retention times on the ocular surface. To overcome these problems, new drug delivery systems such as hydrogels, contact lenses, microneedles, and nanosystems have been developed to increase drug penetration and maintain therapeutic effects.
Drug delivery to the eye can occur via systemic, topical, intravitreal, intracorneal, subconjunctival, and suprachoroidal routes, each with different advantages and limitations. Systemic administration often results in low ocular drug concentrations and systemic side effects. Topical eye drops are easy to apply and localized, but face difficulties in absorption and retention. Intravitreal and suprachoroidal injections provide targeted delivery to the posterior segment but are invasive and carry infection risks. Subconjunctival and intracorneal routes offer less invasive alternatives with improved targeting capabilities. Nanosystems and controlled-release technologies hold promise for overcoming current barriers and aim to increase drug bioavailability, extend release times, and improve patient compliance. Overall, advancing drug delivery methods is important for effective treatment of both anterior and posterior segment eye diseases.

Key Words: *Ocular, intravitreal, nanosystems, hydrogel.*

Oküler İlaç İletim Yolları: Hastalıklara Genel Bakış ve İleri Uygulama Yöntemleri

ÖZ

Görmeyi sağlayan göz, diyabetik retinopati, yaşa bağlı makula dejenerasyonu, glokom ve kuru göz sendromu gibi hastalıklara karşı hassastır. Bu durumlar yaşam kalitesini önemli ölçüde bozabilir ve körlüğe yol açabilir. Göz hastalıkları için geleneksel tedaviler, özellikle göz damlaları, düşük biyoyararlanım ve göz yüzeyinde kısa tutulma sürelerine sahiptir. Bu durumların üstesinden gelmek için ilaç penetrasyonunu artırmak ve terapötik etkileri sürdürmek için hidrojeller, kontakt lensler, mikroiğneler ve nanosistemler gibi yeni ilaç taşıyıcı sistemleri geliştirilmiştir.
Göze ilaç iletilmesi, her biri farklı avantajlara ve sınırlamalara sahip olan sistemik, topikal, intravitreal, intrakorneal, subkonjonktival ve suprakoroidal yollarla gerçekleşebilir. Sistemik uygulama genellikle düşük oküler ilaç konsantrasyonlarına ve sistemik yan etkilere neden olur. Topikal göz damlaları uygulaması kolay ve lokalizedir ancak emilim ve tutulmada zorluklarla karşı karşıyadır. İntravitreal ve suprakoroidal enjeksiyonlar, arka segmente hedefli uygulama sağlar ancak invazivdir ve enfeksiyon riskleri taşır. Subkonjonktival ve intrakorneal yollar, iyileştirilmiş hedefleme yetenekleriyle daha az invaziv alternatifler sunar. Nanosistemler ve kontrollü salım teknolojileri, mevcut engellerin üstesinden gelmede umut vadediyor ve ilaç biyoyararlanımını artırmayı, salım sürelerini uzatmayı ve hasta uyumunu iyileştirmeyi amaçlıyor. Genel olarak, ilaç iletme yöntemlerini ilerletmek, hem ön segment hem de arka segment göz hastalıklarının etkili tedavisi için öneme sahiptir.

Anahtar Kelimeler: *Göz, intravitreal, nanosistem, hidrojel*

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[*] ORCID: 0000-0001-6451-0497, Gazi University Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey.
[**] ORCID: 0000-0002-9468-3329, Gazi University Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey.
[***] ORCID: 0000-0003-4429-9836, Gazi University Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey.

[°] Corresponding Author; Sevgi TAKKA
E-mail: takka@gazi.edu.tr

INTRODUCTION

The eye, a remarkably sensitive organ crucial for vision, comprises a complex system of interconnected structures housed within a spherical shape. Numerous diseases may occur in this sensitive structure due to internal and external factors. While diseases that occur in the eye reduce the quality of life of the patient with symptoms, such as itching, burning sensation, redness, blurred vision, or visual defects, some diseases may cause vision loss in later cases. The eye is basically divided into two: the anterior segment and the posterior segment. These segments contain specialized tissues, such as sclera, choroid, retina, cornea, lens, iris, and pupil (Kearns & Williams, 2009). The most common diseases in these specialized tissues can be listed as diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, dry eye syndrome (DES), retinitis, and various infections. DR and AMD are the leading causes of blindness in older people. According to estimates by the National Eye Institute, the prevalence of conditions like glaucoma, DR, and AMD is expected to double by 2050 (Cabrera, Wang, Reddy, Acharya, & Shin, 2019). Among the oldest and most widely used dosage forms for ocular administration are topically applied eye drops. Conventional eye drops are usually dosage forms, such as solutions, suspensions, and emulsions. However, these topically applied eye drops have a short retention time on the eye's surface (they move away from the eye surface within a few seconds after application) and their ability to penetrate the eye surface is limited (Janagam, Wu, & Lowe, 2017). For this reason, researchers turned to new research on the application of drugs to the eye. Different administration routes such as the subconjunctival route, intracorneal route, suprachoroidal route and different formulation strategies such as gel, lens, microneedle, nanosystems have been developed.

In this review common eye diseases are mentioned and drug administration methods to the eye will be evaluated with the drug delivery systems used.

Diseases of The Eye

Eye diseases are examined according to whether they are effective in the anterior or posterior segment, and a treatment strategy is developed. In general, similar drug application methods can be used for diseases with the same segment of effect. DES, glaucoma, and infections like uveitis, blepharitis, and conjunctivitis are diseases in the anterior segment of the eye. As an example of anterior segment disease, DES is mentioned in detail as a subtitle. Diseases in the posterior segment can be listed as AMD, DR, DME, vitreoretinopathy, endophthalmitis, and cytomegalovirus retinitis (CMVR). Posterior segment diseases are bleeding, tears, or inflammation that occur in the retina, usually due to bacteria, viruses, or various tissue anomalies. It can also be caused by bacteria that cause inflammation in the vitreous, such as endophthalmitis. As subheadings, AMD, DR, and CMVR, as examples of posterior segment diseases, are explained in detail and current treatments are mentioned.

Anterior Segment Diseases

Dry eye syndrome (DES)

Although the causes of DES are not fully elucidated, it can be defined as one of the most common eye disorders affecting the lacrimal glands in general, resulting in insufficient or poor-quality tear production (Dartt, 2004). DES symptoms are often observed in the form of dryness, stinging, burning sensation in the eye, redness, vision problems, and itching (Shoari, Kanavi, & Rasaee, 2021). Additionally, the causes of DES include disruption of the structure of the tear film due to abnormalities in the mucin, lipid, and protein profiles of tears, as well as inflammation of the ocular surface and tear-producing glands (Yellepeddi et al., 2015). Restasis®, Systane®, and Refresh® are commercial drugs that moisturize the eye's surface, while Hylo-Comod® and TheraTears® are commercial drugs that mimic and are used for the symptomatic treatment of DES. While these treatments may provide a short-term solution to symptomatic disorders, they will not treat the pathophysiological problem

of DES. Anti-inflammatory therapies, such as cyclosporines and corticosteroids, are used to permanently treat the disease (Thacker, Singh, Basu, & Singh, 2023). Commercially available Restasis® and Ikervis® are cyclosporine A emulsions for DES. Cequa®, approved by the FDA (Food and Drug Administration), is the first nanomicellar-based system containing cyclosporine A.

Glaucoma

Glaucoma, one of the leading causes of irreversible blindness worldwide, occurs when damage and loss occur in the retinal cells and optic nerves over time. Intraocular fluid is constantly present inside the eye and plays a role in the nutrition of the eye. Intraocular fluid is constantly renewed by being thrown out of the eye through some channels (Feng, Wang, Zhang, Zhang, & Song, 2023). Causes such as blockage in these channels cause intraocular fluid to not drain away and intraocular pressure to rise. As a result, the nutrition of the optic nerve cells is prevented and over time, the optic nerve cells are damaged and die (Weiwei Wang & Wang, 2023). As nerve cells die, vision loss occurs from the periphery to the center. When all the cells die, permanent vision loss occurs. Treatment is aimed at lowering intraocular pressure. Some of the drugs indicated for its treatment are timolol, dorzolamide, brimonidine, latanoprost, and bimatoprost. The current treatment for glaucoma is eye drops applied several times a day.

Posterior Segment Diseases

Age-related macular degeneration (AMD)

AMD affects people over the age of 50-55 and is one of the most common causes of irreversible blindness in humans (Choi, Nawash, Du, Ong, & Chhablani, 2023). The disease is divided into wet and dry AMD. Wet AMD is characterized by choroidal neovascularization, resulting from the accumulation of vascular leaks in the subretinal space caused by anomalies in the blood vessels (Grimes, Aloney, Skondra, & Chhablani, 2023). Wet AMD accounts for approximately 15% of all AMD and is the primary type of AMD that causes blindness. Pharmacological treatment of the disease is performed with anti-vascular endothelial growth factor (anti-VEGF) antibodies. Lucentic® (Ranibizumab), Avastin® (Bevacizumab), Macugen® (Pegaptanib), and Eylea® (Aflibercept) are the current treatment methods for the disease, which are administered Intravitreal at intervals of 4-6 weeks. In the dry form of AMD, drusen formation and atrophies are seen in RPE (Abidi, Karrer, Csaky, & Handa, 2022). Although scarring can cause vision loss, it progresses more slowly than the wet form and is much less likely to cause blindness. Cardiovascular disease, advancing age, and a history of smoking are thought to be factors that influence the disease (Pennington & DeAngelis, 2016; Seddon, Willett, Speizer, & Hankinson, 1996). Although there is no complete cure for dry AMD so far, various treatment strategies (vitamins, carotenoids, antioxidants) can be applied to slow the progression of the disease and relieve symptoms (Chiou, 2011).

Diabetic retinopathy (DR)

DR is one of the leading causes of blindness in the 20-74 age group and the incidence of the disease is reported to be 35% in diabetic patients (Georgiou & Prokopiou, 2023). Proliferative or non-proliferative disease may progress. Non-proliferative DR is the initial stage of DR and the most common form of the disease. It is characterized by several microvascular changes, such as increased permeability of retinal vessels, capillary occlusion, and loss of endothelial intercellular connections (Wei Wang & Lo, 2018). Proliferative DR involves the abnormal formation of new blood vessels on the surface of the retina or optic disc, followed by fibrosis (Osaadon, Fagan, Lifshitz, & Levy, 2014). Macular edema occurs because of the accumulation of subretinal fluid caused by neovascularization and the breakdown of the BRB (Im, Jin, Chow, & Yan, 2022). DME can surface at any stage of DR progression, causing blindness in later stages. Pharmacological treatment of the disease is anti-VEGF agents, as in AMD.

Cytomegalovirus retinitis (CMVR)

Human cytomegalovirus (CMV) is a common virus that is usually asymptomatic in healthy individuals. However, it can cause severe disease in immunocompromised individuals, such as patients receiving immunosuppressive therapy or infected with human immunodeficiency virus (HIV) (Landolfo, Gariglio, Gribaudo, & Lembo, 2003). More than half of adults worldwide are infected with this virus by the age of 40. If CMVR is not diagnosed early and adequately treated, it usually causes a decrease in visual acuity and may cause blindness in advanced cases (Port et al., 2017). In patients with mild CMVR, the infection begins in the retina periphery, and patients may see images, such as flies flying (Eid, Bakri, Kijpittayarit, & Razonable, 2008). In more severe cases, retinal hemorrhages, retinal tears, retinal edema, and vascular leaks are observed (Faber, Wiley, Lynn, Gross, & Freeman, 1992). Current treatment of CMV retinitis is administered by intravenous infusion or intravitreal injection. The intravenous infusion treatment procedure is the administration of ganciclovir, cidofovir, or foscarnet for at least one hour 1-3 times a day for 2-3 weeks (Teoh, Ou, & Lim, 2012). Intravitreal injection treatments on the market are the injection of ganciclovir; or foscarnet 2-3 times a week. The ganciclovir implant (Vitrasert®), developed by Bausch & Lomb, is the first intraocular sustained-release device approved for treating CMV retinitis. Intraocular administration of ganciclovir minimized systemic side effects. The ganciclovir implant consists of a non-biodegradable polymer that releases approximately 1 µg/h of ganciclovir over 5-8 months. Application of the device through an invasive procedure causes complications, such as endophthalmitis, retinal detachment, and vitreous hemorrhage (Wang, Jiang, Joshi, & Christoforidis, 2013). Additionally, since it is not biodegradable, it must be surgically removed after treatment. Considering all these difficulties in the treatment of the disease, Yetgin et al. developed ganciclovir-loaded transfersomes for topical application to provide a controlled release and increase permeability (Yetgin, Tuğcu-Demiröz, & Takka, 2022).

Novel Drug Delivery Systems Applied to The Eye

Hydrogels

Hydrogels are three-dimensional, polymeric networks with physical properties for a variety of biomedical applications, especially controlled release at a specific site (Xu, Wang, Liu, & Gong, 2023). They are formed by physical or chemical cross-linking of amphiphilic and hydrophilic polymers and have swelling properties. One of the most important characteristics of hydrogels is their physicochemical similarity with natural tissues; They are generally very soft and have an elastic texture with a high water content (Duvvuri, Janoria, Pal, & Mitra, 2007). Hydrogels can deliver drugs as microneedles to the cornea and suprachoroidal region (Than et al., 2018). Environmentally sensitive hydrogels gel upon response to a physical (temperature, growing area, etc.) or chemical (pH, ionic strength, enzyme, etc.) stimulus (Rafael et al., 2019). Thermosensitive *in situ* hydrogels can be administered by injection into the vitreous or subconjunctiva, delivered to the suprachoroidal or intracorneal region with hollow microneedles, or applied topically to the surface of the eye. The biggest advantage of *in situ* hydrogels is that they can be injected in liquid form at room temperature and become a gel inside the eye, serving as a reservoir containing the drug.

Contact Lens

The drug-loaded contact lens placed on the cornea acts as a controlled-release reservoir(Ross et al., 2019; Xu et al., 2018). Hydrophobic polymers such as silicone are added to hydrogel-based lenses, which are generally obtained by polymerization of a monomer such as hydroxyethyl methacrylate (HEMA), to increase oxygen permeability (Fan et al., 2020). Contact lenses aim to increase the transfer of the drug from the cornea by prolonging the time the drug stays on the cornea, thus increasing the possibility of the drug spreading to the intraocular tissues (Kim et al., 2023). The ability to wear drug-loaded contact lenses for a long time without the need for daily replacement provides ease of application for the patient.

Microneedle

Ocular microneedles are micrometer-sized needles designed to deliver drugs to ocular surfaces (Glover et al., 2023). There are different types of microneedles, and they can act through different mechanisms after penetrating the ocular surface. Hollow microneedles can inject drugs through these holes. With this method, liquid doses are applied (Jung, Kim, Chung, Hejri, & Prausnitz, 2022). Microneedles can be designed as a drug-loaded nonbiodegradable polymeric matrix and released throughout the ocular surface (Roy, Galigama, Thorat, Garg, & Venuganti, 2020; Suriyaamporn et al., 2023). Dissolving microneedles can dissolve at the application site and release drugs (Datta, Roy, Garg, & Venuganti, 2022; Than et al., 2018). Solid microneedles by coating the outer surface with the drug, the coating material can penetrate the ocular surface after application (Kim, Grossniklaus, Edelhauser, & Prausnitz, 2014).

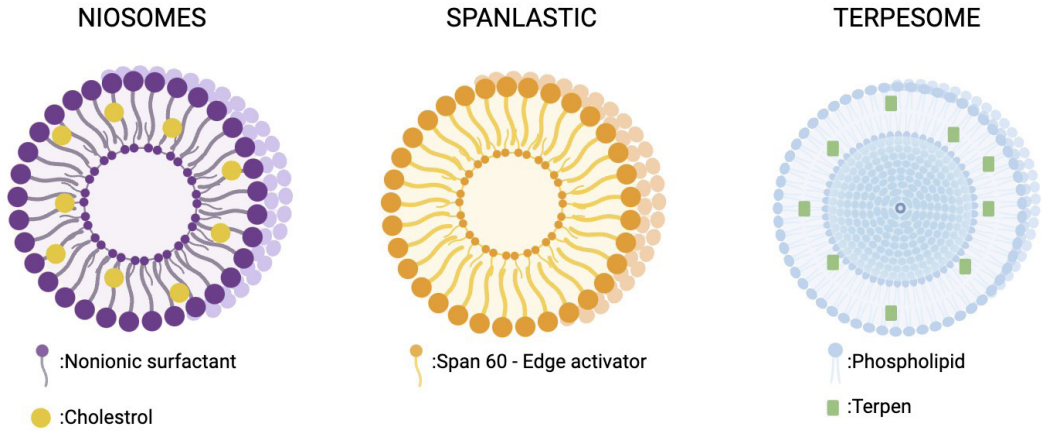

Figure 1. Representation of niosome, spanlastic, and terpesome. Created with BioRender.com.

Nanosystems

The term nanosystems include nano-sized drug carriers systems such as nanoparticles, nanoemulsions, nanosuspensions, liposomes, niosomes, dendrimers, transfersomes, and polymeric micelles (Aminu et al., 2020). These systems generally provide controlled drug release and targeted drug delivery. They are also biocompatible and biodegradable. Nanosystems release drugs to the eye in a controlled manner, allowing dosing intervals to be extended. Additionally, when flexible systems such as liposomes are applied topically, they can more easily penetrate the eye and distribute into intraocular tissues (Agarwal et al., 2016). In Table 1, studies on nanoemulsion, micelle, nanosuspension, solid lipid particle, nanofiber, transfersome, liposome, and dendrimer nanosystems observed through different application routes are presented and briefly explained. It is seen that there are many studies in the literature regarding the application of niosomes to the eyes (Abdelkader et al., 2012; Alyami, Abdelaziz, Dahmash, & Iyire, 2020; Durak et al., 2020; Zeng et al., 2016). Besides these, spanlastics and terpesomes are novel developed systems for applying drugs to the eye topically, with their flexible structure and high penetration properties (Figure 1.).

Niosomes, unlike liposomes, are vesicle-shaped drug carrier systems that contain nonionic surfactants instead of phospholipids in their structure (Villate-Beitia et al., 2018). Since nonionic surfactant provides flexibility to the structure, they are considered more flexible systems than liposomes (Rajera, Nagpal, Singh, & Mishra, 2011; Sankhyan & Pawar, 2012); In addition, nonionic surfactants do not pose a risk to the eye as they are nontoxic, biocompatible and non-immunogenic (Kazi et al., 2010). An essential feature of non-ionic surfactants is that they inhibit p-glyco-

protein, thus increasing intracellular uptake and targeting (Bhardwaj, Tripathi, Gupta, & Pandey, 2020). In the literature, generally, sorbitan esters (Span 60®, span 80®), polyoxyethylene sorbitan esters (Polysorbates (Tween 20®, tween 40®)), macrogol ethers (Brij 30®, brij 35®) are used as nonionic surfactants. Yetgin et al. developed niosomes containing ganciclovir for intravitreal injection to provide a controlled release and increase permeability (Yetgin, Çoban, Tuğcu-Demiröz, Sağır, & Takka, 2022).

Spanlastics are ultra-deformable vesicles based on nonionic surfactant and edge activator, which were introduced to the literature by Kaur and Kakkar (Kakkar & Kaur, 2011). Unlike niosomes, they do not contain cholesterol in their composition, but instead contain an edge activator that helps to form a more flexible double-layered membrane. In the study, a surfactant-based, elastic, vesicular drug delivery system (spanlastics) was developed to target the posterior segment of the eye via a topical route. The system consists of span 60® and tween 80® used as edge activators. As a result of the ex vivo permeation study, spanlastics showed two times better corneal permeability than the niosome. Two hours after topical application to rabbit eyes, fluorescent vesicles were intact in the vitreous and intraocular tissues. The results showed that spanlastics could be used as drug carriers to the posterior segment of the eye.

Terpesomes contain terpenes instead of cholesterol unlike liposome. Terpenes are natural compounds consisting of multiple isoprene (C_5H_8) units, and they accumulate in the lipophilic hydrocarbon molecules of the lipid bilayer of cells, facilitating their passage into the cell. Terpenes are used in the pharmaceutical field, and there are also eye drops on the market called Ectodol® (4-terpene-ol, limonene, eugenol), which contain terpenes to increase ocular permeability (Reyes-Batlle et al., 2021).

There are older and new studies in which terpenes, such as terpene-4-ol, eugenol, limonene, and cineole are used as penetration enhancers in ocular systems (Afouna, Khedr, Abdel-Naim, & Al-Marzoqi, 2010; Anand, Anbukkarasi, Thomas, & Geraldine, 2021; El-Gendy, Mansour, El-Assal, & Ishakb, 2020).

Younes et al. developed cubosome containing sertaconazole nitrate (STZ) targeted to the cornea and added monoterpene (limonene) into the formulation as a penetration enhancer (Younes, Abdel-Halim, & Elassasy, 2018). The ex vivo corneal permeability study indicated that the formulation increased the corneal permeability of STZ. Additionally, studies in rabbits reported good in vivo corneal tolerability and superior in vivo corneal uptake compared to STZ suspension.

Table 1. The administration routes of the drugs to the eye and the drug delivery systems

Administration Route	Drug Delivery System	Active Pharmaceutical Ingredient	Targeted Area	In Vivo/Ex Vivo Studies	References
Topical	Self-nanoemulsifying system	Brimonidine tartrate	Anterior segment	The formulation showed an increase in permeation of about 2.35 times that of the marketed formulation.	(Vikash et al., 2023)
Topical	Micelle	Flurbiprofen	Anterior segment	3D corneal spheroids showed an increase in transcorneal penetration efficiency. A study with corneal epithelial cells indicated prolonged retention of the drug on the ocular surface. According to in vivo study, showed a better ocular anti-inflammation effect.	(Weng et al., 2018)
Topical	Gel containing niosome	Flurbiprofen	Anterior segment	According to an in vivo rabbit study, the formulation showed higher C_{max} and AUC_{0-12} values than those of the solution. The formulation showed rapid anti-inflammatory effects in the inflamed.	(El-Sayed, Hussein, Sarhan, & Mansour, 2017)
Topical	Insert containing nanofiber	Besifloxacin	Anterior segment	Ex vivo transport studies reported that the insert possessed a drug delivery level close to that of the marketed drug. Single-dose application of inserts was effectively reduced bacterial keratitis in rabbit eyes compared to multiple dosing with the marketed drug.	(Polat et al., 2020)
Topical	Electrolyte-sensitive in situ gel containing transfersome	Natamycin	Anterior segment	Transcorneal permeability was significantly higher than the drug suspension. The ocular disposition studies in rabbits demonstrated the superiority of the formulation in terms of drug delivery compared to plain transfersome.	(Janga et al., 2019)
Topical	Contact lens	Betaxolol hydrochloride	Anterior segment	The *in vivo* conjunctivitis treatment of rabbits for 72 h showed that the lens presented a better therapeutic effect than one dose administration of drug solution per day.	(Wei et al., 2020)
Topical	Chitosan film	Brimonidine tartrate	Anterior segment	The permeability of *ex vivo* rabbit corneas was determined to be $1.62\times10^{-}5$ cm/s. They reported that this is much higher than the permeation coefficient from many previous systems.	(Li, Wang, Gui, & Yang, 2020)
Topical	Hydroxypropyl methylcellulose (HPMC)-Eudragit film	Chloramphenicol	Anterior segment	Only *in vitro* studies.	(Boateng & Popescu, 2016)
Topical	Electrospun nanofiber insert Solvent-cast polymeric insert	Dexamethasone	Anterior segment	Only *in vitro* studies.	(Bhattarai et al., 2017)
Topical	Chitosan insert	Bimatoprost	Anterior segment	*In vivo* studies in rabbits showed have sustained reduction of intraocular pressure (IOP) for six days with IOP of 15.9 mmHg and 14.6 mmHg for different inserts at 120 h.	(Jadhav & Yadav, 2022)
Topical	Hyaluronic acid-poly vinyl alcohol (PVA) film	Dexamethasone Levofloxacin	Anterior segment	*Ex vivo* study with porcine eyes demonstrated capability to deliver drugs to the cornea and across the sclera, to potentially target the posterior eye segment.	(Ghezzi et al., 2023)
Topical	Nanofibers-based thermo-responsive gel	Fenofibrate	Posterior segment	According to an *ex vivo* drug permeation study across goat cornea, confocal microscopy showed better penetration efficiency of formulation compared to plain rhodamine B solution.	(Pandit et al., 2023)
Intravitreal injection	Liposome	Sunitinib	Posterior segment	According to a fundus fluorescein angiography study, liposomes revealed an inhibitory effect on neovascularization in a mouse model while the intravitreal injection of sunitinib solubilized with cyclodextrin was inefficient.	(Tavakoli et al., 2022)

Intravitreal injection	Microparticles	Sunitinib	Posterior segment	MPs suppressed choroidal neovascularization in mice for six months in rabbits.	(Tsujinaka et al., 2020)
Intrascleral	Nanosuspension-loaded dissolving microneedle	Triamcinolone acetonide	Posterior segment	*Ex vivo* transscleral deposition studies with porcine sclera showed that deposited into the sclera formulation was 4.5-fold higher than drug-loaded microneedle.	(Wu et al., 2022)
Intracorneal	Dissolving microneedles	Model drug	Anterior segment	Microneedles were applied to mice with keratitis where they were observed to be successfully delivered to the inside of the cornea. Study results showed that the therapeutic efficacy of the microneedles persisted for 7 days.	(K. Lee et al., 2018)
Intracorneal	Hyaluronic acid-based microneedle	DC-101	Posterior segment	*In vivo* studies in mice showed a reduction in neovascularization.	(Than et al., 2018)
Subconjunctival injection	Injectable gel-based dendrimer	Dexamethasone	Anterior segment	*In vivo* study in rats showed favorable clinically relevant outcomes, with reduced central corneal thickness and improved corneal clarity compared to controls treated with the free drug and placebo gel.	(Soiberman et al., 2017)
Subconjunctival injection	Dendrimer	Dexamethasone	Anterior segment	In an *in vivo* study using a rabbit model, the formulation was reported to suppress lacrimal gland inflammation.	(Lin et al., 2018)
Subconjunctival injection	Chitosan coated nanoparticle	Bevacizumab	Posterior segment	A pharmacokinetic study in rats, along with confocal microscopy, showed a higher concentration of the drug and better penetration of the formulation compared to the drug solution. In a retinopathy model, it demonstrated a greater reduction in VEGF levels compared to both topical and intravitreal administration of the formulation.	(Pandit, Sultana, & Aqil, 2021)
Suprachoroidal injection	Poly (lactic-co-glycolic acid) (PLGA) microparticle	Acriflavine	Posterior segment	Intravitreal injection of microparticles in mice suppressed choroidal neovascularization for at least 9 weeks, while suprachoroidal injection in rats suppressed it for at least 18 weeks.	(Hackett et al., 2020)
Suprachoroidal injection	*In situ* hyaluronic acid-polyethylene glycol (PEG) hydrogel	Bevacizumab	Posterior segment	The release time of the formulation was evaluated through *in vivo* studies in rabbits.	(Jung et al., 2022)

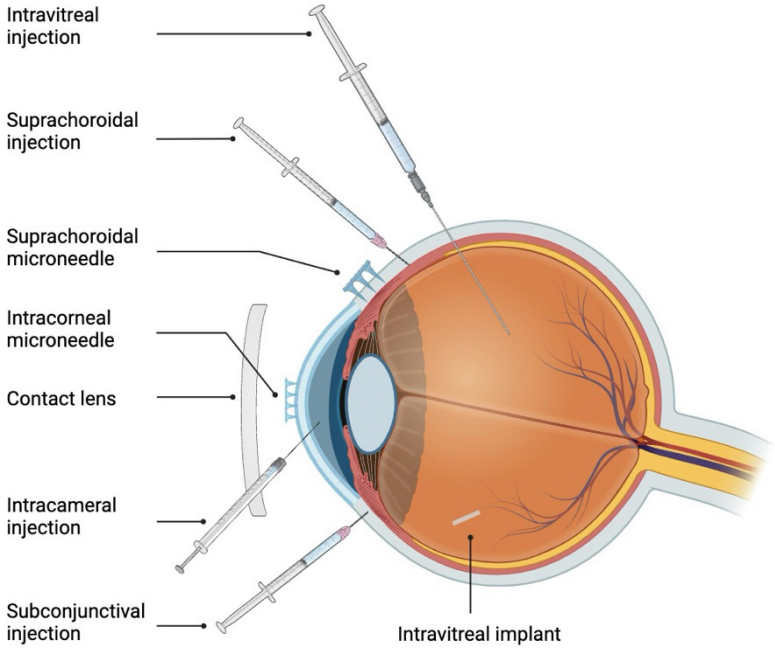

Figure 2. Routes of drug administration to the eye and drug delivery systems. Created with BioRender.com.

Route of Drug Administration to the Eye

Considering the literature studies, drugs can be administered to the eye through systemic, topical, intravitreal, intracorneal, subconjunctival, and suprachoroidal routes. The methods of drug administration approved by the FDA or supported by the literature for ocular delivery are depicted in Figure 2., along with the sites of application. In Table 1, literature studies are presented with dosage forms and the routes of drug administration to the eye. Furthermore, in subtenon, retrobulbar, and peribulbar injection methods, the drug is administered to the tissues around the eye or intramuscularly. These methods are generally preferred to provide regional anesthesia in eye surgeries (Agban, Thakur, Mugisho, & Rupenthal, 2019). In the posterior juxtascleral route, the drug is administered adjacent to the sclera, targeting the posterior segment of the eye. This route enhances application by delivering medication specifically to the posterior segment (Kaiser, Goldberg, Davis, & Group, 2007). The advantages and disadvantages of ocular drug administration methods are presented in Table 2. This section evaluates the routes of drug administration to the eye concerning drug forms, and literature examples are provided.

Table 2. Advantages and disadvantages of ocular drug delivery method.

Administration Route	Advantages	Disadvantages
Systemic	Provides widespread distribution; effective on the entire body. (Especially in cases where the condition, such as a viral infection, spreads systemically.)	May affect non-target organs; low drug concentration in the eye.
Topical	Easy to apply; localized effects; widely used.	Limited absorption due to tear drainage and corneal barrier.
Intravitreal	Direct delivery into the eye; effective for posterior segment diseases.	Requires an injection; risk of infection.
Intracorneal	Direct effect on corneal diseases.	Invasive method; may cause discomfort during application.
Subconjunctival	Direct drug delivery to tissues around the eye; broad distribution.	May require local anesthesia; irritation can occur after application.
Suprachoroidal	Targeted drug delivery for posterior segment diseases.	Difficult to apply; invasive with a risk of infection.
Subtenon/ Retrobulbar	Administered around the eye, often used for local anesthesia during surgery.	Risk of anesthesia complications; discomfort and infection risk in intramuscular applications.
Posterior Juxtascleral	Allows direct drug delivery to the posterior segment; specific targeting.	Only used for posterior segment treatments; the technique can be difficult and invasive.

Systemic Application

When drugs are administered systemically, they distribute throughout the body via the bloodstream. Consequently, systemic drug administration often requires high doses to achieve therapeutic effects in the target area. However, this approach carries a high risk of side effects and toxicity due to the need for elevated drug concentrations throughout the body. Moreover, the eye's lower vascularity compared to other organs poses a challenge, and the blood-retinal barrier (BRB) restricts the transfer of drugs to the retina. Only a small fraction of the drug administered systemically permeates through the inner BRB and reaches the vitreous, where it exerts its effects (29). Visudyne® (Verteporfin), indicated for neovascularization due to age-related macular degeneration (AMD), represents the first clinically validated liposomal photosensitizer system (Thrimawithana, Young, Bunt, Green, & Alany, 2011). It is administered via intravenous infusion over 10 minutes. Approximately 15 minutes after drug application, verteporfin is activated by a non-thermal red laser (50 J/cm2, 83 sec) aimed at the relevant area in the posterior segment of the eye. If necessary, treatment can be repeated every 3 months. Verteporfin has hydrophobic properties, leading to its tendency to aggregate in hydrophilic environments. Therefore, it is loaded into the lipophilic double-layered membrane of liposomes (Ghosh, Carter, & Lovell, 2019). Cymevene®, indicated for cytomegalovirus retinitis (CMVR), is administered via intravenous infusion over at least one hour, 1-3 times daily for 2-3 weeks. High doses of antiviral agents are required to achieve therapeutic levels in the posterior segment through intravenous infusion. Consequently, severe systemic side effects such as neutropenia, anemia, and thrombocytopenia may occur (Hughes, Olejnik, Chang-Lin, & Wilson, 2005). Additionally, long-term treatment may increase the risk of bone marrow toxicity and the development of viral drug resistance (Gilbert & Boivin, 2005).

Local Application

Topical Application

Applying medication to the eye's surface in the form of eye drops is the most common and traditional method. While eye drops are widely used for ocular treatment, they have limitations such as low bioavailability and short retention time on the ocular surface due to factors like tearing and reflexive blinking. Typically, liquid medications applied as eye drops are washed away from the eye's surface within about 5 minutes after application. Consequently, less than 3% of the administered dose manages to penetrate through the eye's surface and reach the intraocular

tissues. (Kearns & Williams, 2009). Although topical application is effective for treating diseases in the anterior segment of the eye, it poses challenges in reaching the posterior segment with traditional eye drops.

In cases where a disease primarily affects the anterior segment of the eye, enhancing the effectiveness of topically applied drugs can be crucial. Here are some strategies to achieve this:

1. The time the formulation remains on the eye surface can be increased. For this purpose, formulations can be designed to increase viscosity (e.g. gel, ointment) (El-Sayed et al., 2017; Fang et al., 2021; Gupta et al., 2007; Shi et al., 2019; Srividya, Cardoza, & Amin, 2001) or increase mucoadhesive properties (Swain et al., 2023; Verma et al., 2019; Zeng et al., 2016).

2. Strategies to increase penetration can be developed by adding penetration enhancing substances to the formulation (Afouna et al., 2010; Afouna, Khedr, & Al-Marzoqi, 2009; Asim et al., 2021; El-Gendy et al., 2020) or by choosing high elasticity nanocarriers.

When commercial drugs are evaluated, eye drops in the form of solution, suspension, or emulsion are the usual preparations. Besides, dosage forms in the form of ointment or gel and applied topically are also available in the market. Through drug forms that can be applied topically to the eye, such as drug-loaded contact lenses, film, insert, or in situ gel, retention time on the eye's surface can be extended, and as a result, its transfer rate can be increased (Gade, Nirmal, Garg, & Venuganti, 2020; R. C. Li et al., 2020; Maulvi et al., 2017; Pollard et al., 2023; Sarmout, Xiao, Hu, Rakhmetova, & Koole, 2023).

In recently study, it was reported that spanlastic containing levofloxacin increased the penetration of the drug through the rabbit cornea by approximately 1.5 times compared to the drug solution (Agha, Girgis, El-Sokkary, & Soliman, 2023).

In a different recent study, terpesomes containing fenticonazole nitrate were developed as an ocular carrier system. In formulations containing a single terpene species, fenchone, eugenol, or limonene were used as terpenes. As a result of the *in vivo* study, it was reported that terpesomes loaded with fenticonazole nitrate optimized for drug suspension remained on the eye surface significantly longer than the drug suspension (Albash, Al-Mahallawi, Hassan, & Alaa-Eldin, 2021).

Subconjunctival Route

In this method, the drug solution is administered under the conjunctiva by implant or liquid injection. Since the application area is close to the surface, a smaller needle is used compared to intravitreal injection, and applying a form of drug, such as an implant, is much easier. In general, there is no damage to the tissues, and it is a less invasive and painless method (Soiberman et al., 2017). Administration via the subconjunctival route eliminates the conjunctival epithelial barrier, which is rate-limiting for the permeation of water-soluble drugs. There are studies on hydrogel, in situ hydrogel, solution or implant placement under the conjunctiva (Lin et al., 2018; Misra et al., 2009; Pandit et al., 2021; Voss et al., 2015).

Rong et al. developed a hydrogel system containing insulin-loaded chitosan nanoparticles and applied it to rats with DR by subconjunctival injection (Rong et al., 2019). After subconjunctival injection, it was observed that structural damage in the retina, retinal cell apoptosis, and VEGF protein expression decreased significantly. There was no apparent damage to retinal function, structure, or neurons after injection. As a result, they reported that subconjunctival injection is safe.

Intravitreal Route

The intravitreal route is the administration of the drugs directly into the vitreous. This method provides the highest amount of drug reaching the vitreous with minimal systemic absorption and has been used in clinical practice for a long time. However, since it is an invasive method, it may cause some ocular complications. Inserting a needle through the sclera or making an incision here may cause bacterial inflammation. In

these patients, cataract formation, increased intraocular pressure and glaucoma, choroidal hemorrhage, endophthalmitis, vitreous hemorrhage, retinal breaks, and retinal detachment (separation of the retinal nerve layer from the underlying pigment epithelial layer) may develop over time (Thrimawithana et al., 2011). When the literature is examined, studies are on developing intravitreal implants that are biodegradable and have an extended release period (Bendicho-Lavilla et al., 2023; Guerra et al., 2023). Intravitreal injections on the market are in solution form and dose intervals are short. Examples of these are presented in the diseases of the eye section. To extend the release time of a formulation administered by intravitreal injection, in situ gels can be used or the drug can be loaded into a nanocarrier (Famili, Kahook, & Park, 2014; S. Lee et al., 2023; López-Cano et al., 2021).

Tsujinaka et al. self-aggregating microparticles containing the VEGF receptor inhibitor sunitinib have been developed (Tsujinaka et al., 2020). *In vivo* experiment results indicated that the effect persists for 6 months after a single dose of microparticles injection containing sunitinib. Factors influential in the sustained release were the sustained release of sunitinib from microparticles and the formation of a solid depot by microparticles containing sunitinib.

Intracorneal Route

Drugs can be applied into the cornea via microneedles. Than et al. developed a tape carrying microneedles containing a series of drugs, which is applied to the cornea by the patient (Than et al., 2018). In the study, a controlled-release hyaluronic acid-based microneedle containing DC101, an anti-angiogenic monoclonal antibody, was designed. The *in vivo* study results reported approximately 90% reduction in neovascular area in eyes treated with the microneedle they developed. An eye patch applied over the cornea is an easy and non-invasive method to increase patient compliance. Such intracorneal drug delivery strategies promise the ability to easily treat many eye diseases at home.

Suprachoroidal Route

Suprachoroidal space (SCS) is the space between the sclera and choroid surrounding the posterior segment of the eye. Drug delivery to the SCS is a new and exciting way to deliver medication to the posterior segment. It does not involve risks related to penetration into the eye and can accommodate up to 1 mL of fluid. While BRB is not omitted in this method, it may be the preferred method for administration of drugs targeting the RPE. Drug delivery from SCS to the vitreous has been shown to decrease as drug lipophilicity and molecular weight increase. SCS can be injected with small-sized microneedles, an implant can be applied or a catheter can be placed (Bhattacharyya et al., 2022; Hackett et al., 2020; Jung et al., 2022; Patel et al., 2012; Sher, Goldberg, Bubis, Barak, & Rotenstreich, 2021). In 2004, microcannulated sclerotomy for SCS was approved by the FDA (iScience catheter, Ellex Medical, Adelaide, Australia) (FDA, 2004). Clinical trials testing the safety and effectiveness of microneedle injections into the SCS are ongoing. Studies to date reported the safety and effectiveness of this procedure and that it can be performed under local anesthesia (Chiang, Jung, & Prausnitz, 2018). Ongoing clinical trials testing the safety and effectiveness of microneedle injections into the SCS have shown that this procedure is safe and efficient and can be performed under local anesthesia.

Jung et al. developed a hyaluronic acid crosslinked with poly(ethylene glycol) diacrylate hydrogel containing bevacizumab (Bev-HA) and applied it to SCS in rabbit eyes with microneedle (Jung et al., 2022). They reported that Bev solution cleared from SCS within 5 days, even if formulated with high viscosity. To extend the release time, they synthesized in situ Bev-HA hydrogel. *In vivo* studies in rabbits reported Bev release from the Bev-HA to be >6 months. The Bev-HA hydrogel was well tolerated as assessed by clinical, histological analysis, fundus imaging, intraocular pressure measurement, and examination.

CONCLUSION

Drug delivery to the eye can be administrated via topical, periocular, intravitreal, and other intraocular routes, depending on the disease area. Although the intravitreal route is the most effective method for diseases affecting the posterior segment, it has many side effects and being invasive is a great difficulty. Studies are being carried out to extend the release time of the formulation applied intravitreally and to reduce the side effects caused by drug administration into the vitreous. Nanosystems are promising in this regard. Drug administration via the subconjunctival and suprachoroidal route can be considered a less invasive and safer method. Effective and safe drug carrier systems can be developed by applying a controlled release system with an extended dose range via subconjunctival route, suprachoroidal route, and intracorneal route.

Considering the topical method, it is a method that is easy to apply because the patient can apply it herself without the need for a healthcare institution and has a low probability of side effects since it is not an invasive method. It is aimed at developing topically applied drug carrier systems that have an extended stay on the eye surface and can pass through the eye surface for anterior and posterior segment diseases. The primary issue in topical application is the low ocular residence time, leading to a significant part of the drug being removed before exerting its effect. In connection with this matter, with penetrating and flexible nano drug carrier systems, the bioavailability of the topically applied drug can be increased by extending its release time and increasing its permeability.

AUTHOR CONTRIBUTION STATEMENT

Determination of the subject (CY, FNT, ST). Literature research and writing (CY). Reviewing the text (FNT, ST). Supervision (ST).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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