Chapter

Recent Strategies for Ocular Drug Delivery: Promises and Challenges

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Abstract

Ocular diseases include various anterior and posterior segment diseases. Due to the unique anatomy and physiology of the eye, efficient ocular drug delivery is a great challenge to researchers. The emerging nanoscience is playing an important role in the development of novel strategies for ocular disease management. Various active molecules have been designed to associate with nanocarriers to overcome ocular barriers and interact with certain ocular tissues. In this chapter, highlights will be made on barrier to intraocular delivery, general pathways for ocular absorption, and factors affecting intraocular bioavailability. The recent attempts of nanotechnology for treating anterior and posterior ocular diseases will be explored. This will include nanomicelles, nanoparticles, nanosuspensions, vesicular systems, in situ gel, dendrimers, contact lenses, implants, microneedles, and cell-based delivery systems. In addition, gene-based ocular delivery systems will be discussed. In this chapter, we will also provide a comprehensive overview of drug-device combinations used for ocular diseases such as glaucoma, dry eye disease, infections, and inflammations. Furthermore, drug delivery devices for ocular surgeries are discussed. Finally, challenges and future prospective of ocular delivery systems will be explored.

Keywords: nanocarriers, microneedles, gene, cell-based therapy, ocular devices

1. Introduction

Globally, eye diseases and consequential visual impairment are considered as the nation's absolute threat, compromising physical and mental health. As reported by the World Health Organization, worldwide, the number of people suffering from visual impairment is more than 2.2 billion [1]. Additionally, an analysis by Lancet Glob Health stated that, as population gets older, the number of moderate to severe vision impairment and blindness cases would increase to 600 million and 115 million by 2050, respectively [1].

Anatomically speaking, the human eye consists of two regions: the anterior segment including aqueous humor, cornea, conjunctiva, iris, ciliary body, and lens. Whereas the posterior segment includes vitreous humor, retina, choroid, and optic nerve. In other words, the eye consists of several attached tissue layers. In the anterior segment, the collagenous layer providing the mechanical strength is the cornea that is responsible for focusing the light on the retina. In the posterior segment, the opaque collagenous layer is the fibrous sclera. The middle layer in the anterior segment is called Uvea, which involves the iris and ciliary body. The ciliary

body contains smooth muscles that produce the aqueous humor. The latter has many functions such as suppling nutrients to the avascular tissues in the anterior segment, maintaining the intraocular pressure, and drainage of waste from lens and cornea. In the posterior segment, the middle layer comprises enormous network of capillaries called vascular choroid that provides the retina with all the essential nutrients. The innermost layer is the retina, which transports the light signal to the brain [2].

Based on the aforementioned background, the eye comprises unique anatomical and physiological barriers hindering effective intraocular drug delivery that would be discussed in the following section.

2. Barriers to intraocular drug delivery

The eye consists of numerous barriers and defense mechanisms to protect it from the environment. Barriers to intraocular drug delivery are categorized as physiological and anatomical. Physiological barriers involve blinking, tear turn over and naso-lachrymal drainage. Whereas anatomical barriers include various static and dynamic barriers that impede drug entry into the eye segment [3].

In the anterior chamber, the static barriers are corneal epithelium, stroma, and blood aqueous barrier (BAB). Whereas dynamic barriers are the conjunctival blood and lymph flow along with tear drainage. BAB consists of tight junctions between the non-pigmented epithelial cells in the ciliary body, junctions of the iridial tissues as well as the blood vessels of the iris. BAB restricts the movement of molecules from blood to aqueous humor through iris ciliary capillaries [3].

In the posterior chamber, static barriers are sclera, bruch's membrane in choroid, and blood retinal barrier (BRB), which involves tight junctions in retinal capillary endothelial cells and retinal pigmented epithelium. While dynamic barriers comprise the drainage of administered drugs by blood and lymphatic vessels [3].

It is worth mentioning that the blood ocular barrier consists of both BAB and BRB. Its function is to maintain optimum intraocular pressure via preserving the fluid composition of the eye [3].

Mucin, covering the corneal and conjunctival surfaces for protection, constitutes an additional ocular barrier for diffusion of large drugs molecules. Moreover, the expression of many efflux pumps (P-glycoprotein, multidrug-resistant protein, and breast cancer resistant protein) on the capillary endothelium represents another barrier limiting drug ocular bioavailability [3].

3. General pathways for ocular absorption

Absorption of drug into the inner eye occurs through two major pathways, either corneal or non-corneal. The corneal route is considered as the major pathway for ocular drug absorption after topical administration. This route involves the penetration of the administered drug through the corneal epithelium. Afterward, the drug gets to the corneal stroma, endothelium, and aqueous humor. Subsequently, the drug may either be eliminated by the drainage of the aqueous humor through trabecular meshwork into Schlemm's canal, or it may reach the iris-ciliary body blood vessels and then enter the systemic circulation. Additionally, drugs also may distribute to a lesser extent to the lens and vitreous humor from the aqueous humor [4].

On the other hand, the non-corneal route for ocular drug absorption encompasses the passage of drugs across the conjunctiva and sclera. After that, they reach the ciliary body followed by the iris without access to the aqueous humor. Concerning the non-corneal route, it is important to highlight that the conjunctiva contains numerous blood vessels. Accordingly, a large portion of the drug dose is suspected to enter the blood circulation rather than diffusing into the sclera [4].

The next section designates the different factors affecting intraocular drug bioavailability, which makes ocular delivery challenging.

4. Factors influencing intraocular drug bioavailability

Poor ocular bioavailability of the topically administered drugs represents a main concern associated with ophthalmic dosage forms. The presence of numerous physiological and anatomical constraints resulted in absorption of a very small portion of the topically instilled dose. The several factors affecting drug ocular bioavailability will be discussed in detail in the following subsections.

4.1 Precorneal fluid drainage

It constitutes one of the major reasons for poor ocular drug absorption. A large portion of the topically instilled volume (~80–90%) is drained into the nasolacrimal duct. The nasolacrimal drainage aids in preserving a fixed volume of the precorneal fluid (~7–10 μl). Consequently, it represents a natural protective physiological mechanism that is responsible for loss of any excess fluid.

The factors affecting the drainage rate include the Instilled volume, viscosity, pH, tonicity, and drug type. Concerning the instilled volume, the larger the volume, the more the drainage. For viscosity, increasing viscosity of an instilled dose results in prolongation of its ocular residence time. Regarding the pH effect, instillation of alkaline or acidic solutions gives rise to excessive lacrimation and hence loss of the administered medication. Therefore, the pH of the ophthalmic formulations must be adjusted to 7–7.7 to mimic the physiological pH of tear fluid (7.4). Regarding tonicity, preparations intended for ocular use should be isotonic with tear fluid. Severe irritation with excessive tear secretion occurs upon instillation of hypertonic solutions. As for drug type, it was reported that certain drugs can affect tear secretion. For instance, epinephrine can induce lacrimation, while tetracaine can suppress it [3].

4.2 Binding of drugs to tear proteins or melanin

The protein content of the tear fluid is ~0.7% of total body protein. Binding of drugs to tear proteins may bring about a significant decrease in drug concentration reaching the target site [3].

Concerning melanin binding, certain drugs such as ephedrine and timolol were reported to possess a high binding affinity to melanin pigment present in the iris and ciliary body, thereby lowering their ocular bioavailability [3].

4.3 Drug absorption to the systemic circulation

It may occur either directly from the conjunctival blood capillaries or after drainage of the instilled solution to the nasal cavity. Accordingly, this can result in

remarkable drug loss into the systemic circulation, hence lowering its ocular bioavailability [3].

4.4 Corneal barrier

Cornea is a complex tissue that is made of six different layers. It plays an essential role in decreasing drug ocular bioavailability acting as a physical constraint impeding drug permeability [3].

4.5 Drug metabolism

Several metabolizing enzymes (cytochrome P450, cyclooxygenases, aldehyde oxidases, and monoamine oxidases) are expressed in various ocular tissues as cornea, lens, iris, ciliary body, and retina. These enzymes have the ability to metabolize the instilled drugs, decreasing their ocular bioavailability [3].

5. Nanocarriers for ocular drug delivery

As illustrated previously, drug delivery to the eye is challenging for formulators owing to its barrier nature. Additionally, the chronic nature of various ocular diseases necessitates frequent administration of drugs. In this context, nanocarriers are elaborated to overcome the limitations of conventional ocular formulations as well as guarantee controlled and targeted drug delivery [5].

Nano delivery systems are colloidal systems with a particle size in the nanometer range (10–1000 nm) and a certain surface charge. They have various biomedical applications depending on their size. Additionally, their surface charge contributes to their retention at the specific site. For example, the negative charge on the surface of both the corneal and conjunctival tissues paves the way for cationic nanoparticles to be interacted to these tissues via electrostatic attraction. Consequently, increasing their residence in the anterior segment of the eye [5].

Based on the aforementioned background, nanocarriers are predicted to overcome the numerous ocular barriers thanks to their unique nano-size and surface characteristics. The different nanocarriers and their targeting ability for ocular drug delivery will be presented in detail in the following subsections.

5.1 Nanomicelles

Nanomicelles are nanostructures (10–100 nm) formed spontaneously in the aqueous environment by the self-assembly of certain block copolymers having amphoteric properties. They have many advantages for ocular drug delivery such as enhancing the aqueous solubility and stability for the hydrophobic drugs, prolongation of drugs' ocular retention, improving drug corneal permeability, and modification of drug release [1]. The amphoteric nature of the nanomicelles facilitates their penetration through both lipophilic (corneal epithelial and endothelial cells) and hydrophilic matrices. As well, their small size permits their uptake by the corneal cells. Moreover, they were reported to improve drug bioavailability by inhibiting the efflux transporter proteins by the use of the proper surfactants in their backbone structure [1, 6].

Accordingly, nanomicelles have attracted increasing attention as noninvasive ocular drug delivery systems owing to their unique properties.

Concerning the targeting potential of the nanomicelles to the anterior segment of the eye, several studies have reported that the administration of the drug in a nanomicellar formulation rather than ointment, suspension, or emulsion formulations resulted in improved corneal, trans-corneal, and conjunctival uptake [7]. The clear Cyclosporine-A nanomicellar formulation prepared by Cholkar et al. [8] for treatment of dry eye disease in rabbits was approved by the United States Food and Drug Administration (FDA) in 2018. Cequa® (cyclosporine-A 0.09%) is a unique nanomicellar formulation, that is a clear solution approved for clinical use. In another study, Safwat et al. [9] prepared poly ethylene glycol-block-poly lactic acid nanomicelles containing triamcinolone acetonide. The selected formulations were dispersed into chitosan hydrogel to evaluate their anti-inflammatory potential in a carrageenan-induced ocular inflammatory rabbit model. The prepared micelles had good in-vitro characteristics (size: 176.80 ± 2.25 nm, drug loading: 15–25%, sustained drug release over a period of 1 week and 10-fold increase in drug aqueous solubility). Furthermore, the elaborated micellar hydrogel formulation resulted in complete disappearance of the corneal inflammatory signs in tested rabbits based on histopathological examination [9].

For targeting posterior segment of the eye, Xu et al. [10] prepared chitosan oligosaccharide-valylvaline-stearic acid nanomicelles to actively target peptide transporter-1 for topical ocular dexamethasone delivery to treat macular edema. Fluorescence microscopical images of frozen sections for various ocular tissues from tested animals indicated that the coumarin-6 labeled nanomicelles reached the posterior segment mainly through conjunctival route. Following topical administration, dexamethasone concentration in the posterior segment reached the therapeutic levels at 0.5 h and 1 h and can still be detected at 1.5 h post administration [10].

5.2 Polymeric nanoparticles

Polymeric nanoparticles made of biodegradable polymers and having sizes from 10 to 100 nm are widely used in ocular therapy. These nanocarriers consist of various polymers, in which the drug may be just adsorbed on the surface or incorporated into the polymer matrix. Polymeric nanoparticles offer numerous advantages for ocular delivery, which mainly related to their unique properties, as biodegradability, biocompatibility, and muco-adhesiveness. Therefore, pericorneal retention time is prolonged, and hence drug bioavailability is improved. For that purpose, many researchers prepared ocular drug delivery systems coated with mucoadhesive polymers (poloxamers, hyaluronic acid, chitosan, sodium alginate, among others) to increase drug ocular bioavailability [11].

For instance, Radwan et al. [12] prepared bovine serum albumin nanoparticles coated with chitosan by the desolvation method for the topical delivery of tetrandrine for management of glaucoma. The optimized formulation had a size of 237.9 nm and zeta potential of 24 mV and high % EE > 95% with a sustained-release drug profile. Moreover, the prepared nanosystem exhibited a significantly enhanced ex -vivo transcorneal permeation with improved in-vitro antioxidant and antiproliferative action on corneal stromal fibroblasts. In addition, the elaborated formulation succeeded to increase the drug bioavailability in the aqueous humor of treated rabbits by twofold compared with the free drug together with a remarkable reduction in intraocular pressure in a rabbit model for glaucoma.

In order to achieve active targeting to the posterior eye chamber for treatment of diabetic retinopathy, apatinib -loaded bovine serum albumin nanoparticles coated

with hyaluronic acid were developed [13]. Hyaluronic acid was exploited to achieve a dual role as a mucoadhesive polymer with capability to target the CD44 receptors expressed on retinal cells. The elaborated nanoplatform had good colloidal and mucoadhesive properties with no in-vitro cytotoxicity on rabbit corneal epithelial cells. The in-vivo evaluation revealed the ability of the topically instilled nano formulation to alleviate the corneal histopathological manifestations in diabetic retinopathy rat model with improved retinal accumulation as evidenced by confocal microscopy [13].

5.3 Lipid-based nanoparticles

Solid lipid nanoparticles (SLNs) are nanocarrier systems (10–500 nm) consist of lipids dispersed in an aqueous surfactant system. They are reserved for the delivery of hydrophobic drugs. The main method of their preparation depends on solidification of the produced nanoemulsion. SLNs were reported to have enhanced retinal permeation in addition to prolongation of drug ocular retention [5].

Nanostructured lipid carriers (NLCs) were introduced as next-generation lipid nanocarriers to overcome the limitations of SLNs, such as low drug loading capacity due to its expulsion by crystallization of lipids. NLCs are composed of both solid and liquid lipids and thereby have asymmetric structure, which prevents drug expulsion and brings about comparatively slower drug release [5].

The aqueous dispersion of lipid nanoparticles is mainly applied topically for delivery of the entrapped medication to the anterior segment of the eye. The aim of the use of this nanocarrier is to prolong retention time at surface of the cornea by muco-adhesion as well as enhance corneal permeation.

For this purpose, cationic lipid nanoparticles were prepared by using cationic lipids [14, 15] that can interact with the negatively charged mucus. Additionally, coating lipid nanoparticles with bio-adhesive polymers such as hydroxypropyl methyl cellulose [16], hyaluronic acid [17], and chitosan [18–20] was also employed.

For example, Wang et al. [18] prepared chitosan-coated solid lipid nanoparticles loaded with methazolamide for glaucoma treatment. Their findings proved the enhanced lowering in intraocular pressure effect of the coated formulation compared with either the uncoated one or a commercial methazolamide eye drop.

Furthermore, the lipid nanocarrier could be incorporated in a thermo-sensitive gel aiming to increase corneal contact time [20].

Nanostructured lipid carriers as well have gained popularity in ocular drug delivery [21–25]. They were reported as an efficient drug delivery system for the posterior segment of the eye due to their lipid nature, high drug-loading capacity, and enhanced trans-corneal penetration [5]. For instance, palmitoylethanolamide-loaded nanostructured lipid carrier was prepared for treatment of diabetic retinopathy in rat model [25]. In-vivo evaluation of the developed system confirmed its ability to reach the retina upon topical administration as evidenced by the significant inhibition in the levels of retinal tumor necrosis factor-α compared with the free drug in diabetic rats [25].

5.4 Nanosuspensions

Nanosuspensions are a nanometric colloidal dispersions of hydrophobic drugs stabilized by polymers or surfactants. The ocular bioavailability of many hydrophobic drugs could be improved using nanosuspension technology via increasing their retention time [26]. Numerous corticosteroids such as prednisolone,

dexamethasone [27], and hydrocortisone [27, 28] were formulated as nanosuspensions for their anti-inflammatory effect in the anterior eye segment. This resulted in elimination of the expected adverse effects associated with administration of large doses of theses corticosteroids such as production of glaucoma, cataract, and the most serious optic nerve degeneration [27]. Moreover, other drugs such as the cyclosporine [29] and antibacterial sparfloxacin [30] demonstrated a sustained drug release profile with better therapeutic efficacy when prepared as in nanosuspension form.

5.5 Vesicular delivery systems

5.5.1 Liposomes

They are spherical lipid vesicles composed mainly of phospholipids and cholesterol. A good biocompatibility, sustained release properties together with their ability to encapsulate both hydrophobic and hydrophilic drugs make liposomes ideal candidates for ocular drug delivery to both anterior and posterior segments of the eye [26]. Liposomes as an ocular delivery system were first introduced in 1981 for the delivery of the antiviral idoxuridine for treatment of keratitis [31]. Afterward, they were widely used to deliver various drugs to the eye.

For anterior eye disorders, Cyclosporine A-liposomes showed a significantly higher AUC $_{0–24\,h}$ in rabbits tears film compared with Restasis® (commercial cyclosporin A emulsion) with lower irritation potential [32]. Additionally, ciprofloxacin loaded liposomes exhibited a three-fold increase in ocular bioavailability in rabbits when compared with Ciprocin® eye drops [33]. Similarly, in-vivo evaluation of cationic liposomes containing ibuprofen versus ibuprofen eye drops revealed improved precorneal retention time and ocular bioavailability [34].

For posterior eye disorders, liposomes were extensively studied for effective drug delivery to the back of the eye. For instance, a novel liposomal formulation succeeded to enhance the bioavailability of flurbiprofen by 11.3 times compared with the free drug in the vitreous humor after intravitreal injection in rabbits [35]. In addition, the use of multivesicular liposomes to deliver the antibody Bevacizumab to the posterior eye chamber after intravitreal injection in rabbits was reported in treatment of choroidal neovascularization [36]. The elaborated system demonstrated an increase in intravitreal retention time as confirmed by in-vivo imaging of rat vitreous cavity, and hence the number of injection times was reduced [36]. Interestingly, the topical application of triamcinolone acetonide loaded chitosan-coated liposomes achieved better therapeutic outcomes in management of retinal edema instead of intravitreal injection of the drug [37, 38].

Despite the huge research conducted in the field of liposomal ocular drug delivery, their industrial production is limited owing to poor long-term stability, limited drug loading capacity, and difficulty during sterilization [6].

5.5.2 Niosomes

Niosomes were developed to overcome the limitations encountered by liposomes. Similar to liposomes, they are nontoxic vesicles and can encapsulate both hydrophilic and hydrophobic drugs, but they are chemically stable and do not require special techniques for handling. Niosomes are submicron-sized non-ionic surfactant vesicles that have potential applications in ocular drug delivery [39].

There are tremendous research articles reporting the use of niosomes in ocular therapy. Niosomes have been investigated for the ocular delivery of wide range of drugs such as anticholinergic drugs, anti-inflammatory drugs, anti-glaucoma drugs, and antibiotics [40].

To name a few, the antibacterial vancomycin was incorporated in niosomes integrated in pH-sensitive in-situ gel aiming to minimize drug-induced ocular irritation and prolong its effect [41]. The prepared formulation succeeded to eradicate infection with methicillin-resistant *Staphylococcus aureus* infection in rabbits as confirmed by the increase in the antibacterial effect by 180- and 2.5-fold compared with untreated animals and those treated with free drug solution, respectively [41].

For glaucoma management, latanoprost-loaded niosomes in thermo-sensitive Pluronic® F127 gel were developed [42]. The in-vivo evaluation of the prepared gel in rabbits confirmed its biocompatibility besides its longer duration of action (3 days) as compared with the commercial eye drops [42].

5.5.3 Discosomes

Discosomes are considered as modified niosomal formulations. They differ from niosomes by the addition of solulan C24 (non-ionic surfactant derived from lanolin). Interestingly, their large size (12–16 μm) prevents their drainage into the systemic circulation. Furthermore, their disc shape guarantees better fitting into the conjunctival sac [2]. Discosomes were reported to entrap larger quantity of timolol maleate compared with niosomes, thus increasing ocular bioavailability [43].

5.5.4 Spanlastics

They are elastic span containing vesicles that are composed of non-ionic surfactants (Span 40/60/80) and edge activators (sodium taurocholate, sodium deoxycholate, and Tween 80). The edge activators are responsible for providing flexibility to these vesicles. In addition, they were reported to be non-irritant and safe for ocular use. Furthermore, they are superior to niosomes in being highly deformable and thus can effectively deliver the entrapped drugs to the posterior eye segment. Therefore, the topical instillation of spanlastics can replace the intravitreal injections and hence increase patient compliance [44].

For instance, ketoconazole-loaded spanlastics demonstrated two times better corneal permeation compared with the niosomal formulation [45]. Fluorescently labeled spanlastics were detected in the virtuous humor of the rabbit's eye after 2 hours from topical instillation confirming their entry to the back of the eye. Similar observations were reported for the use spanlastics to deliver fluconazole, which showed enhanced permeability coefficient compared with either niosomes or Zocon ® eye drops [46].

6. New and advanced ocular drug delivery systems

6.1 Contact lenses

They are thin curved plastic lenses of disc shape that are placed on the cornea. Drug-releasing contact lenses are considered as drug reservoirs that permit continuous drug release near the tear fluid [47]. The first and most frequently used polymer for the manufacture of these lenses was poly hydroxy ethyl methacrylate cross-linked

with ethylene glycol dimethyl acrylate. Recently, the use of silicone lenses was employed. Substantial research was conducted on the use of lenses as a drug carrier for ocular delivery. For example, they were investigated for many drugs such as ciprofloxacin [48], cyclosporine [49], dexamethasone [50], timolol [51], antifungal drugs [52], among others. Drug-eluting lenses were reported to increase drugs ocular bioavailability via prolongation of their duration of action and increase their corneal penetration [47].

Various methods of loading drugs on the contact lenses were reported. The simplest method is soaking the lenses with the drug solution. However, this method suffers from many limitations such as low drug loading capacity and rapid drug release within few hours failing to provide extended drug release [51]. In this context, Wei et al. [51] studied the effect of encapsulation of the antiglaucoma drug, timolol, into microemulsion before loading on contact lenses by soaking on the drug loading efficiency versus soaking the lenses with free drug solution. The use of microemulsion technology achieved a two-fold improvement in loading efficiency with sustained drug release pattern up to 48–96 h. In addition, it provided prolonged reduction in the intraocular pressure for 96 h in rabbit model for glaucoma. Additionally, they reported that the entrapment of timolol in microemulsion before loading on contact lenses did not alter either the swelling or the transmittance of the developed lenses [51]. Similar findings were reported for the ability of liposomes [53] or polymeric nanoparticles [54] to extend and control the release rate of the entrapped drugs from the contact lenses.

It is also worth mentioning that Johnson & Johnson company lunched Acuvue® Theravision™ (etafilcon A drug-eluting contact lens with ketotifen). This product is the world's first and only drug-eluting contact lenses indicated for prevention of ocular itching due to allergic conjunctivitis upon daily application. Additionally, this product is used for vision correction in patients having no red eyes [55].

6.2 Implants

Implants are a solid form of a drug that is intended to achieve controlled drug release over an extended period of time. The implants can be surgically inserted in the subconjunctival, epidural, or vitreous areas. They provide sustained and localized drug delivery with higher patient compliance compared with the topical drops [47].

Surodex ® (Oculex Pharmaceuticals, Inc., Sunnyvale, CA, USA) is a dexamethasone containing a biodegradable implant (1×5 mm) made of poly (lactic-co-glycolic acid). It is inserted in the anterior segment of the eye for the relief of inflammation after cataract surgeries. The drug is released at a constant rate for 7–10 days [47].

Lux Biosciences produced a silicone-based episcleral implant (LX201) for delivery of cyclosporine-A to the anterior chamber of the eye for 1 year. LX 201 is also being assessed in phase III clinical trials for prevention of corneal graft rejection [47].

Vitrasert® (Bausch & Laumb, Inc.) is the first intravitreal delivery system loaded with ganciclovir for treatment of cytomegalovirus retinitis. It is designed to release the drug over a period of 6–8 month [47].

Retisert® is another intravitreal implant (Bausch & Laumb, Inc.) that can release fluocinolone acetonide up to 3 years into the vitreous humor. It is approved for treatment of posterior uveitis [47].

Fluocinolone acetonide is also included in the Iluvien® intravitreal implant (Alimera Sciences, Inc.). It is indicated for treatment of diabetic macular edema.

Iluvien is being assessed in phase II clinical trials for its efficacy in dry and wet age-related macular degeneration as well as macular edema secondary to retinal vein occlusion compared with Lucentis® injection containing ranibizumab [47].

The Ozurdex® intravitreal dexamethasone implant is designed to release the drug for 3–6 months. It is approved for use in diabetic macular edema, posterior uveitis, and retinal vein occlusion [47].

Recently, a lot of sustained-release intraocular implants have been developed for glaucoma treatment. For example, Durysta™ (Allergan plc, Dublin, Ireland) is bimatoprost implant, which was approved by FDA in March 2020 for treatment of open-angle glaucoma and ocular hypertension. It can provide a sustained drug release up to 3–4 months [56]. Another example is the iDose® implant (Glaukos, California, USA) containing travoprost. It is a titanium implant of dimensions 1.8 mm x 0.5 m that is anchored within the trabecular meshwork. It achieves a zero-order drug release over a period of 6 months or longer. It showed promising results in phase II clinical trials versus topical solution of 0.5% timolol. Currently, the recruitment of patients for phase III clinical studies has started [56].

6.3 Microneedles

Microneedles (MNs) are a revolutionary delivery method that facilitates drug delivery to a variety of eye ailments with potential healthcare applications. MNs now allow localized, effective, less invasive, and targeted drug delivery in the eye. MNs were originally created as a painless, minimally invasive, and effective transdermal medication conveyance technique [57].

Microneedle applications on various ocular targets of the suprachoroid space of the rabbit eye [58, 59], the cornea of the mouse eye [60], and the sclera of a human cadaver eye [61] have been reported.

The use of MN in the eye may also have numerous advantages over invasive intraocular injections using long, typical hypodermic needles. MNs possess long enough dimensions to pass through the ocular obstacles of both the anterior and posterior sectors of the eye, allowing for targeted administration to the sclera, stroma, and suprachoroidal area [62].

MNs, as opposed to hypodermic needles, lower the risk of pain, tissue injury, and infection. Because little research has been done in this field, using MNs in ocular drug delivery is a relatively novel approach.

Applying MNs to biological membranes can establish microdimensional transport channels and improve drug penetration across biological membrane boundaries. They're produced from a variety of materials, such as silicon, stainless steel, glass, and polymers, and available in a variety of shapes, including solid and hollow design [63]. Many techniques such as micro molding, laser drilling, and lithography can be used to fabricate microneedles [63].

Using MNs, it's possible to deposit medicines or drug delivery systems into the sclera or the suprachoroidal region, which is the space between the sclera and the choroid (SCS). Micropuncturing the sclera layer may allow for more drugs or drug carriers to be deposited in the sclera, resulting in enhanced drug permeation into the deeper ocular tissues [64].

To inject particles of sizes 20–100 nm, a minimum pressure of 250 kPa and a minimum microneedle length of 800 μm should be maintained; on the other hand, a minimum pressure of 300 kPa and a needle length of 1000 μm are required for particles sizes between 500 and 1000 nm to penetrate the sclera [65].

Numerous research studies, according to Gupta and Yadava, have lately shown the use of MNs in ocular diseases such as glaucoma, age-related macular degeneration, uveitis, retinal vascular occlusion, retinitis pigmentosa, and others [66].

Patel et al. invented the hollow MN, which was injected into the SCS using a hollow glass microneedle [67]. SCS targeting allows for precise dosing and reduces medication exposure to non-targeted tissues. Patel et al. showed that clearance of molecules and particles injected into the SCS occurred at varying speeds depending on their size in a rabbit cadaver model [58].

Thakur et al. in 2014 utilized hollow MN devices of heights of 400, 500, and 600 μm made from hypodermic needles. These hollow MNs were used to inject a thermo-responsive poloxamer-based hydrogel containing sodium fluorescein as a model drug into the scleral tissue of a rabbit to form an in-situ implant within the micro-channels, resulting in a sustained release of fluorescein sodium over 24 hours in an in-vitro experiment. This type of implant production, which does not require surgery, would improve patient acceptability and could also deliver sustained medication levels, decreasing the need for frequent application of eye drops [68].

For targeted drug delivery, intrascleral hollow microneedles are being created. These microneedles can transport medications into the posterior portion of the eye via suprachoroidal, subconjunctival, and transcleral pathways. This delivery method can transfer nanoparticles, microparticles, and drugs solutions in a less intrusive way. However, to distribute microparticles, administration must be accompanied with spreading enzymes such as hyaluronidase and collagenase, which aid in the quick hydrolysis of the sclera's collagenous and extracellular matrix structure [69].

Datta et al. developed a fast-dissolving polyvinyl pyrrolidone MN ocular patch to deliver cyclosporin-A (CsA) to the cornea. CsA diffuses slowly into deeper ocular tissues and promote drug retention in the excised porcine cornea and resulted in effective ocular administration [70].

Dissolvable polyvinyl alcohol and polyvinyl pyrrolidone matrix were used to produce a dissolving microneedle ocular patch in the shape of a contact lens. These MNs, which include either amphotericin B loaded liposome or free amphotericin B, were found to be efficient in treating *Candida albicans* infection in both ex-vivo and rabbit models as well as improving corneal membrane epithelial and stromal differentiation [71].

In 2022, Shi et al. created a dissolving microneedle array patch based on poly(D,L-lactide) (PLA) and hyaluronic acid (HA) and containing fluconazole to develop a minimally invasive delivery system for treating fungal keratitis (FK). Interestingly, the rabbit model of FK reveals that the medicated topical MN patch has superior effect compared with the traditional eye drop formulation and is also equivalent to the clinical intrastromal injection technique [72].

For treatment of corneal neovascularization, a flexible double-layer microreservoir polymeric eye patch with a row of biodegradable detachable microneedles demonstrated to be more effective than topical eye drops. These biodegradable microneedles can penetrate through ocular barriers and self-implanted as a drug reservoir matrix for controlled drug release. Furthermore, rapid diclofenac release followed by extended monoclonal antibody release produces a synergistic effect in the treatment of corneal neovascularization [60].

In conclusion, MNs are thought to have the capacity to deliver other substances such as protein pharmaceuticals and DNA across the corneal epithelium with excellent effectiveness, which needs further exploration. MNs may serve as micro-drug reservoirs for targeted, regulated, and efficient ocular medication administration.

MNs are acceptable, harmless, and painless approach, resulting in a cost-effective treatment for a variety of ocular disorders.

6.4 Cell-based ocular therapy

Cell therapy is used to treat retinal degenerative illnesses by injecting cells into the subretina, usually with a microcatheter. Generally, in this method stem cells were injected into the retinal layers to stimulate cell regeneration. While animal studies imply that this approach is safe and nontoxic, the significant risk of consequences is an important concern [73]. Recently, Gandhi et al. have showed the safety and efficacy of degradable fibrin hydrogels for subretinal implantation to aid in the accurate implantation of retinal pigment epithelium monolayer. These promising hydrogels completely disintegrated after 8 weeks, making them the first fully biodegradable scaffold designed to treat macular degeneration disease [74].

6.5 Gene-based ocular delivery systems

The practice of transferring genetic material to remove, replace, repair, or introduce a gene to treat disorders is known as gene therapy [75]. Viral vectors, naked DNA, and nonviral vectors such as nanoparticles, microinjection, electroporation, sonoporation, and iontophoresis might all be used to deliver genes. Furthermore, cutting-edge approaches such as Genome Editing System, CRISPR-Cas Delivery, and siRNA treatment have been examined [76].

Retrovirus, adenovirus, and lentivirus are viral vectors that have shown excellent potential for transgene delivery to target cells in the eye because of the high transduction efficacy [75]. Kopone et al. reported that intraocular gene therapy for neovascularization has been found to be safe in clinical trials, with no serious side effects. Clinical trials, however, have not progressed beyond Phase II trials [75].

Although there are benefits to employing viral vectors, there are also numerous constraints. Preexisting immunity to viral vehicles (e.g., adenovirus) is a major concern, since it may result in low transduction rates and reduced expression of the therapeutic gene within cells. Furthermore, the residual viral proteins have the potential to trigger inflammation in their intended target [77].

Naked DNA can be used for gene therapy without a vector; however, its structural instability may limit adequate cell uptake [76]. Stechschulte et al. reported that naked DNA delivery to the cornea was safe, effective, titratable, and has the potential to alter the treatment of a wide variety of corneal and anterior segment diseases [78].

Nonviral vectors including metal [79], polymeric [80], lipid nanoparticle [81], and dendrimers [82] are also employed to deliver therapeutic genes to cells in the anterior and posterior portions of the eye. Nonviral vectors, in contrast to viral vectors, have been demonstrated to be more biologically safe, with reduced immunogenicity and pathogenicity. Nonviral vectors also have the advantage of being inexpensive and easy to produce. However, nonviral vehicles may have a lower transfection yield [83].

Physical methods are also applied to force DNA cellular entry, such as microinjection, electroporation, sonophoresis, and iontophoresis.

To facilitate plasmid gene transfer, electroporation uses high-intensity electric impulses to create pores within the cell membrane. To avoid corneal injury, edema, or inflammation, the ideal electrical field strength for this type of gene transfer is 200 V/cm. When compared with DNA injection alone, gene transfer in the cornea is 1000-fold higher [84].

On the other hand, sonoporation uses ultrasound waves to physically create transitory and limited pores inside cell membranes, allowing DNA to be transferred to the nucleus. Sonoporation can improve the amount of therapeutic gene expression by up to 15-fold when compared with naked DNA [85].

Concerning iontophoresis, it is a technique that uses low currents to create transitory and localized pores in the cell membrane, allowing ionized molecules to pass through. Iontophoresis has been shown to boost gene or drug transport across the cell membrane by 2.3 and 2.5 times in the cornea and 4.0 and 3.4 times in the conjunctiva, respectively; however, after the current was removed, the transfer recovered to baseline levels in rabbit cornea and conjunctiva [86].

Small interfering RNAs (siRNAs) are a type of non-coding, double-stranded RNA molecules with about 20–25 base pairs in length that influence mRNA gene expression. Several eye diseases have been treated with siRNAs, including retinal abnormalities, glaucoma, wound healing, and neovascularization [87]. The majority of these research used animal models, while some were evaluated in human disorders and other siRNAs still under clinical trials [88].

CRISPR-Cas9 genome editing is becoming a hot topic in gene therapy [76]. The effectiveness demonstrated in delivering this gene-editing system to the posterior eye [89] via viral and nonviral approaches provides a starting guide for additional research concerning anterior segment diseases.

In conclusion, the future development of efficient gene treatments will rely on a better knowledge of the mutations and mechanisms that cause visual abnormalities, as well as the development of more efficient clinical vectors.

6.6 Drug-device combinations used for ocular diseases

Several drug devices and combinations have been designed to improve drug delivery to the eye, but only a few have reached the market. They boost medication retention and penetration while allowing for long-term drug release. They also have a lower level of toxicity and better patient compliance. Genes, drugs, and cell-based pharmaceuticals, as well as their combinations with medical devices, all fall within the category of advanced therapeutics medicinal products (ATMPs).

In 2017, Rupenthal reported that devices, namely collagen shield and contact lenses that gradually dissolve into a gel are effective for dry eye management and enhance wound healing after corneal surgery. They're also employed as antibiotic and anti-inflammatory medicine reservoirs before and after surgery [90].

Yellepeddi et al. described a device known as punctal plugs (PPs) that prevents tears from draining via the canaliculi, which connects the eye to the nose. PPs are recommended in some cases of laser in situ keratomileusis and contact lens intolerance due to their capacity to preserve tears. The insertion of PPs has also been shown to increase tear film stability, tear osmolarity, and functional visual sharpness in dry eye patients. Silicone has been used to create PP designs. Another example produced by (Medenium, CA, USA) and commercialized as SmartPLUG™ was designed to improve PP retention in the puncta. SmartPLUG™ comprises a biocompatible hydrophobic thermosensitive copolymer [91].

In another study, PPs loaded with the antibiotic moxifloxacin (Ocular Therapeutix, MA, USA) were produced for prolonged drug administration in the treatment of bacterial conjunctivitis [92].

Eibl-Lindner and coworkers created erufosine-loaded intraocular lenses (IOLs) for prophylaxis against posterior capsule opacification. They stated that the designed IOP

could have a therapeutic potential. They also reported that heparin-coated IOLs could be useful for reducing intraocular inflammation after cataract surgery [93].

Some of the devices mentioned in the literature are studied in clinical trials. For example, a live-cell delivery system that allows ciliary neurotrophic factor to be released from genetically engineered retinal pigment epithelium (RPE) cells. Implants utilizing this technique, designated as "Encapsulated Cell TechnologyR" (ECT) by the production company, have been shown to deliver protein drugs efficiently. ECT is made up of live cells loaded in an implanted matrix that acts as a medical device, allowing proteins generated by the cells to enter the body's fluids.

Finally, we can assert that manufacturing these devices under a pharmaceutical quality assurance system is a crucial step toward a faster production and efficient clinical application. This necessitates the formation of diverse research teams as well as the creation of infrastructure that adheres to GMP standards and meets the regulatory requirements of pharmaceutical quality systems.

7. Conclusions

The development of innovative, noninvasive, safe, and patient-compliant drug delivery techniques is the focus of intense ocular research.

Numerous drug delivery carrier systems utilizing nanotechnology, cell-based systems, microneedles, contact lenses, implants, and different devices are being developed. Ocular gene therapy has recently emerged as a promising method for treating, curing, or preventing diseases by altering the gene expression in the eyes. However, the creation of future effective treatments using gene delivery will depend on a deeper comprehension of the mutations that lead to visual impairments.

Assessment of in-vivo effect utilizing ocular models of cell lines may help to further generate accurate data at the preclinical and clinical phases since many ocular drug delivery studies are only confined to in-vitro performances.

In spite of numerous research articles published in this field, there is still a large gap in the study on ocular therapeutic systems. The absence of valid and reliable ex-vivo models that can accurately simulate the physiology of the ocular tissues is the main essential obstacle to establishing highly optimized ocular drug delivery systems.

Finally, we might anticipate that within the next 10 years, the market would have a significant increase in the development of novel drug delivery technologies due to the pace at which ocular research and efforts are being done.

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