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Challenges and opportunities for drug delivery to the posterior of the eye

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Drug delivery to the posterior segment of the eye remains challenging even though the eye is readily accessible. Its unique and complex anatomy and physiology contribute to the limited options for drug delivery via non-invasive topical treatment, which is the prevalent ophthalmic treatment. To treat the most common retinal diseases, intravitreal (IVT) injection has been a common and effective therapy. With the advancement of nanotechnologies, novel formulations and drug delivery systems are being developed to treat posterior segment diseases. Here, we discuss the recent advancement in ocular delivery systems, including-sustained release formulations, IVT implants, and preclinical topical formulations, and the challenges faced in their clinical translation.

Introduction

The physiology of the eye is unique. The anterior of the eye, specifically the cornea, is avasculature and transparent for unobstructed vision and is exposed to the environment. The posterior segment of the eye is vascularized, delicate, and not readily accessible for non-invasive therapy. The retina, a complex multicellular layer responsible for vision, is the site of many diseases. The most common and severe retinal diseases are diabetic retinopathy (DR) and age-related macular degeneration (AMD), affecting, for example, more than 10 million patients in the USA. The National Eye Institute estimated that the number of people affected by glaucoma, DR, and AMD will double by 2050, with an estimated US$139 billion annual economic burden associated with eye diseases and vision disorders [1,2]. DR is the leading cause for vision loss among middle-age adults, and anyone with diabetes is at risk. The disease is characterized by the breakdown of the blood–retinal barrier, resulting in hypoxia and leading to retinal neovascularization [3,4]. AMD is another leading cause of blindness, especially in the Western world. In its early stage, AMD is a chronic inflammatory eye disease that damages retinal pigment epithelium (RPE) and photoreceptor cells. The progressive degeneration of RPE cells ultimately results in blindness [1]. Unfortunately, there is no cure for posterior segment diseases, including DR and AMD. However, there are several procedures and treatment options available to delay disease progression. Here, we discuss the existing treatment for posterior segment diseases and advances in the development of minimally invasive or non-invasive, nanotechnology-based drug delivery systems for posterior segment diseases.

Types of available treatment for posterior segment diseases

Currently available procedures to delay disease progression include laser photocoagulation and photodynamic therapy [1,5]. These procedures had been considered as the standard treatment of care to prevent further choroidal neovascularization (CNV) for patients before the development of anti-vascular-endothelial growth factor (VEGF) therapy. Briefly, laser photocoagulation is a minimally invasive procedure using a tiny laser to burn thickened areas of the retina to localize destruction of the diseased tissue [6]. Photodynamic therapy is a systemic therapy that involves the intravenous administration of verteporfin, a photosensitizer. After the drug is administered, the laser is illuminated on the targeted area of the CNV and its cascade, thereby prevent-

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ing CNV proliferation [1]. Despite its success, these treatments have a limited effect on the patients' overall vision, and CNV recurrences along with vision loss have been reported. In addition, these treatments for posterior segment diseases are not suitable for everyone given that individual conditions and disease progressions vary.

Given that the various isoforms of VEGF have a crucial role in the pathogeneses of both DR and AMD, IVT injections of anti-VEGF agents, including ranibizumab, bevacizumab, and aflibercept, are effective in reverting retinal neovascularization [4,7–9]. IVT injection is the local administration of therapeutics in the vitreous chamber. This route of administration increases local drug concentrations in cell-free gelatinous vitreous between the lens and retina. The nature of IVT injections is inconvenient because they have to be administered by specialists, require frequent clinic visits, and can be painful for patients. In addition, repeated IVT injections may cause complications, such as retinal detachment, subconjunctival hemorrhage, retinal toxicity, corneal abrasion, temporary elevation of intraocular pressure (IOP), and endophthalmitis, a visually devastating intraocular infection [9,10], although the risk of endophthalmitis is low (0.1% per injection) because of standardized injection procedures [2,9]. Nonetheless, the development of anti-VEGF therapy has positively shifted such treatment regimens from fixed monthly dosing to 'treat-and-extend' approaches [8]. An increasing number of retinal specialists now recognize the need for personalized treatment based on individual's disease progression and outcome. This individualized treat-and-extend dosing regimen reduces the frequency of injections, which in turn may affect the visual acuity of patients with AMD [8].

Nanotechnology in ocular delivery systems

The main objective of a drug delivery system is to efficiently deliver a therapeutic agent to a targeted site at the optimal dose, to enhance therapeutic efficacy. In the field of drug delivery, the emergence of nanotechnology has changed the scientific approach to developing drug formulations. Nanotechnology, in general, involves the fabrication of materials and devices that are <100 nm in size, and nanomedicine refers to an application to diagnose and treat diseases using nanosystems <1000 nm in size [11,12]. Nanomedicine has attracted scientific interest over the past few decades and provides advantages such as its versatility to engineer and design drug delivery systems. With the advancement of nanotechnology, drug formulations have improved pharmacokinetics (PK) to extend and control the release of therapeutic agents by enhancing the drug solubility, bioavailability, and stability with minimal adverse effects [5,13–15]. In numerous studies involving nanoformulations, researchers have demonstrated the superior therapeutic outcome in animal models compared with conventional formulations [15–18]. Specifically, in ocular drug delivery to the posterior segment, nanotechnology or nanomedicine can be beneficial. Given that there is no cure for many posterior segment eye diseases, patients with such conditions are expected to receive life-long treatments to manage or slow the progression of the disease. Thus, the goal of developing sustained-release formulations is to reduce the frequency of injections while minimizing the adverse effects caused by multiple injections [19,20]. Nanotechnology allows flexible design considerations because physical and functional properties of nano-sized systems can be easily altered to prolong the drug release and to increase bioavailability in the intraocular tissues, particularly in the vitreous [5,16,18,21,22].

Optimizing the size of nanosystems can improve the distributions in the eye. For example, it was reported that, upon IVT injection of different sizes of polystyrene particles, 2-μm particles remained in the vitreous cavity, whereas 200-nm and 50-nm particles were evenly dispersed in the vitreal cavity and were observed in the retina 2 months after injection [23]. However, in another study, similar-sized particles showed different intraocular distribution when the surface property of particles was modified with polyethyleneimine, hyaluronic acid, or human serum albumin [24,25]. Positively charged NPs aggregated and adhered to the vitreous network, which is anionic, whereas negatively charged NPs were able to diffuse through the vitreous and reach the retina in rat eyes [24,25]. These findings illustrate that size and surface modification of NPs should be carefully considered when designing delivery systems to augment their intraocular distribution, bioavailability, and biocompatibility.

The aforementioned observation that 2-μm particles had remained in the vitreous cavity offered another insight that the microparticles can be used as sustained release systems [23]. Poly (lactic-co-glycolic) acid (PLGA) is one of the most widely used biodegradable polymers in drug delivery as a controlled drug delivery vehicle. Peters and colleagues developed polyesteramide (PEA) or PLGA microspheres, 10–20 μm in size, as a sustained-delivery system in rats. These microspheres encapsulating dexamethasone were intravitreally injected and remnants of microspheres were observed in the vitreous cavity without functional abnormality even after 3 months [26]. Another study investigated IVT-injected PLGA microspheres loaded with triamcinolone acetonide as a treatment for DR in humans. In a Phase I/II study, a triamcinolone acetonide microsphere treatment was safe for a 1-year period in patients with diabetic macular edema even though no significant improvement in visual acuity was observed [27,28]. Although the clinical usage of PLGA for a variety of applications is approved by the US Food and Drug Administration (FDA), it is often associated with local inflammation upon degradation [29]. In an effort to avoid any possibility of inflammation in the eye caused by PLGA, Graybug Vision developed a hydrophilic coated PLGA microparticle formulation to deliver sunitinib malate via IVT injection using a 27-gauge needle and was expected to release the drug over 4–6 months [14,29,30]. Phase I/II trials of this novel formulation are expected to begin in 2019.

NP or microparticle formulations are not the only feasible approach for IVT injection. Verisome® Technology, a hydrogel-based delivery system, is a clear solution in a syringe but forms a small sphere that is a bioerodable viscous gel when injected with a 30-gauge needle into the vitreous. In the vitreous, the gel containing therapeutic agents degrades or shrinks over several months while releasing the therapeutics. The shrinkage of the gel can be monitored by physicians [31,32]. Utilizing this technology, DEXYCU™ was developed as a long-acting dexamethasone suspension and was approved by the FDA in early 2018 to treat inflammation [5,33]. A single intracameral injection of DEXYCU forms a sphere gel <2 mm in diameter and the gel can release dexamethasone over 1–6 months [33].

Intravitreal implants

In addition to the injection method, IVT implants have been gaining attention because of their ability to release drugs over a longer time. Ocular implants are surgically inserted into the vitreous chamber and devised to be able to administer drugs in a more controlled release fashion, which in turn increases the therapeutic benefits to the retina and choroid. The surgical procedure usually takes less than 1 h, with local anesthesia [31,34]. Surveys conducted by the American Society of Retina Specialists revealed that most clinicians preferred at least 6 months as a minimum time of therapeutic effect when a treatment requires surgical implantation [35]. The first IVT implant in the market, Vitrasert®, was made of a nonbiodegradable polymer to control the release of an antiviral drug for 3 months [5,20]. Although Vitrasert® is no longer on the market, another implant, Retisert®, has been developed using the same technology to release fluocinolone acetonide over 2.5 years [20,31]. The major drawback of nonbiodegradable implants is that a surgical procedure is required for their replacement or removal once the drug is depleted [5,34]. Common adverse effects from this route of treatment include endophthalmitis, retinal detachment, and retinal damage, among others [14]. A more recently approved injectable implant, Iluvien™, is a free-floating implant made of polyimide to treat diabetic macular edema. This cylindrical implant requires a simple procedure with a 25-gauge needle and the entry wound is self-healing. Upon insertion, the loaded drug, fluocinolone acetonide, is released over 18–36 months [5,36,37]. During late 2018, the FDA approved another fluocinolone acetonide implant, YUTIQ™, which can deliver the drug for up to 3 years with high drug loading and linear sustained release kinetics [38]. The first biodegradable IVT implant, Ozurdex, is made of PLGA and delivers dexamethasone upon implantation using a 22-gauge needle in the vitreous. The rod-shaped Ozurdex releases dexamethasone for up to 6 months to treat diabetic macular edema [31,34].

Another advancement of injectable implants was the development of a refillable implant, the Port Delivery System, for the sustained release of ranibizumab to treat AMD. A small implant comprising polysulfone, similar to a rice grain in size, is surgically placed in the pars plana via a 3.5-mm scleral incision [39,40]. The implant is filled with the drug during the procedure and releases the drug for several months. A customized needle is used to refill the drug in a minimally invasive procedure. In 2018, its Phase II clinical trial outcome showed that patients who received implants that went 6 months or longer between implantation and the first refill had visual acuity comparable to that of patients who had received monthly injections [20,35].

Ocular topical administration and topical formulations for posterior segment diseases

The use of topical administration for the treatment of anterior segment diseases is the preferred treatment option of patients [5,19]. Eye drop therapy, accounting for >90% of topical formulations, is convenient because it is self-administered, noninvasive, and causes little discomfort. Despite its convenience, eye drop therapy is not an efficient drug delivery system because most of the administered eye drop is lost as a result of rapid clearance by the blinking reflex during dose administration and nasolacrimal drainage. In addition, tight junctions in the corneal epithelium and systemic absorption limit drug penetration and distribution, resulting in only a minute amount of the administered medication reaching the target tissues [13,16,41]. As a result, frequent dosing is required to achieve therapeutic efficacy, but has led to poor patient compliance and systemic adverse effects [42,43]. Nonetheless, eye drop therapy is still a viable and commonly used option to treat corneal diseases and glaucoma.

The anatomical and physiological barriers of the eye pose challenges when treating posterior segment diseases. Intraocular drug delivery faces two main physiological barriers in the eye; the blood–aqueous and blood–retina barriers. A nonpigmented epithelium, the blood–aqueous barrier limits drug entry to the inner part of the eye from the bloodstream. The blood–retina barrier comprises inner RPE and outer retinal vascular endothelium, which limit the passage of drugs, particularly high-molecular-weight drugs, to the vitreous cavity and retina [22,44,45]. Although it is not fully understood why, topically administered lower molecular weight drugs may reach the retina via corneal and noncorneal pathways. In the corneal pathway, a drug is absorbed through tear ducts, cornea, anterior chamber, lens, posterior chamber, vitreous chamber, and retina. In the noncorneal pathway, drug absorption and distribution occur via conjunctiva and sclera and then across the choroid and RPE, and this is a more probable pathway for topically administered drugs [46–48].

There is no topical formulation approved by the FDA to treat posterior segment diseases. At best, eye drop treatment can be an adjunctive therapy to IVT injections [49]. When patients with AMD were given eye drops of glaucoma drugs along with monthly anti-VEGF intraocular injections, improved visual acuity and OCT were observed [50]. In a pilot study with patients with newly diagnosed diabetic macular edema, twice daily, topical treatment of bromfenac reduced the thickness of the central macula [51]. However, as discussed by David Boyer, a retina specialist [49], eye drop treatment as an adjunctive therapy is less likely to be approved by the FDA unless the topical drug can either completely replace the injection or significantly reduce the burden of IVT injections on patients and physicians. For better treatment and management of posterior segment diseases, an efficacious eye drop formulation might be used prophylactically to reduce neovascularization. It can also be used as an alternative treatment for patients whose conditions do not allow IVT injections and for patients with only one diseased eye [49]. In a successful topical drug delivery system for the treatment of retinal diseases, the drug should be capable of penetrating the cornea or sclera to reach the posterior segment at its therapeutic concentration with minimized toxicity. Table 1 presents a comparison of topical and IVT injections.

Many research efforts have focused on developing topical formulations to successfully deliver drugs to the back of the eye. An eye drop formulation comprising dexamethasone and a cyclodextrin complex suspension was shown to enhance drug delivery to the posterior segment in rabbit eyes [53]. Cyclodextrins are starch-derived oligosaccharides and form aggregates entrapping the lipophilic drug in aqueous solution. These nano-aggregates in the eye

TABLE 1

Comparison of topical and IVT administration for posterior segment diseases[a]

Feature	Topical administration	IVT Injection
Ease of administration	++++; self-administration	+; by trained physician
Safety	++++	+
Compliance	+	+++
Drug reaching retina	+	++++
Systemic exposure	++	++
Cost of drug delivery	+	++++
Adverse effects	+	+
Dosing frequency	Can vary; once or a few times a day	Once every 4–6 weeks
Regular monitoring	Quarterly	Monthly/bimonthly
Common formulation	Eye drops	Solutions, suspensions, implants
Drug delivery systems currently under investigation	Mucus-penetrating peptides; cell-penetrating peptides; hydrogel rings	Depot formulation for sustained release; injectable gels and/or suspensions

[a] Based on Ref. [52].

drop formulation prolong the drug residence time on the ocular surface, thus increasing drug absorption and penetration to the back of the eye [53]. Chitosan, a polysaccharide, has been regarded as a promising formulation excipient for ophthalmic preparations because of its low irritation and mucoadhesiveness. Through protonation of one of its amino groups, chitosan exhibits stronger binding to the negatively charged corneal mucin [42]. Therefore, chitosan-based or chitosan-coated NP formulations can increase the corneal residence time and improve the bioavailability of the drug. Another study showed the feasibility of delivering surface-modified-PLGA NPs prepared with chitosan to the retina upon topical administration in mouse eyes [54].

Lipid or phospholipid bilayers have been widely used in ophthalmic formulations because their functional characteristics can be easily tuned [16,45]. Small liposomes (<80 nm) tagged with transferrin prepared by microfluidizers were able to permeate to the RPE in rat eyes after topical administration [44,55]. Araujo and colleagues demonstrated that the topical administration of triamcinolone acetonide using 170-nm lipid carriers in a mouse model prolonged drug residence time on the ocular surface and enhanced ocular absorption [56]. Topical administration of an annexin A5-associated phospholipid vesicle formulation of Avastin® (bevacizumab)was demonstrated in rat and rabbit eyes. When compared with the delivery of bevacizumab alone, the formulation with annexin A5, a calcium-dependent phospholipid-binding protein, enhanced the delivery of bevacizumab to the back of the rabbit eye [57].

By contrast, a Mucus Penetrating Particles (MMP) technology has been developed by Kala Pharmaceuticals. Drug-loaded polymeric NPs coated with a poloxamer can penetrate mucus to bypass corneal barriers, allowing drugs to reach a higher concentration in the posterior segment possibly via the sclera [58,59]. Topical administration of loteprednol etabonate formulated as MPPs showed that these MPPs could deliver therapeutically effective drug concentrations to the back of the eye in a rabbit vascular leakage model [59]. Another promising study involved a non-invasive cell-penetrating peptide drug delivery system for posterior segment treatment. A team at the University of Birmingham developed an eye drop formulations of cell-penetrating peptide (CPP)-drug complexes with anti-VEGF drugs, either ranibizumab or bevacizumab.The authors demonstrated that the CPP- anti-VEGF drug complexes were delivered to the back of the eye when topically administered in rat, rabbit and porcine eyes [60,61]. In a CNV-induced mouse model, the equivalent therapeutic efficacy of CPP-complexed anti-VEGF drugs was reported compared with the IVT injection of anti-VEGF drugs [60]. CPPs can penetrate cell membranes across the corneal barrier, reaching the posterior segment; thus, this technology, now owned by Macregen Inc., could significantly reduce the treatment burden of AMD [49]. Additionally, it is suggested that the site of topical administration is important because a drug should be applied to the conjunctival area to maximize the drug transport to the posterior segment [62]. Hence, a hydrogel ring comprising 2-hydroxyethyl methacrylate (HEMA) was designed to deliver an antibiotic agent to the posterior segment, demonstrating drug delivery via the sclera and conjunctiva in rabbits [62].

Challenges in clinical translations

Despite the tremendous effort in the development of efficient ocular delivery systems, many technologies have not been successfully translated into a product on the market. This is not a hurdle specific to ocular drug delivery systems.

Most technologies that advanced to clinical trials show adequate efficacy and safety in animal models. However, the promising results demonstrated in animal models do not always lead to similar outcomes in human trials. It is not possible for any animal models manifesting diseases and conditions to replicate the physiological responses in humans, especially for ophthalmic diseases. Although rodent models are well established, cost-effective, and easy to handle, rodent eyes, compared with human eyes, are smaller and have a proportionally larger lens and corneal surface; rodent eyes also have nictitating membranes [14,63]. Rabbits are commonly used to evaluate ophthalmic therapeutics because of they are more comparable in size to that of the human eye compared with rodent eyes. However, rabbit eyes produce more mucus, blink less, and produce fewer tears compared with human eyes [14,64]. These differences in anatomy and physiology affect PK, and this illustrates the difficulty in predicting clinical success based on positive preclinical results [63]. Given that *in vivo* therapeutic evaluations are necessary, it is important to select appropriate animal species to recapitulate human disease states when evaluating the therapeutic efficacy of any drug delivery system. There are genetically engineered animal models available to evaluate therapeutic efficacy. Although it is more

likely that naturally occurring diseases models will accurately represent the pathophysiology, the feasibility of having animal models on-demand is challenging [14].

As mentioned earlier, preclinical studies with positive outcomes do not accurately predict similar outcomes in humans, especially in studies involving nanoformulations. It is expected that the successful clinical translation of nanomedicine would improve drug therapies for human diseases; however, nanomedicines have not been very successful in reaching the clinic and have remained as 'potential' treatments over the past few decades [65,66]. Still considered 'new' technologies, there are many aspects of nano-sized systems that are not well characterized. For successful clinical translation, reliable scale-up production is required to minimize batch-to-batch variations. In addition, the *in vivo* fate of nanoformulations, such as degradation, distribution, clearance, and toxicity, needs to be thoroughly investigated, although this can contribute to a slower clinical translation [67].

Concluding remarks

From a physician's viewpoint, the severity of a condition is never the only factor taken into account when determining the appropriate treatment for a patient. The type of drug and duration of the treatment; drug formulation and administration routes; or the half-life of the drug; and physiological barriers are a few factors that need to be considered when choosing the right treatment for the patient. These factors should also be considered by pharmaceutical and/or biomedical researchers when designing an efficient drug delivery system, in addition to the type and composition of polymers used, the size and surface modification of the drug delivery system, and its stability and degradability. As discussed here, different scientific approaches have been used to develop more efficacious drug delivery systems. It is evident that no one system satisfies the clinical needs to treat retinal diseases and no one system is superior to any other. The need for efficacious drug delivery systems is ongoing to provide higher quality treatment options for both physicians and patients, especially given the increasing incidence of ophthalmic diseases among the aging population. Given the complexity of the eye, recent developments in ophthalmic delivery systems to treat posterior segment diseases are encouraging and the potential of topical treatments could be fully realized in the near future.

Declaration of Competing Interest

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