Drug delivery to the posterior segment of the eye

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Delivery of drugs to the posterior eye is challenging, owing to anatomical and physiological constrains of the eye. There is an increasing need for managing rapidly progressing posterior eye diseases, such as age-related macular degeneration, diabetic retinopathy and retinitis pigmentosa. Drug delivery to the posterior segment of the eye is therefore compounded by the increasing number of new therapeutic entities (e.g. oligonucleotides, aptamers and antibodies) and the need for chronic therapy. Currently, the intravitreal route is widely used to deliver therapeutic entities to the retina. However, frequent administration of drugs via this route can lead to retinal detachment, endophthalmitis and increased intraocular pressure. Various controlled delivery systems, such as biodegradable and non-biodegradable implants, liposomes and nanoparticles, have been developed to overcome such adverse effects, with some success. The periocular route is a promising alternative, owing to the large surface area and the relatively high permeability of the sclera. Yet, the blood–retinal barrier and efflux transporters hamper the transport of therapeutic entities to the retina. As such, the efficient delivery of drugs to the posterior eye remains a major challenge facing the pharmaceutical scientist. In this review, we discuss the barriers of the posterior eye drug delivery and the various drug-delivery strategies used to overcome these barriers.

Introduction

Diseases of the eye vary from minor conjunctivitis to irreversible visual impairment caused mainly by diseases of the posterior eye. The most prevalent posterior eye diseases which cause visual impairment include age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion, uveitis, diabetic retinopathy, cytomegalovirus (CMV) retinitis and retinitis pigmentosa [1].

Depending on the disease origin, ocular drug-delivery systems vary from simple topical ocular formulations to systems that require complex engineering solutions, such as intraocular implants [2,3]. Nonetheless, the tight cellular membranes of the eye and the various barriers that restrict the transport of fluids and solutes to the visual cells hinder the successful administration of therapeutic agents. As such, many novel strategies have been developed to circumvent these ocular barriers. This review provides an overview of the routes of drug delivery to the posterior eye, the biological barriers to posterior eye drug delivery and the novel strategies utilized to overcome these challenges.

Routes of drug delivery to the posterior eye

Topical, systemic, intravitreal and periocular routes can be used to deliver pharmaceuticals to the posterior segment of the eye. The topical route is inefficient in delivering therapeutic concentrations of a drug to the posterior segment, owing to rapid drainage through the nasolacrimal ducts, low permeability of the corneal epithelium, systemic absorption and the blood–aqueous barrier.

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Conversely the blood–retinal barrier (BRB) hinders the diffusion of systemically administered drugs to the posterior segment of the eye. Frequent systemic administration of high doses is also likely to exacerbate drug-related toxicities owing to nonspecific absorption [1,4]. Consequently, the ideal routes of drug delivery to the posterior segment are the intravitreal and the periocular routes [5,6] (Table 1).

Intravitreal route

Intravitreal injection of drugs to the eye involves direct injection of the formulation, in the form of solution, particles, suspension, depot or implants, into the posterior segment through the pars plana (Fig. 1). Many pharmaceuticals aimed at treating posterior eye diseases are delivered via this route. Intravitreal injection provides increased drug concentrations at the neural retina and minimizes systemic side effects. Nonetheless, frequent administration of drugs via this route can lead to retinal detachment, retinal haemorrhage, endophthalmitis and increased intraocular pressure [7,8]. To minimize some of these complications, novel drug-delivery systems have been developed in the form of biodegradable or non-biodegradable implants, which can be placed long term in the vitreous [5,6,9]. Even so, various factors affect the pharmacokinetics of drugs administered via the intravitreal route.

The two main routes by which a drug is eliminated from the vitreous humour are either via the anterior chamber or across the retinal surface. The elimination and distribution kinetics are affected by the rate of drug diffusion through the vitreous and the geometry of the eye. Consequently, larger molecules are retained in the vitreous for long periods (weeks); but molecules that are <500 Da and are in the form of a solution need frequent administration, owing to a limited retention half life of approximately 3 days. This generalized elimination and distribution pathway is complicated in elderly patients with collapsed vitreous structure and in patients with vitrectomy [10,11].

Early studies have demonstrated a gradually decreasing concentration gradient of fluorescein from the posterior surface of the lens to the retina. In healthy eyes, the fluorescein concentration is

TABLE 1

Drug-delivery systems targeting the posterior eye

Delivery approach	Drug	Route	Disease targeted	Refs
Episcleral implants	Fluorescein	Transscleral	N/A	[57]
	Betamethasone	Transscleral	N/A	[56]
Film (PLGA)	Ethacrynic acid	Intrascleral	Glaucoma	[82]
Gels (polyortho esters)	Dexamethasone and 5-fluorouracil	Subconjunctival	Post-glaucoma filtering surgery	[83]
Gels (collagen matrix)	Cisplatin	Subconjunctival	Retinoblastoma	[40]
Implant	Betamethasone	Intrascleral	Uveitis	[81]
Implant	Ciliary neurotrophic factor	Intravitreal	Retinitis pigmentosa and AMD	[84]
Implant (biodegradable)	Dexamethasone (Posurdex®/Ozurdex®)	Intravitreal	Diabetic macular oedema, uveitis, post-cataract surgery	[85]
Implant (non-biodegradable)	Ganciclovir (Vitrasert®)	Intravitreal	CMV retinitis	[51,86]
	Fluocinolone acetonie (Retisert®, Iluvien™ and Medidur®)	Intravitreal	Chronic non-infectious uveitis, diabetic macular oedema	[54,87]
	Triamcinolone acetonide (I-vation®)	Intravitreal	Wet AMD	[88]
Iontophoresis (OcuPhor™/Visulex™)	Antibiotics, steroids and antiviral	Transscleral	Various	[75]
Liposomes	Verteporfin (Visudyne®)	Intravenous	Wet AMD	[89,90]
Micelles	Dendrimer porphyrin	Intravenous	Choroidal neovascularization	[68]
Microcannulation	Triamcinolone acetonide	Suprachoroidal	Wet AMD	[91]
Microneedle	Pilocarpine and sulforhodamine	Transscleral	Various	[80]
Microparticles	Celecoxib	Subconjunctival	Diabetic macular oedema	[92]
Microspheres	PKC412	Periocular	Choroidal neovascularization	[59]
	Antisense TGF-β2 phosphorothioate oligonucleotides	Subconjunctival	Post-glaucoma filtering surgery	[60]
	RNA aptamer	Transscleral	Choroidal neovascularization	[93]
Nanoparticles	Nile red, Rh-6G	Intravitreal	N/A	[62]
	Plasmid DNA	Intravitreal	N/A	[63]
	Budesonide	Subconjunctival	Diabetic macular oedema	[94]
Osmotic pump	Immunoglobulin G	Transscleral	N/A	[33]
Solution	Pegaptanib sodium (Macugen®)	Intravitreal	Wet AMD	[95]
	Fomivirsen: antisense oligonucleotide (Vitravene®)	Intravitreal	CMV retinitis	[96]
Suspension	Triamcinolone acetonide (Retaane®)	Transscleral	Wet AMD	[39,97]
Vectosomes (light-sensitive)	Oligonucleotides	Intravitreal	N/A	[69]

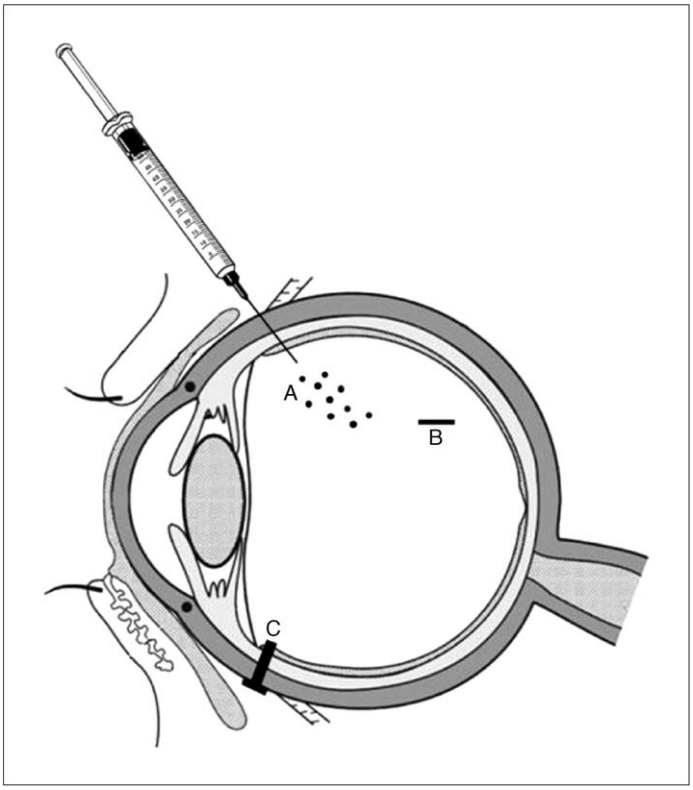

FIGURE 1

Schematic presentation of the intravitreal route of drug administration to the posterior eye. **(a)** Micro- or nanoparticles injected using a needle. **(b)** Biodegradable or non-biodegradable implants surgically introduced into the vitreous. **(c)** Scleral plugs or implants sutured onto the sclera.

minimal in the midvitreous space and only infinitesimal concentrations are present at the anterior vitreous, closer to the ciliary body [12,13]. This well-regulated convective flow within the viscoelastic gel structure of the vitreous is disrupted with liquefaction and vitrectomy, leading to significant changes in the diffusion coefficient of administered drugs [10]. The density of a given formulation might also affect the distribution within the vitreous, with high-density formulations depositing on the inferior retina causing localized adverse effects. In addition, the long-term accumulation of intravitreal implants might significantly impact the vision of patients [11].

The inner limiting membrane (ILM) and the BRB are the main biological barriers to drug transport from the vitreous to the retina. The ILM forms a border between the vitreous humour and the retina and is the primary barrier to drug diffusion to the retina [14]. The BRB, which is composed of the endothelial cells of retinal blood vessels and the retinal pigmented epithelium (RPE), forms the secondary barrier to the transport of lipophilic drugs to the inner retinal cells. Studies have shown rapid clearance of lipophilic molecules administered into the vitreous by passive diffusion via the BRB. Furthermore, the efflux transporters in the endothelium lead to rapid elimination of molecules that are substrates for this innate active transport mechanism [15].

Present evidence therefore suggests that, although the intravitreal route is useful in attaining high drug concentrations at the retina, it is not the ultimate strategy for drug delivery to the posterior ocular tissue.

Periocular routes

The periocular route of drug delivery enables the deposition of molecules against the external surface of the sclera, thereby minimizing the risk of endophthalmitis and retinal damage associated with the intravitreal route of administration [16,17]. It is considered to be the least painful and the most efficient route of drug delivery to the posterior eye [1,18–24]. Periocular pathways used for the delivery of drugs to the posterior tissues of the eye include the retrobulbar, peribulbar, subtenon and subconjunctival routes (Fig. 2).

Both the subconjunctival and the subtenon routes are widely used in research into transscleral drug delivery owing to their proximity to the sclera. With subconjunctival injection, the formulation is placed beneath the conjunctival membrane that covers the sclera. This enables the drugs to bypass the conjunctiva–cornea barrier, giving direct access to the transscleral route. Subtenon injection involves the placement of a formulation between the sclera and Tenon's capsule, an avascular membrane. As such, the contact time between the administered drug and the sclera is prolonged. Consequently, the subtenon route is considered to be one of the most promising routes for targeting the posterior segment of the eye [1,25].

The direct penetration pathway is the main route in achieving high concentrations of a drug in the vitreous following subtenon injections [26–28]. The sclera, with its large surface area (16.3 cm^2), is less resistant to permeation of molecules and has lower protease activity compared to the cornea [29,30]. However, there are a few static and dynamic barriers to transscleral drug delivery.

Scleral permeability depends on the molecular radius rather than the molecular lipophilicity [31] and molecules of up to 70,000 Da can readily penetrate the sclera [31–35]. It also depends on scleral hydration and intraocular pressure; however, the latter has negligible effects at normal intraocular pressures (15–20 mmHg) [23,24]. Nevertheless, only minute concentrations of a drug administered via the transscleral route end up in the vitreous [36,37]. This low bioavailability can be attributed to the loss of the drug from the periocular space, BRB, choroidal

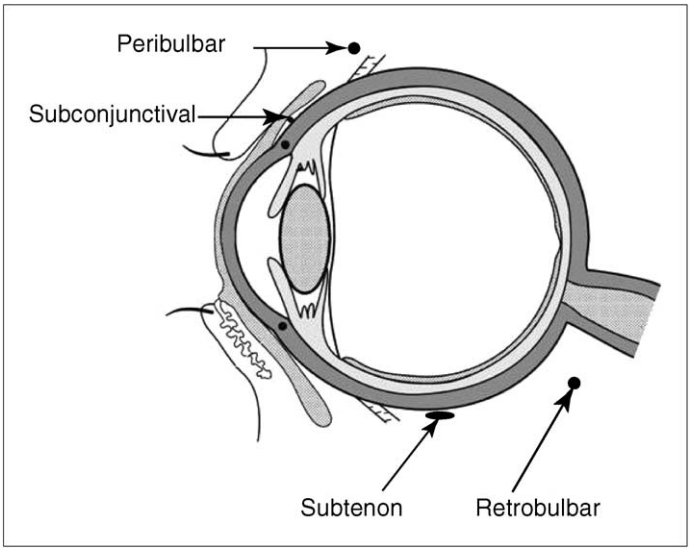

FIGURE 2

Schematic representation of the periocular routes of drug administration.

circulation and the binding of drugs to tissue proteins as well as efflux transporters.

Reflux of an administered drug from the injection site is the initial loss factor that contributes to low bioavailability [38]. It has been shown that use of a proper injection technique, volume and formulation can minimize this loss and improve transscleral bioavailability [38–40]. Elimination of an administered drug through the conjunctival lymphatics and episcleral veins also has an important role in periocular drug loss [37,41,42]. The choroid, a network of blood vessels located between the sclera and the retina, forms the secondary elimination pathway for molecules that diffuse through the sclera. However, Robinson *et al.* [43] demonstrated greater influence of lymphatic clearance on retinal bioavailability of a corticosteroid compared with the choroidal circulation. Further assessment of the significance of these clearance pathways is necessary as a function of drug properties. The outer BRB (oBRB), which consists of the RPE, is the inner barrier to drug transport across the sclera to the retinal layers. Only selected molecules are exchanged between the choroid and the retina, owing to the tight junctions of the RPE. As such, the flux of a compound across the BRB depends on its permeability and the concentration gradient [24,43–47]. Various transporters, including amino acid transporters, oligopeptide transporters, folate transporters, organic cation and anion transporters, nucleoside transporters and efflux transporters, are also found in the BRB. These restrict the transport of solutes across the BRB, but can be utilized to deliver transporter-specific solutes into the retina [46]. The binding of drugs to various proteins in ocular tissues, including melanin, also affects the transport of a drug into the vitreous [28,32,48,49].

Current and future ocular drug-delivery systems

To meet the demand of treating the increasing incidence of chronic posterior eye diseases in ageing populations, various forms of drug-delivery system have been developed. These systems vary in their design and duration of action to suit the route of delivery and properties of the drug, to minimize complications associated with drug delivery and to improve patient compliance. In addition, breakthroughs in gene therapy, stem cell research and protein therapy have highlighted the need for advanced drug-delivery systems capable of increasing the stability and bioavailability of these new therapeutic entities [50].

Implants: biodegradable and non-biodegradable

Ocular implants provide a platform for the sustained release of molecules from either biodegradable or non-biodegradable polymeric matrices over several months to years. These implants are either injected into the vitreous or sutured onto the sclera for intravitreal or transscleral drug delivery. Biodegradable implants do not require post-treatment removal, but can cause more erratic drug-release profiles. Polymeric materials commonly used to fabricate biodegradable implants include poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polyanhydride and poly(ortho ester) (POE). Conversely, non-biodegradable implants require invasive surgical removal, but provide more accurate controlled release over longer release periods. Polymers commonly used for the fabrication of non-biodegradable implants are silicone, polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) [51].

Currently, two surgically implanted, non-biodegradable intravitreal implants (Vitrasert® and Retisert®) are in clinical use. Vitrasert® contains ganciclovir for the treatment of CMV retinitis for up to eight months and is the mainstay therapy for patients with CMV retinitis. The ganciclovir implant study group demonstrated a significant difference between the implant treatment groups and the intravenous (IV) treatment group; the median time for disease progression in the implant group was more than twofold longer than that of the IV treatment group (196 days versus 71 days, respectively). The study, however, noted a 7.8% risk of vitreous haemorrhage and a twofold increase in retinal detachment owing to treatment with the implant [52]. Retisert®, which contains fluocinolone acetonide, is used for the treatment of chronic non-infectious posterior uveitis. This reservoir system releases fluocinolone for up to 2.5 years. Clinical studies have shown a significant decrease in disease recurrence in fluocinolone-implanted eyes (from 51.4% to 6.1% post implantation) and also a reduction in the need for adjunctive therapy. Nonetheless, Retisert® has been shown to increase intraocular pressure and cataract progression, with 51.1% of implant-treated eyes requiring ocular antihypertensive medication and 9.9% of patients requiring cataract surgery [53].

Several more non-biodegradable implants are currently in clinical studies and these include Iluvien®, I-vation™ and a novel cell encapsulation device (NT-501). Iluvien® (formerly known as Medidur®) is a rod-shaped implant containing fluocinolone acetonide and is in Phase III clinical trials for the treatment of diabetic macular oedema. Unlike Retisert®, this device can be inserted into the vitreous using a 25-gauge needle and is expected to release fluocinolone for up to three years [54]. I-vation™ is a novel technology that incorporates a titanium helical coil to increase the surface area of drug release. The coil is coated with triamcinolone acetonide (TA) and non-biodegradable polymers and is expected to release TA for at least two years. Currently, I-vation™ is in Phase I clinical trials in patients with diabetic macular oedema [55].[a]

The cell encapsulation technology developed by Neurotech (http://www.neurotech.co.uk) is an implant (NT-501) that contains human RPE cells genetically engineered to secrete ciliary neurotrophic factor (CNTF), a growth factor that inhibits photoreceptor degeneration. The implant, which consists of a sealed semi-permeable membrane, is sutured onto the sclera through a titanium loop. This unique device enables the influx of oxygen and nutrients into the cells within the implant and the CNTF secreted by the RPE cells diffuses out of the semi-permeable membrane. As the cells are encapsulated, the device also prevents host immune responses to the implanted cells. Currently, NT-501 is in Phase II clinical trials for the treatment of dry AMD and retinitis pigmentosa[b], and represents a unique platform for the delivery of protein therapeutics.

[a] SurModics: Intravitreal drug delivery capabilities. Available from: http://www.surmodics.com/clinical-ophthalmology-intravitreal.html (accessed 6 December 2010).

[b] Neurotech: About encapsulated cell technology. Available from: http://www.neurotechusa.com/ect/about_encapsulated_cell_technology.asp (accessed 6 December 2010).

Recently, a biodegradable intravitreal implant, Ozurdex® (formerly known as Posurdex®), has also been approved for the treatment of macular oedema secondary to retinal vein occlusion and for non-infectious uveitis. This implant is composed of PLGA and releases incorporated dexamethasone over four to six weeks. At present, it is also in Phase III clinical trials for the treatment of macular oedema owing to diabetes. The Phase II clinical trial of Posurdex® has demonstrated that, after 180 days of treatment with 700 μg of dexamethasone implant, 19.4% of patients achieved at least a three-line improvement in visual acuity compared with only 8% in the control group. The trial also reported a few minor adverse effects, which included increasing intraocular pressure in patients treated with the implant [55].

Implants are also becoming increasingly popular for transscleral delivery of therapeutics. Kato *et al.* [56] initially investigated the efficacy of scleral implants in delivering drugs to the retina–choroid by placing a non-biodegradable implant containing betamethasone in the episcleral space of rabbits. The authors determined the betamethasone concentration in ocular tissue up to four weeks after implantation and showed that the implant was able to maintain the concentration of betamethasone within the therapeutic range in the retina–choroid. Furthermore, the vitreal concentration was shown to be lower than that of retina–choroid. A similar study using non-biodegradable exoplants loaded with fluorescein was carried out by Pontes de Carvalho *et al.* [57]. The authors demonstrated more efficient delivery with the exoplants compared with periocular injection, with significantly higher concentrations of fluorescein being observed in the posterior ocular tissue of the exoplant-treated rabbits. Moreover, the exoplant reduced the systemic absorption of fluorescein, indicating scleral implants to be of value in achieving high drug concentrations at the target tissue.

Micro- and nanoparticles

Microparticles (1–1000 μm) and nanoparticles (1–1000 nm) also provide sustained release of encapsulated molecules, but with a typical duration of action ranging from weeks to months. Nonetheless, these particles can be modified for tissue-specific uptake and to protect the therapeutic molecules from degradation [58]. Micro- and nanoparticles have yet to be tested in clinical trials for ocular diseases, but are promising tools for targeted drug delivery.

Various preclinical studies have demonstrated the efficacy of micro- and nanoparticles in delivering drugs to the posterior ocular tissue via the periocular routes and the intravitreal route of administration. Saishin *et al.* [59] successfully used microspheres of PKC412, a kinase inhibitor, for the treatment of choroidal neovascularization (CNV) in a porcine model. The authors detected PKC412 in the choroid of the treated porcine eyes ten days after periocular injection of the microspheres and found the area of CNV to be significantly smaller in PKC412-treated eyes. PKC412 was also detected in the retina and vitreous of the treated eyes for up to 20 days after treatment, although the concentration detected was lower than that in the choroid. The success of microspheres in localized controlled delivery of molecules was also demonstrated by Gomes dos Santos *et al.* [60] in a rabbit model of glaucoma filtering surgery. The authors formulated PLGA microspheres containing anti-transforming growth factor (TGF)-β2 phosphorothionate oligonucleotides (PS-ODN) and administered them subconjunctivally to rabbit eyes; the results demonstrated a 100% bleb survival or prevention of post-surgical fibrosis for six weeks in the treated eyes.

Intravitreal administration of nanoparticles containing anti-TGF-β2 PS-ODN has also been evaluated for retinal drug delivery [61]. *In vivo* data demonstrated homogenous retinal distribution of the particles within 24 hours of intravitreal administration. Interestingly, the authors also found an accumulation of the anti-TGF-β2 PS-ODN in retinal muller glial cells after 72 hours of intravitreal administration, demonstrating targeted gene delivery. Likewise, Bourges *et al.* [62] demonstrated the efficacy of intravitreally administered PLA nanoparticles (loaded with Rh-6G and Nile red fluorochromes) in retinal drug delivery in rats. The authors found an accumulation of the nanoparticles at the ILM one hour after intravitreal injection, followed by a transretinal distribution six hours after administration. At 18–24 hours after intravitreal injection, the nanoparticles were localized within the RPE cells and were found to be present in the RPE cells up to four months after injection. Bejjani *et al.* [63] also evaluated the efficacy of RPE gene transfection using nanoparticles in rats. The authors observed selected gene expression in the RPE within four days of intravitreal injection and the expression was maintained for 14 days. The present evidence suggests polymeric micro- and nanoparticles to be of value in targeted and controlled gene delivery for posterior eye diseases. However, a few barriers have to be overcome before micro- and nanoparticles can be tested in clinical trials for posterior eye diseases. These include improvement in encapsulation efficacy, control of particle size and drug release rate, stability of molecules during manufacturing and large-scale manufacturing of sterile preparations [64].

Light-induced systems

Both light-activated drugs (photodynamic therapy, PDT) and light-activated drug-delivery systems are classified as light-induced systems. Such systems use a delivery method to localize a photosensitizing compound in the target tissue followed by activation using a non-thermal laser light. Verteporfin (Visudyne®) is a clinically available light-activated drug used for the treatment of wet AMD. Verteporfin is activated 15 min after IV administration using a non-thermal red laser light. The activated drug causes the occlusion of neovascular vessels; however, this is only used as an adjunctive therapy owing to the reappearance of neovascular vessels [65–67]. In recent years, polymeric micelles have been investigated for the delivery of photosensitizers to improve the selectivity and effectiveness of PDT and to minimize the risk of skin hypersensitivity. Ideta *et al.* [68] evaluated the efficacy of micelles loaded with dendritic porphyrins (DP) in managing CNV in rats and reported an accumulation of micelles in the CNV sites. Application of a laser at 0.25 or 4 hours after administration of the DP-loaded micelles resulted in a 60–78% occlusion of CNV lesions and ~80% of the occlusions were maintained seven days after treatment.

Vectosomes are also of interest for targeted ocular gene delivery. These are vesicles made of VP22, a structural protein of herpes simplex virus. Antisense oligonucleotides (ODNs) can be bound to the C-terminal amino acids of the purified VP22 protein, forming spherical particles of 0.3–1 μm in diameter. These particles are stable within the cell cytoplasm for weeks, but can be destabilized

by the illumination of a laser light, releasing the incorporated ODN. Normand *et al.* [69] evaluated the efficacy of these vectosomes *in vivo* by intravitreal injection into rat eyes and the results demonstrated vectosome distribution in all the retinal layers, with an accumulation at the external limiting membrane and the cytoplasm of the RPE cells. Once activated, the fluorescence redistributes and accumulates in the nuclei of the ganglion cell layer, inner nuclei layer and the nuclei of the RPE cells.

Paasonen *et al.* [70] also evaluated a light-sensitive drug-delivery system based on gold nanoparticle-loaded liposomes. The gold nanoparticles (2–3 nm) were embedded in the inner and outer layers of the liposomes loaded with a marker substance, calcein. The liposomes were intact under physiological conditions but released calcein upon light irradiation. Heat absorbance by the incorporated gold nanoparticles followed by transfer to the surrounding microenvironment is considered to be the underlying mechanism of liposomal phase transition and release of calcein.

Light-sensitive hydrogels also have potential application in ocular drug delivery. These systems can be stimulated by either UV light or visible light, the latter of which is inexpensive, safe and readily available. Suzuki and Tanaka [71] developed such a polymeric system by incorporating a tri-sodium salt of copper chlorophyllin, a light-sensitive chromophore, in poly(*N*-isopropylacrylamide) hydrogels. Upon irradiation with light, the chromophore absorbs the light and transfers the energy as heat to the surrounding polymer molecules. The resultant increase in temperature alters the swelling behaviour and the drug-release characteristics of the hydrogel. Cross-linked hyaluronic acid with photosensitizers has also been studied, with biocompatibility as an added advantage [72]. Nonetheless, the clinical application of these hydrogels is impeded by their slow response time [65].

Light-sensitive drug-delivery systems have opened up new perspectives in the targeted control delivery of therapeutics to the posterior ocular tissue, with minimal systemic adverse effects. However, the wavelength of the light source used to activate these systems should be selected carefully to avoid associated retinal damage.

Iontophoresis

Iontophoresis has been shown to increase the transscleral permeability of many drugs, including fluorescein, steroids, antibiotics, antivirals and macromolecules. It is a non-invasive technique that involves the application of a small electric current to enhance the penetration of an ionized drug into the tissue. Transscleral iontophoresis delivers high concentrations of the applied drug to the choroid and the retina with minimal side effects [24,73]. However, Molokhia *et al.* [74] recently demonstrated that transscleral iontophoresis is unable to deliver significant amounts of macromolecules to the vitreous of rabbits. The model macromolecule, Galbumin, was only detected in the conjunctiva, sclera and the nearby tissue at the site of application. This could be because of the RPE lying between the choroid and the retina resisting diffusion of molecules into the retina. Vascular and lymphatic clearance might also have contributed to the elimination of macromolecules from the site of application [75,76]. By contrast, Davies *et al.* [77] demonstrated that iontophoresis can be used to deliver RNA and DNA molecules up to 8 million Daltons in size across the sclera. However, the authors used human cadaver eyes and the electric field was applied for a longer time (two hours). Nonetheless, iontophoresis is a promising tool for the delivery of hydrophilic macromolecules, such as DNA, across the sclera.

Adverse effects of iontophoresis include epithelial oedema, a decrease in endothelial cells, inflammatory infiltration and burns, the extent of which depends on the site of application, current density and duration. At higher current densities, iontophoresis has been shown to damage the choroid and destroy retinal layers [78]. Recently, several iontophoresis devices have been developed with better tolerability and ease of use. These include Ocuphor® [78], EyeGate® [79] and Visulex® [66]. Further assessment of these types of device is needed to determine the optimal protocol and conditions for safe and efficient application of ocular iontophoresis.

Microneedles

Microneedles are solid or hollow needles of micron dimensions that were initially developed for transdermal drug delivery. Recently, microneedles have been utilized in transscleral drug delivery for the targeted delivery of therapeutic entities to ocular tissue, as they can be used in a minimally invasive manner. The needles can be used to deliver free as well as encapsulated drugs via the sclera in a controlled manner. Hollow microneedles have been used for the delivery of insulin and vaccines, whereas solid microneedles have been used either to form micro-holes in the skin to enhance permeability or to deliver drugs that are coated onto the needles [80]. Jiang et al. [80] evaluated the use of microneedles in ocular drug delivery of a small model drug and micro- and nanoparticles using human cadaver eyes. The soluble molecule and nanoparticles were delivered using an insertion–retraction protocol, whereas the microparticles needed hyaluronidase to disrupt the scleral structure to obtain similar tissue distribution. The study showed that an individual needle was able to deliver 10–35 μl of a fluid into the sclera, forming an intrascleral drug depot. However, further preclinical studies are needed to determine the efficacy and safety of microneedles in posterior eye drug delivery.

Concluding remarks and future directions

Efficient drug delivery to the posterior eye is becoming increasingly vital with the escalating prevalence of posterior eye diseases and the development of novel, yet challenging, therapeutic entities. Novel drug-delivery systems are required to overcome the anatomical and physiological barriers of the eye and, most importantly, to improve patient safety and compliance. New technologies are primarily designed to provide prolonged action, increased bioavailability of the therapeutic entities, improved patient safety and minimal adverse effects. In addition, intravitreal injection and implants will need to be customized to accommodate the increasing number of patients requiring multiple treatments and patients presenting with co-morbidities. As such, the future of posterior eye drug delivery lies in the multidisciplinary integration of delivery technologies to optimize drug bioavailability. The development of a smart technology that can be self-administered by patients is as yet unrealized, but the advances in biomaterials and nanotechnologies could provide the ultimate solution.

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