Posterior drug delivery via periocular route: challenges and opportunities

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Posterior Drug Delivery *via* Periocular Route: Challenges and Opportunities

Abstract

Drug delivery to the posterior segment *via* periocular route is a promising route for delivery of a range of formulations. In this review, we have highlighted the challenges and the opportunities of the posterior segment drug delivery *via* the periocular route. Consequently, we have discussed different types of periocular routes, physiological barriers that limit effective drug delivery, practical challenges regarding patient compliance and acceptability and recent advances in developing innovative strategies to enhance periocular drug delivery. We conclude with a perspective of how we envisage the importance of understanding complex barrier functions so as to continue to develop innovative drug delivery systems.

Keywords: periocular, posterior segment, drug delivery.

Introduction

Drug delivery to the eye, even to the present day, is a difficult task and even more so when it comes to treating diseases and disorders that require drug delivery to the posterior segment [1]. The anatomical and physiological barriers that the ocular environment presents are unique and have led to various routes of administration, each with its own advantages and disadvantages [2]. Despite the issues in getting therapeutic drug levels in this part of the eye, the importance of successful delivery to the posterior segment cannot be underestimated, with the treatment of many proliferative, vascular and degenerative ocular diseases requiring it as a matter of course [3]. This review paper will highlight some of the major posterior segment diseases, routes of administration used to treat them – with a particular focus on the periocular route and the challenges it presents. Current research into this area is also discussed, to establish whether these challenges are being overcome, ~~to~~ and the future direction in periocular drug delivery.

Diseases of the Posterior Segment

Most prevalent eye diseases that cause visual impairment typically originates in the posterior segment of the eye (or back of the eye) and include age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME), uveitis and retinitis. AMD is the leading cause of blindness among the aging population. A chronic disease of the central retina, specifically the macula, this disease is one of the leading causes of blindness and manifests itself in two broad types: neovascular ("wet") AMD or geographic atrophy ("late dry") AMD. In the "wet" form, choroidal neovascularization breaks through the retina leading to leaking fluids, lipids and blood resulting in fibrous scarring. The "late dry" form manifests as progressive atrophy of the RPE, choriocapillaris, and photoreceptors. Treatment methods for neovascular AMD consist of laser photocoagulation, photodynamic therapy and more recently the use of anti-VEGF (vascular endothelial growth factor) therapies [4]. The latter of these treatments is particularly significant here, as ranibizumab and bevacizumab, two of the drugs of this type, are currently delivered *via* intravitreal injection, showing the importance of delivery of the therapeutic agent into the 'local' area of the posterior segment for a therapeutic effect [5].

Uveitis is simply inflammation of the uvea, a structure not just confined to the posterior segment of the eye, resulting in many sub-types of this [6], with posterior uveitis being the focus here. Posterior uveitis involves inflammation of the choroid, retina or both or the retinal vessels, with infection being the cause in over 40% of cases and includes toxoplasmosis, tuberculosis, candida, herpes simplex, zoster or cytomegalovirus [7]. Typically, this disease is treated with corticosteroids and immunosuppressant agents. While periocular delivery of steroids is an option; the oral route is preferred due to issues surrounding administration and

potential for ocular hypertension [8]. Some studies have also highlighted the use of intravitreal steroid injections as a treatment option, albeit with the recommendation being as a short-term treatment [9].

DR is commonly linked to patients that have diabetes mellitus [10], and it is the leading cause of blindness in adults of working age [11]. The loss of vision associated with this can be due to the non-clearance of vitreous humor or fibrosis, which then leads to retinal detachment through traction. Blood vessels can then leak causing permanent central vision loss-diabetic macular edema [12]. DME is the leading cause of visual impairment that occurs with DR. Lots of factors play a role in the development of the disease including; the degree of retinopathy, hypertension, glycemic control or lack thereof blood lipid and albumin levels and fluid retention [11,13]. Treatment options consist of focal or grid laser photocoagulation depending upon the nature of the DME, with the diffuse form being treated with the grid laser to cover the whole area [14]. Pars-plana vitrectomy has to be used in some cases to prevent visual loss, and intravitreal and sub-tenon delivery of corticosteroids have also been used [14,15]. Anti-VEGF treatments, again delivered by intravitreal injection, are also being investigated as treatment options [16]. Once again, while the treatments show promise, delivery of the drugs to the posterior segment in a safe and repeatable fashion is the issue.

The diseases alluded to above and many others that affect the posterior segment of the eye have an influence on the patients' vision and so have a significant impact on quality of life. As a result, treatment of these is of the utmost importance, requiring successful delivery of appropriate drugs, within the therapeutic window in a safe and repeatable fashion. While many drugs have shown promise in treating some of these, effective and safe delivery to the posterior segment is proving difficult.

Drug Delivery to the Posterior Segment of the Eye

Drug delivery to the eye can be achieved through different routes (Fig. 1), as discussed below.

Topical Route

Topical delivery is the most commonly used method of ocular drug delivery, more often for delivery to the anterior segment, to treat diseases such as glaucoma and conjunctivitis. Certain drugs ~~are~~ delivered *via* this route for the treatment of issues in the posterior segment. However, it is highly inefficient as less than 5% of the drug reaches the aqueous humor, with an even smaller proportion reaching the posterior segment due to a variety of barriers [17]. These include the dilution and flushing out of the drug by the tears, nasolacrimal drainage and tear turnover [18].

Moreover, the cornea is a very effective barrier, possessing both lipophilic epithelial and endothelial layers and a hydrophilic stromal layer in between them, giving extremes of polarity as drugs would move through it, restricting their movement. There are also tight junctions present between the epithelial cells, making drug diffusion *via* the paracellular route difficult. A particular difficulty is seen with macromolecules, with only those of less than 50,000 Da being able to move through the stroma [19]. The endothelial layer within the cornea is also lipophilic, meaning that any drug would need an amphiphilic carrier and to possess both hydrophilic and lipophilic groups to move through the cornea effectively. Drugs are often rapidly cleared from the aqueous humor upon penetrating the cornea [20], but diffusion through the highly dense matrix of the vitreous humor is difficult [21]. Therefore, achieving therapeutic drug levels in the posterior segment through topical route such as eye drops, ointments, gels and drug-containing contact lenses is highly problematic.

Systemic Route

Systemic delivery, in the form of a patient taking an oral formulation, would be highly convenient and acceptable to patients it is not an automatic choice. Only a small proportion of systemically delivered drug gets to the posterior segment of the eye, largely due to the barrier properties of the blood-retinal barrier (BRB) [18] and low cardiac output to the retina [22], and thus large systemic doses are often required to achieve a therapeutically-effective drug concentration, which in turn can lead to significant side-effects [18]. Indeed, one study showed the intravitreal drug levels of poorly lipid soluble antibiotics, such as penicillins and cephalosporins are at maximum 10% of serum levels, resulting in frequent administration being necessary and systemic side-effects as a result [23]. Furthermore, with many drugs now being proteinaceous in nature, utilisation of the systemic route would lead to issues such as denaturation and low therapeutic effect as a result.

Intravitreal Injections

A drug delivery method that involves direct injection of a formulation into the vitreous humor *via* the pars-plana (Fig. 1) [24]. It achieves high concentrations of drug in the vitreous and at the neural retina with less systemic side effects than systemic delivery [25]. Solutions, suspensions, depots, liposomes and implants have all been delivered by this route, and many drugs used for the treatment of posterior segment diseases are delivered *via* this pathway [26]. However, the drugs of lower molecular weight are rapidly eliminated, thereby frequent administration becomes necessary, which in turn leads to an increased chance of problems associated with frequent injections, such as retinal detachment, retinal hemorrhage, and endophthalmitis [25,27]. There are also barriers to the retinal area, despite the proximity of the injection site to it. The inner limiting membrane (ILM) is immediately adjacent to both the retina

and the vitreous, and so is the primary barrier to diffusion of drugs into the retina [21]. Furthermore, the BRB, made up of both endothelial, epithelial cells and efflux transporters poses a barrier to inner-retinal cells [17,28]. Although the usefulness of this route cannot be debated due to the drug concentrations it is able to provide in the posterior segment, the invasiveness of the technique, especially if frequent administration or withdrawal of a non-biodegradable implants, does prevent it from being the perfect answer.

Periocular Routes of Drug Delivery

Periocular route involves the delivery of drugs to the periocular area, the area that immediately surrounds the eye, and is thought to be a good compromise between lack of pain on delivery and efficiency for drug delivery to the posterior segment (Fig. 1) [1]. Furthermore, since this route targets the area surrounding the eye, there are less chances of some of the more worrying complications associated with intravitreal injections such as endophthalmitis, rise in intraocular pressure and retinal detachment [3], while simultaneously providing a close enough proximity to deliver detectable levels of the drug within 20-30 minutes after administration [1]. In comparison to intravitreal delivery, this method is found to be more efficient for delivery to the outer retina whereas intravitreal delivery is superior in the context of treating retinal ganglion cells and inner retinal interneuron disorders [29]. This type of delivery involves the insertion of drugs or drug delivery systems close to the sclera and consists of five sub-divisions; subconjunctival, retrobulbar, peribulbar, sub-tenon and posterior juxta-scleral route [24,30]. Following periocular delivery drugs move to the sclera *via* one of three pathways; the transscleral pathway, in the circulation *via* the choroid and through the anterior pathway (tears film, cornea, aqueous humor then vitreous humor) [31].

Subconjunctival route

The subconjunctival route involves insertion of a formulation underneath the conjunctiva, which gives direct access to the sclera and therefore provides the transscleral pathway for drug diffusion. This route eliminates the need for the drug to diffuse through the conjunctival surface, which limits hydrophilic drug permeation [32] and the loss of drug due to the cleaning action of the mucus layer secreted by its goblet cells [1]. Typically, a needle of up 25 to 30-gauge and 30 mm long can be used, with a maximum injection volume of 0.5 ml [3]. A variety of drugs have been successfully delivered *via* this route with high concentrations in the posterior segment achieved. For example, in a study dexamethasone showed higher levels in the subretinal fluid than those obtained with oral or peribulbar routes, suggesting that this method is capable of delivering a greater proportion of the drug load to the retina [33].

Retrobulbar route

This route of delivery involves an injection into the retrobulbar space, within the muscle cone [1] that is composed of the four rectus muscles and their intermuscular septa. This route is preferable when direct contact of the formulation with the macula is required [1], usually using a blunt 25 or 27-gauge needle due to there being a reduced chance of eye injury [3]. The retrobulbar space can accommodate up to 2-3 ml of a solution [1].

Peribulbar route

An injection that is external to the four-rectus muscles and their intermuscular septa, this route is an alternative to the retrobulbar route, with a lower chance of ocular injury [3]. Injections can be either inferior or superior in nature [3], with an injection into the inferior-lateral quadrant using a 26-gauge 0.25 inch needle [34] and temporal administration (a type of superior injection) using a 25-gauge 1.25 inch needle. Volumes of 8-10 ml can be delivered using this route. Despite being a safer route in comparison to the retrobulbar route, it is also less effective when being used for anesthesia of the globe [3].

Sub-tenon route

Anatomically speaking the tenon's capsule is made up of connective tissue located between the conjunctiva and episcleral plexus and the space between the capsule and the sclera is the sub-tenon's space containing anterior and posterior segments [35]. It surrounds the eye and extraocular muscles in orbit, originating in the limbus and extending back to the optic nerve [36]. For anesthesia, a 1-inch blunt-tipped cannula is used, with a volume of administration of up to 4 ml [3,36]. Posterior sub-tenon injections use a 26-gauge, 5/8-inch needle to administer the drug into the posterior sub-tenon space [3]. This route has its advantages because the avascular nature of the tenon's capsule increases drug contact time with the sclera and when the blunt cannula can be used for anesthetic delivery [35], sharp-needle issues are removed[3]. The route does, however, suffer from poor penetration of drug through the sclera and choroid and choroidal clearance [35].

Posterior Juxtascleral route

This route is a more recent method that was used to deliver anecortave acetate for the treatment of subfoveal neovascularization in AMD. It utilizes a blunt-tipped curved (56º) cannula to place the drug on the surface of the sclera without penetration of the eyeball. This method was used to deliver the drug close to the macula to maximize treatment effectiveness [30]. Studies have shown that this method of delivery to be a safe and effective for delivery of drug molecules to the choroid and retina in the macular region for up to six months [37]. Table 1 summarizes overall benefits and challenges of different routes of drug delivery to the posterior segment of the eye.

Challenges of Periocular Drug Delivery

Despite the advantages that periocular delivery has, it is not without challenges when it comes to delivery of therapeutically effective concentrations of drug to the target site in the posterior segment. There are many physiological barriers, safety concerns and issues that would hinder patient compliance.

One of the major issues faced using periocular delivery are the physiological barriers that need to be crossed to get therapeutically effective drug concentrations at the target site within the posterior segment. The direct penetration pathway is *via* the sclera, choroid, RPE, retina, outer limiting membrane, ILM and then into the vitreous, in that order [3]. Furthermore, drugs can also move *via* the anterior chamber to the vitreous humor and *via* the systemic circulation, where it moves out of the periocular space in conjunctival, episcleral or choroidal vessels into the systemic circulation and then back into the ocular circulation. The drug can also permeate through the anterior chamber where it diffuses into the aqueous humor either directly or *via* the sclera and ciliary body or *via* the tear fluid and cornea after it has been refluxed through the conjunctiva. Within these different pathways, there are three main types of barriers namely static, dynamic and metabolic [38].

Static Barriers

The Sclera

The scleral barrier is continuous with the cornea, with its origin in the limbus from which it extends throughout the globe [32]. Anatomically the sclera is similar to the stromal layer of the cornea [39], consisting of an extracellular matrix with embedded collagen fibers and proteoglycans [40]. As a result, the sclera's permeability is also similar to that of the corneal stroma [39,40], with greater permeability than that of the overall cornea, having a larger surface area (16.3 cm^2 compared to around 1 cm^2 [40]) and lower protease activity [24]. Permeability is inversely proportional to molecular radius and this property, rather than lipophilicity is what has the main effect on scleral permeability [39]. However, increased lipophilicity causes a decrease in permeability [41]. It has also been found that positively charged molecules permeate the sclera less effectively, due to the negatively charged proteoglycans within the extracellular matrix [42]. Although certainly not entirely permeable, the sclera is not one of the main rate-limiting barriers to be overcome for drugs to reach the posterior segment.

The Choroid and Bruch's Membrane

The next rate-limiting barrier is the choroid [3]. Choroid majorly consists of blood vessels, providing a blood supply for the outer retina [43]. The choroid and Bruch's membrane form a static layer to drug permeation, with permeability decreasing with increasing molecular weight and lipophilicity and similar to the sclera, permeation is reduced with positively charged molecules [44]. The barrier property changes with age, as the choroid, gets thinner and the Bruch's membrane thickens, which alters drug permeation over time [45]. For example, the permeability of taurine through the Bruch's membrane-choroid complex reduces with increased thickness of the Bruch's membrane, suggesting it may be a significant barrier to the permeability of small solutes [46].

The Retinal Pigmented Epithelium (RPE)

The RPE is another static barrier and is also known as the outer blood-retinal barrier (oBRB), which in combination with the inner blood-retinal barrier (iBRB) make up the blood-retinal barrier [38], which is the barrier responsible for restricting movement between the blood and the retina. The iBRB relies on Müller cells and retinal capillary vessels to maintain its proper function, which is to control the uptake of nutrients and the release of metabolites. If drugs move into the circulation they can then bypass the iBRB *via* the choroid, so the oBRB is responsible for restricting movement of drugs from the choroid into the retina, and is, therefore, a highly significant static barrier [38]. Formed from specialized hexagonally shaped cells, the RPE forms a cellular barrier, and its efficiency is further augmented due to the presence of tight junctions between the cells, restricting movement via the paracellular route [38,42]. Studies have shown that permeability decreases with an increase in molecular radius and increase with increasing lipophilicity [42,44] and also that taurine permeability across BC-RPE barriers was lower than across BC alone, which would suggest that RPE is the layer that limits its penetration [47].

Dynamic Barriers

Dynamic barriers that can reduce the drug levels in the posterior segment of the eye, including blood flow, lymphatic clearance, transport proteins present on the RPE, bulk fluid flow, drug efflux pumps and organic ion transporters [38,42].

Conjunctival/Episcleral Clearance

Many studies have shown that the drug present in conjunctival and episcleral tissues is cleared due to blood and lymphatic flow. For example, when a 'conjunctival window' was made by an incision to inhibit blood and lymphatic clearance, higher triamcinolone acetonide levels were attained in the vitreous humor, which clearly shows this is a noteworthy barrier and in this case of greater significance than clearance due to choroidal blood flow [48].

Choroidal Blood Flow

Choroidal flow is considered in some quarters to be one of the main barriers to drug permeability into the posterior segment [3], but as referred to earlier, this is up for debate. The issue is that the extent to which choroidal blood flow is a barrier cannot be determined by simply by measuring systemic drug levels because there are more paths that the drug can take than just choroidal blood flow including the clearance *via* conjunctival vessels mentioned earlier. The study involving the sub-tenon delivery of triamcinolone acetonide utilized cryotherapy to eliminate the effect of choroidal blood flow, and those rabbits that received the cryotherapy didn't have higher vitreous drug levels suggesting that choroidal blood flow doesn't significantly contribute to a reduction in drug levels in the posterior segment *via* transscleral delivery [48]. Conversely, another study involving subconjunctival delivery found that clearance by the blood was of greater significance than that of lymphatic clearance [49], although the type of periocular delivery and drug used were different. More studies must be done, however, as it is clear that this finding is not universally accepted [3,32]. Convective flow within the eye is also thought to play a role in drug elimination, moving most of the drug into the choroidal and conjunctival vessels [42].

Osmotic and Hydrostatic Pressure

Osmotic and hydrostatic pressure differences between certain areas in the eye also contribute to outward bulk flow and drug elimination. There is an osmotic pressure difference between the choroid and the vitreous which leads to bulk flow in the direction of the choroid [42], while there is also a hydrostatic pressure difference between suprachoroid and episcleral tissue also lead to outward bulk flow [50].

RPE Transporters

Transporters are present on the RPE may have a significant role in drug transport, however much more research into this area is required [51]. There are various types of ion and amino acid transporters and significantly drug efflux pumps. Transporters for amino acids such as glutamate, taurine, gamma-aminobutyric acid (GABA) and leucine have been found on the RPE, and it is thought that these may have some role in drug transport, as well as physiologically. There are also oligopeptide transporters that have been shown to have a role in cephalosporin transport across the retina [52] and organic cation transporters, of interest due to many current drugs being of this nature including sympathomimetics, antihistamines and vitamins [51]. Efflux proteins are thought to be of high importance when it comes to drug permeation through the RPE, although they haven't been widely studied [51]. Efflux pumps of the ATP-binding cassette family include P-glycoprotein (P-gp) and multidrug resistant proteins (MRP) and these pump drugs from cells into the extracellular space [53]. Generally speaking,

P-gp pumps eliminate large neutral or cationic compounds, and the MRP pumps eliminate large neutral or anionic compounds [54]. It has been found that both of these pumps move compounds, including drugs, towards blood in the BRB [55]. They remove compounds *via* the choroidal circulation and ultimately the systemic circulation. Overall the RPE is thought to be equal in importance to the sclera in terms of the permeation of small lipophilic molecules and more importantly large or hydrophilic molecules [56].

Metabolic Barriers

These barriers involve the cytochrome P450 system, a family of haem-containing isozymes that are involved in around 80% of oxidative drug metabolism and around 50% of drug elimination [57], and lysosomal enzymes [38,42]. Both types of the enzymes can detoxify or even degrade drug compounds, ultimately reducing drug concentration in the posterior segment. High levels of cytochrome P450 enzymes have been found in both mouse and bovine RPE, and this combined with the high level of interaction this enzyme system has with modern drugs, means this barrier is certainly worthy of serious consideration. Lysosomal enzymes are found in lysosomes within cells, and some drugs can enter these structures *via* passive diffusion [58]. Exposure to the lysosomal enzymes could, therefore, lead to degradation since these enzymes are known to have a broad spectrum of activity [59]. Hydrolytic enzymes are also present in the retina as well as aldehyde oxidase, ketone reductase and conjugating enzyme systems which have been characterized in the ocular tissues of different animals as detailed by Attar et al. [54]. This evidence would suggest that there is a lot more research to be done in understanding the presence of different ocular enzymes in humans and its effect on the ocular bioavailability of drugs.

Clearly, when it comes to the dynamic and metabolic barriers to the ocular delivery, there is a lot less information and evidence of understanding of these in the literature. To get a more detailed picture of the barriers to periocular delivery more research needs to be done into these areas, something that was also concluded by Kim et al. in their review of the barriers to transscleral drug delivery [42].

Practical Challenges

Even though the periocular route is less invasive and safer than the intravitreal route, it is not entirely without complications. Sub-tenon injections are associated with chemosis and subconjunctival hemorrhage with incidence rates of 39.4% and 32-56% respectively, and this is despite the fact that this is one of the ‘safer’ periocular delivery methods. Retrobulbar injections are associated with retrobulbar hemorrhage, globe perforation and respiratory arrest

(when used for anesthetic delivery due to brainstem anesthesia), with incidences of 1.7%, 0.75%, and 3% respectively. The peribulbar route is associated with a significantly lower rate of globe perforations (0.0008% compared to 0.75%) than retrobulbar and no incidence of the other two issues [3,32].

The very nature of periocular delivery means that specialist ophthalmologists and centers are required to administer treatment *via* this route, especially with technology such as real-time tomography reflection of sonographic images are being used in efforts to make peribulbar and retrobulbar delivery safer. The requirement of specialist equipment means that compliance is likely to be affected, especially if repeated treatments are required. Logically, this can be overcome by using implantable devices to deliver the drug over a prolonged period, reducing the number of separate treatment procedures, but these in themselves present significant challenges, such as burst release, dose dumping, and low bioavailability [60]. Biodegradable implants are useful, as they don't need to be retrieved after implantation, but are more likely to have issues such as burst release and poor linearity of release [61]. Non-biodegradable implants do give a more predictable and controlled release over time but are more invasive due to their removal being necessary. Moreover, non-biodegradable systems can potentially trigger immune responses, while larger implants produce foreign bodies like reaction – resulting in the surface attraction of fibroblasts, foreign body giant cells, and macrophages, leading to the formation of a fibrous capsule which in turn can prolong its degradation and elimination [62]. This reaction, in turn, restricts drug bioavailability and the longevity of the treatment period for the implant.

Strategies to Improve Periocular Delivery

A variety of different formulations and techniques are currently researched for periocular delivery, including implants, gels, microparticles (1-1000 μm) and nanoparticles (1-1000 nm) alongside many other colloidal systems to provide formulations that give controlled and sustained release of their active pharmaceutical ingredient (API). Moreover, non-invasive or minimally invasive techniques such as iontophoresis and microneedles have also been researched for transscleral delivery to improve the penetration of drug or sustained release formulations. Table 2 shows some examples of small and large drug molecules and routes for administration for treating posterior segment eye diseases. These drug molecules vary widely in their molecular size that causes significant challenge in effective permeation across trans-scleral/periocular barriers. Therefore, a range of formulation approaches have been investigated to improve periocular delivery, as described below.

Micro-/Nano-particles have seen varying levels of success. For example, subconjunctival administration of budesonide solution and budesonide-loaded microparticles (3.6 μm) and nanoparticles (345 nm) achieved higher retinal levels, with the microparticles showing superiority to other formulations in terms of sustained delivery. It is likely due to the greater retention potential of the microparticles in the periocular space compared to the nanoparticles. There was, however, an initial burst release of 25 % from the nanoparticles, something that is often seen with this type of formulation. The microparticles exhibited no discernible burst release, probably due to the reduced surface drug due to a surface area of microparticles, but the sheer size of the particles means that local tissue irritation is more likely [63].

A study by Amrite et al. also showed that an increase in particle size leads to higher residence times at the injection site, which ultimately leads to greater drug levels in the target tissue for longer. Similarly, higher particle size (approximately 200 nm) is also shown to reduce removal clearance by the lymphatic and choroidal circulation [64,65]. Furthermore, the periocular route has been used to deliver celecoxib-containing microparticles to the posterior segment, following subconjunctival injection and were capable of providing drug release over a 14-day period and reducing diabetes-induced biochemical markers [66]. More recent research in a collaborative effort between Santen Pharmaceuticals and Oakwood Laboratories is showing promise, with the development of a biodegradable PLGA microsphere using Oakwood Laboratory's Chroniject system that is capable of releasing betamethasone periods from 10 days to 1 year [67,68].

Liposomes are vesicular systems, with very similar structures to that of a phospholipid bilayer. Typically, these systems range from 10 nm to 10 μm in size, with the small unilamellar vesicles being 10-100 nm and the large unilamellar vesicles being 0.1-10 μm. It is also possible to have multilamellar systems consisting of more than one bilayer [1,17]. Due to the presence of both hydrophilic and hydrophobic compartments, these formulations can incorporate drugs of both types into their structure and have been used for delivery of a variety of antibiotics and antiviral agents [69]. Liposomes have been used to a limited degree in periocular drug delivery, with one example being in the delivery of a periocular vaccine against HSV infection in rabbits. This vaccine was actually shown to be more effective in this capacity than systemic vaccination [70].

Hydrogels are another formulation strategy that has been researched to improve periocular delivery. In particular, for posterior segment delivery, hydrogels have been placed subconjunctivally. For example, a hydrogel formulation has been used to deliver insulin for the treatment of DR. The ratio of N-Isopropylacrylamide (NIPAAm) to dexamethasone-lactate-

Hydroxyethylmethacrylate (HEMA) was altered with the best formulation achieving insulin release for 18 days, with the activity of the insulin being similar to that of control insulin [71].

Implants have also been investigated and while zero-order *in vitro* and *in vivo* release has been demonstrated, the release time was only for four weeks [72] – far shorter than what would probably be required for patient compliance and acceptability in posterior segment treatments. A bioerodible dexamethasone implant has also been developed for the treatment of uveitis and postoperative cataract inflammation, that was capable of near zero-order release for six weeks with histological studies showing no signs of inflammation [73]. As mentioned above these come in biodegradable and non-biodegradable forms, with different advantages and disadvantages, but with polymer research always evolving an implant that meets the needs from a pharmacological and practical point of view is not too far away. Essentially, non-biodegradable implants can provide the controlled release and release duration required, but their size, the need for surgical attachment and the fact that they need to be removed again are major drawbacks.

Huang et al. also very recently used a capsular drug delivery system inserted into the sub-Tenon's sac of New Zealand rabbits, which showed sustained release of dexamethasone sodium phosphate over a 56-day period [74]. However, this hasn't yet been carried out *in vivo* in humans, and the release period is probably too short for patient compliance if they have chronic conditions. Nevertheless, it shows research into sustained release systems delivered *via* the periocular route is heading in the right direction.

Iontophoresis, a technique that utilizes the application of a small electrical current to the outside of the eye, is designed to enhance drug penetration into the posterior segment without the need for a surgical procedure. This technique has been shown to improve the transscleral penetration of a variety of drugs, including steroids, antibiotics, and macromolecules and can deliver high concentrations of drug to the choroid and retina. Many devices such as Eyegate [75], Eyegate II [76] and Ocuphor [77] have been developed with ease of use is a primary concern. Although promising, the technique does have some problems, such as epithelial edema, decrease in endothelial cells and even burns depending on the levels of current used and the exposure times [77].

Microneedles initially developed for transdermal delivery, are a novel approach for minimally invasive delivery of drugs across the sclera using needles in the micron's range (e.g. 100 - 1000 μm). As discussed in the review paper by Thakur et al. they are a relatively new periocular approach that allows for local and minimally invasive drug delivery thereby holds the potential for improving patient compliance. They also reduce the clinical and technical complications associated with the use of hypodermic needles, whilst still potentially allowing

for penetration of ocular barriers for the localized delivery of both drug and formulations. When they have been used in studies to deliver small amounts of drug formulations to areas such as the sclera and suprachoroidal space, no damage to the sensitive tissue has been noticed [78]. These systems can be used to deliver controlled release formulations such as microparticles and nanoparticles. One example of such research is that of Jiang et al. which involved the use of hollow microneedles to deliver, 10-35 µl, of model drug solution, nanoparticles, and microparticles. For the former two substances researched, the microneedles were simply allowed direct deposition of the payload, whereas in the latter enzyme (hyaluronidase) was used to accommodate microparticles due to its large size [79]. Patel et al. used hollow microneedles for the delivery of bolus drug, microparticles, and nanoparticles into the suprachoroidal space via the sclera, consistently achieving delivery volumes of 35 µl [80]. Microneedles have also been in our group used to deliver intrascleral thermoresponsive implants that were capable of localizing delivery of thermo-responsive hydrogel implants (Fig. 2), which was then able to provide sustained release [81]. Our group also investigated dissolving implant forming microneedles to increase penetration across the scleral tissue, and whilst their effectiveness for small molecules was limited, they did show significant penetration enhancement with macromolecules (Fig. 3), so could have a significant role in the future of periocular delivery [82]. This technique is limited though due to the very limited nature of research that has been done, so there is a need to demonstrate safety and efficacy. The injection volumes achieved are also very small, so the duration of action of any would-be intrascleral depot would be limited as a result.

Unlike delivery of small molecules, periocular delivery of high molecular weight proteins (e.g. anti-VEGFs such as bevacizumab, ranibizumab, and aflibercept) needs special attention. This is due to the challenges associated with physicochemical properties of the proteins, stability, permeation and formulation issues. Therefore, proteins are directly injected into the eye using intravitreal injections [83]. For example, the static and the dynamic barriers, as discussed above, also restrict adequate permeation of protein drugs in the target ocular tissues. Furthermore, due to the large size, charge, *in vivo* interaction with other chemical moieties, enzymatic degradation, periocular clearance and stability issues - proteins delivery results in low efficiency and low bioavailability, posing additional challenges for the successful delivery of protein drugs to the target sites [84]. The unique physicochemical properties of the proteins posses' significant challenges in developing suitable formulations. However, recently some formulation approaches have been developed to overcome these concerns, including nanoparticles, microparticles, in situ-forming gels and preformed implants, as discussed above. Importantly, the rationale behind these innovative formulations for protein-based therapeutics are to (i) improve *in vivo* stability and protecting from denaturation; (ii) increasing

the permeability of the protein across biological membranes to achieve higher bioavailability; and (iii) providing sustained protein release at the target site.

Injectable protein-loaded nano/micro-particles can provide sustained release and facilitate protein permeation across ocular barriers [85]. One advantage of nanoparticles is that they can enter cells, which provides the possibility of delivering protein intracellularly [86]. Sustained drug delivery to the target ocular tissue, especially the posterior segment, through periocular administration would require prolonged retention time of the delivery systems at the periocular site. The size of nanoparticles greatly affects their retention time after periocular administration. For example, particles ranging from 200 to 2000 nm were almost completely remained after subconjunctival administration for at least two months, while 20 nm particles were cleared rapidly from the site of administration [65,87]. For example, the release of bevacizumab (Avastin®) loaded polylactic-co-glycolic acid (PLGA) nano- and microparticles can be sustained for over 91 days [88]. However, the exposure of bevacizumab to organic solvents during the particle preparation can compromise its activity, which was overcome by using albumin as a stabilizer in the particle formulation process [89].

Hydrogels usually possess high compatibility and have been used as ocular drug delivery systems to prolong the retention time and bioavailability of the incorporated drugs [90]. Several polymeric gelling systems, such as chitosan, poloxamers, hydroxypropyl cellulose, hydroxypropyl methylcellulose, poly (N-isopropylacrylamide) and copolymers composed of polycaprolactone (PCL), polyethylene glycol (PEG) and PLGA, have been used as ocular delivery systems. Hydrogel-based ocular drug delivery systems can be divided into *in situ*-forming gels and preformed gels. *In situ*-forming gels involve polymeric solutions which undergo a sol-gel transition to form a gel in response to a stimulus, including changes in temperature, pH, and ionic composition, as well as UV exposure [91]. Thermo-responsive gelling systems are one of the most studied *in situ* gelling systems since these systems undergo *in situ* gelation once injected into the body, providing a great opportunity for the development of injectable ocular drug delivery system [90]. In situ gelling systems are generally used to prolong the residence time of protein drugs at the administration site and enhance bioavailability. In an *in vivo* study, ovalbumin concentrations can be maintained at measurable levels in the sclera, choroid, and retina of rats for up to 14 days after subconjunctival injection of a PLGA-PEG-based thermo-gelling delivery system [92]. Preformed gels are usually administered by subconjunctival implantation to delivery therapeutic agents to the posterior segment of the eye. The main advantage of preformed gels is that the sol-gel transition happens *in vitro*. This will minimize *in vivo* tissue irritation and systematic toxicity caused by the burst release during the sol-gel transition, which is the major drawback of *in situ*-forming gels [93]. Misra et al, developed insulin-loaded hydrogels

synthesized by UV photopolymerization of N-isopropylacrylamide (NIPAAm) monomer and a dextran macromere [71]. The hydrogels can release biologically active insulin *in vitro* for at least one week. The hydrogels showed no toxicity to retinal neuron cells and high compatibility after subconjunctival implantation. In an *in vivo* study, these insulin-loaded hydrogels were administered *via* subconjunctival implantation in diabetic rats. The results indicate that insulin released from the implanted hydrogels can penetrate into the rat retina in a sustained manner, and rescue retinal cells from apoptosis in diabetic rats [94].

Future Perspective

Drug delivery to the posterior segment of the eye is clearly very important for the treatment of many of the more serious ocular diseases and with an ever-growing and aging population, its importance is only going to increase. The periocular route offers clear advantages over the topical and systemic routes of administration for delivery to the posterior segment and has advantages over the intravitreal route too, particularly in the context of invasiveness and patient safety.

Strides are always being made in ocular drug delivery, and in particular to periocular delivery the future probably goes hand-in-hand with the ever-evolving field of polymer science, which could potentially yield a biodegradable and indeed biocompatible system that can deliver its yield over a period of months to years, without the all too familiar issues of dose dumping and burst release. Although a system such as this may not be imminently available for patients, it is certainly not an unrealistic aim for the future, and if it were possible for it to be self-administered, as stated by Thrimawithana et al. – an 'ultimate solution' [24]. There is significant evidence of research into protein delivery *via* the periocular route, with nano/microparticles and hydrogels being popular. Other formulations could be utilized for this purpose and will probably be seen more regularly in the future, as well as formulations capable of delivering their protein over longer time periods, which will be key in the treatment of chronic posterior ocular disease. Furthermore, techniques such as iontophoresis and microneedle delivery are clearly promising and improve drug and formulation penetration through the numerous physiological barriers within this delivery route, so a combination of this with the above could be very beneficial for the treatment of disease in the posterior ocular segment and patient acceptability. Ultimately research is going to be focused on improving the bioavailability of therapeutic agents in the posterior segment *via* periocular delivery, while also striving for patient safety, a reduction in the complications and minimal adverse effects. That being said, if the possibility of a device that allows for safe and effective, self-administered periocular delivery becomes a reality-combining effective periocular delivery and patient compliance it would revolutionize the treatment of ocular diseases. However, these studies

will have to take into account the different barriers to periocular delivery, particularly the dynamic and metabolic barriers, due to the lack of research in these areas. Moreover, physiological barriers are often very different in the disease state, something which will need to be considered to a greater detail for development of successful treatment strategies *via* periocular delivery.

Executive Summary

Posterior Segment Drug Delivery

- Posterior segment of the eye diseases are on the rise with increasing aging population.
- Drug delivery to the posterior segment can be achieved by a number of routes such as topical, systemic, periocular, and intravitreal routes

Periocular Drug Delivery

- Periocular route offers clear advantages over the topical and systemic routes of administration and has advantages over the intravitreal route too, particularly in the context of invasiveness and patient compliance.
- Following periocular administration, static, dynamic, and metabolic barriers must be overcome to get therapeutically effective drug concentrations at the target site within the posterior segment.
- Periocular injections are not without side effects such as chemosis, hemorrhage, globe perforation and respiratory arrest. And, need for sophisticated facilities such as real-time tomography reflection of sonographic images being used in efforts to make peribulbar and retrobulbar delivery safer.

Ongoing developments

- A variety of different formulations and techniques have and are being researched for periocular delivery, including hydrogels, implants, devices, and micro/nanoparticles so as to provide sustained release of the API.
- Modified release systems provide great opportunity to reduce the frequency of periocular injections and thereby improve patient compliance. Non-invasive and minimally invasive techniques such as iontophoresis and microneedles provide new opportunities to further reduce the invasiveness of periocular drug delivery. However, more research is needed in this area.
- Periocular ocular route combined with innovative sustained release systems provides safe and effective posterior drug delivery than its counterparts. However, a thorough

understanding of barriers, both in healthy and disease state, is much needed for successful treatments *via* periocular delivery.

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Figure captions

Figure 1. Different routes of periocular delivery.

Figure 2. Optical coherence tomography images showing 30 G hollow microneedle injection of thermoresponsive hydrogel (coloured in red) injected into sclera to a depth of 400 μm at (a) 0, (b) 1 and (c) 2 h. The arrow indicates empty space in sclera created following hollow microneedle application and its subsequent closure over time. **Adapted with permission [81], 2014, Wiley.**

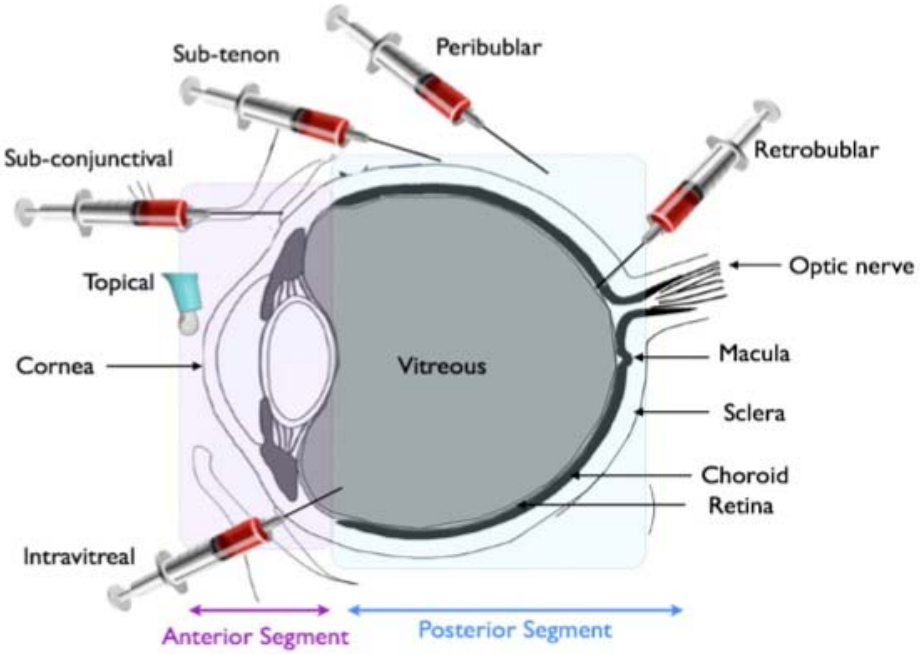
Figure 3. A schematic diagram of periocular administration of dissolving microneedles (MNs) – the left hand side represents the collection and processing of confocal images of scleral tissues following application of MN arrays, where (a) topical image of tissue after 5 min following insertion of MN array, (b) cross section image of tissue after 5 min following MN array insertion, (c) topical image at a depth of 80 μm from surface of the tissue after 1 hr following MN insertion, and (d) cross section image of tissue 1 hr after applying an aqueous drug solution. **Adapted with permission [82], 2016, Springer**

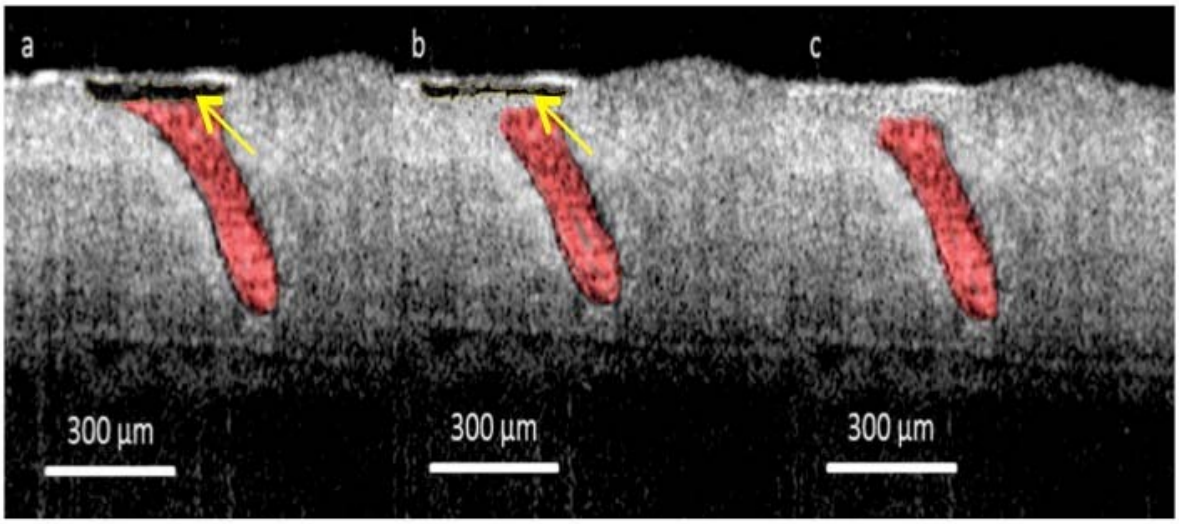
Table 1. Benefits and challenges of different routes of drug delivery to the posterior segment of the eye. **Adapted with permission [39], 1998, Wiley.**

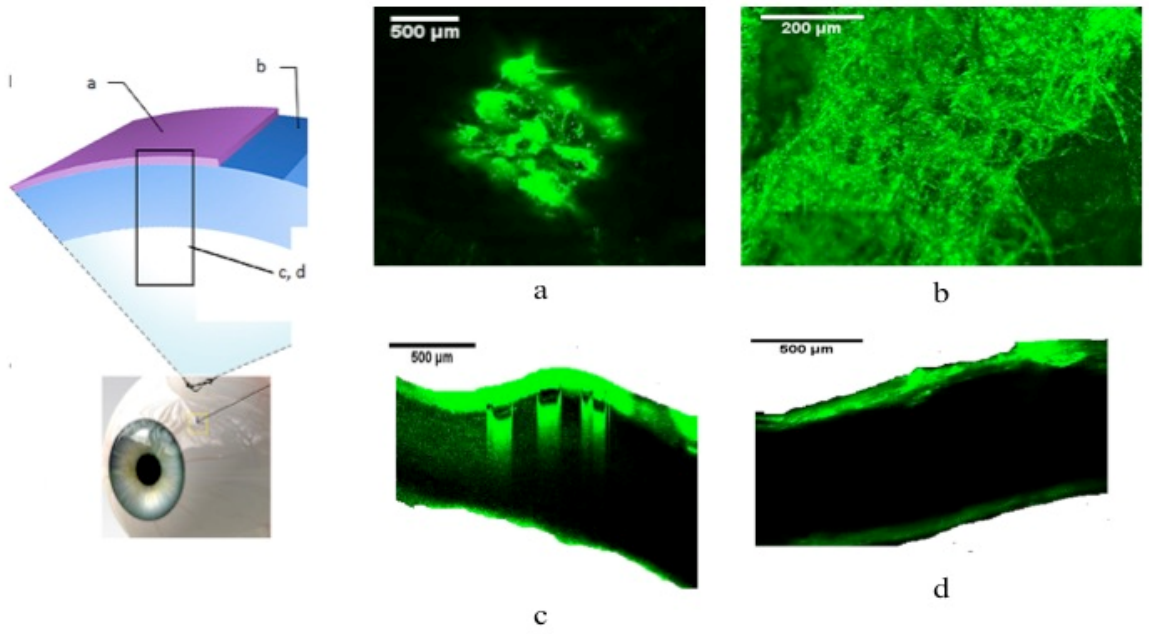
Route of Administration	Benefits	Challenges
Topical	High patient compliance, self-administrable and non-invasive	Higher tear dilution and turnover rate; cornea acts as a barrier, efflux pumps, and low bioavailability (< 5%)
Oral (systemic)	Patient compliant and non-invasive route of administration	Blood-aqueous barrier, BRB, high doses causing toxicity and low bioavailability (< 2%)
Intravitreal	Direct delivery to the vitreous and retina; overcomes BRB function	Highly invasive, retinal detachment, hemorrhage, cataract, endophthalmitis, and low patient compliance
Subconjunctival	Delivery to both anterior and posterior segment and easy administration of depot formulations	Conjunctival and choroidal circulation act as barriers
Subtenon	High vitreal drug levels, relatively noninvasive, fewer complications unlike intravitreal delivery	Retinal pigmented epithelium (RPE), chemosis, and subconjunctival hemorrhage
Retrobulbar	Administer high local doses of anesthetics, more effective than peribulbar, minimal influence on intraocular pressure	Retrobulbar hemorrhage, globe perforation, and respiratory arrest
Posterior juxtascleral	Safe for delivery of depot formulation, sustain drug levels up to 6 months to the macula, avoids risk of endophthalmitis and intraocular damage	Requires surgery and RPE acts as barrier

Table 2. Examples of small and large drug molecules used in the treatment of the posterior segment eye diseases.

Drug molecule	Indication	Delivery route
Dexamethasone	DME and uveitis	Intravitreal
Fluocinolone acetonide	Chronic non-infectious uveitis, DME	Intravitreal
Celecoxib	Diabetes	Periocular injection
Insulin lispro	Diabetic retinopathy	Subconjunctival hydrogel
Ganciclovir	Antiviral	Intravitreal
Budesonide	Anti-VEGF treatment	Subconjunctival micro/nanoparticles
Triamcinolone acetonide	Wet-AMD	Transscleral (sub-tenon injection) or intravitreal injection
Bevacizumab (Avastin®)	Wet-AMD and DME	Intravitreal
Ranibizumab (Lucentis®)	Wet-AMD, DME and retinal vein occlusion	Intravitreal
Afibercept (Eylea®)	Wet-AMD, DME and retinal vein occlusion	Intravitreal


Sub-tenon
Peribublar
Retrobublar
Sub-conjunctival
Optic nerve
Topical
Cornea
Vitreous
Macula
Sclera
Choroid
Retina
Intravitreal
Anterior Segment
Posterior Segment


a
b
c
300 µm
300 µm
300 µm


a
b
c, d
500 µm
200 µm
a
b
500 µm
500 µm
c
d