‘Principles of Pharmacology in the Eye’

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Abstract

The eye is a highly specialised organ that is subject to a huge range of pathology. Both local and systemic disease may affect different anatomical regions of the eye. The least invasive routes for ocular drug administration are topical (e.g. eyedrops) and systemic (e.g. tablets) formulations. Barriers that subserve as protection against pathogen entry also restrict drug permeation. Topically administered drugs often display limited bioavailability due to many physical and biochemical barriers including the pre-corneal tear film, the structure and biophysiologic properties of the cornea, the limited volume that can be accommodated by the cul-de-sac, the lacrimal drainage system and reflex tearing. The tissue layers of cornea and conjunctiva are further key restrictors to drug delivery. Using carriers that enhance viscosity or bind to the ocular surface increase bioavailability. Matching the pH and polarity of drug molecules to the tissue layers allows greater penetration. Drug delivery to the posterior segment is a greater challenge and currently the standard route is via intravitreal (IVT) injection, notwithstanding the risks of endophthalmitis and retinal detachment with frequent injections. Intraocular implants that allow sustained drug release are at different stages of development. Novel exciting therapeutic approaches include methods for promoting transscleral delivery, sustained release devices, nanotechnology and gene therapy.

Abbreviations

AADS	Airless Antibacterial Dispensing System
AAV	Adeno-associated-virus
ADAs	Anti-drug antibodies
AIDS	Acquired immune deficiency syndrome
AMD	Age-related macular degeneration
BAC	Benzalkonium chloride
BRB	Blood retinal barrier
BRVO	Branch retinal vein occlusion
CMV	Cytomegalovirus
CNTF	Ciliary neutrophic factor
CNV	Choroidal neovascularisation
CRVO	Central retinal vein occlusion
DALYs	Disability-adjusted life-years
DR	Diabetic retinopathy
ECM	Extracellular matrix
ESC	Embryonic stem cells
EVA	Ethylene vinyl acetate
FA	Fluocinolone acetonide
Fab	Fragment antigen-binding
FDA	Food and Drug Administration
GA	Geographic atrophy
GAGs	Glycosaminoglycans
GFS	Glaucoma filtration surgery
HA	Hyaluronic acid
HAART	Highly active antiretroviral therapy
HPMC	Hydroxypropylmethylcellulose
hPSCs	Human pluripotent stem cells
IL-6	Interleukin-6
IOP	Intraocular pressure
iPSCs	Induced pluripotent stem cells
IVT	Intravitreal
MEMS	Microelectromechanical system
MW	Molecular weight
PAMAM	Poly amidoamine
PDGF	Platelet-derived growth factor
PDS	Port delivery system
PEGDA	Poly(ethylene glycol) diacrylate
PET	Polyethylene terephthalate
PLGA	Poly(lactic–co-glycolic acid
PMMA	Poly(methyl methacrylate)

pNIPAAM	Poly(N-isopropylacrylamide)
PVA	Polyvinyl alcohol
rAAV	Recombinant adeno-associated virus
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
RVO	Retinal vein occlusion
TA	Triamcinolone acetonide
VEGF	Vascular endothelial growth factor

Introduction

Vision is often considered as the most important of senses, and the one that most people fear losing. Vision is often thought to be the key enabling sense for a person to work and function independently. Considerable efforts to combat vision loss continue to be made as blinding ocular diseases are more prevalent with an increasingly ageing population. All measurements for quality of life, such as disability-adjusted life-years (DALYs), confirm that visual impairment is a highly ranked burden in all countries (Chiang et al. 2006). The leading causes of vision impairment and irreversible blindness are posterior segment related diseases (Pascolini & Mariotti 2012), which include glaucoma, age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (RVO), cytomegalovirus (CMV) retinitis, posterior uveitis, diabetic retinopathy (DR), and retinitis pigmentosa (Thrimawithana et al. 2011; del Amo et al. 2015; Waite et al. 2017).

Glaucoma is a term used to describe a group of conditions with an optic neuropathy, characteristic morphological changes in the optic nerve head and visual field defects. It remains a leading cause of irreversible blindness throughout the world and one of the most common neuropathies. It is estimated that 60.5 million people suffered from it in 2010 and 7 million believed to be bilaterally blind (Quigley & Broman 2006). The number of people with glaucoma is projected to increase to 111.8 million in 2040 (Tham et al. 2014). Over the last century, in fact, the proportion of blindness attributed to glaucoma in developed countries has changed very little (10%) (Taylor 2009). In developed countries the main cause of blindness 100 years ago was corneal disease, fifty years ago it was cataract and in the present day it is AMD. No reduction in the proportion of blindness due to glaucoma is not simply because there have been no advances in treatment. A major factor is the ageing population. As a population becomes healthier and people live longer, the incidence of this degenerative optic neuropathy that reaches a clinically detectable threshold will increase. The mainstay of treatments involves trying to slow the optic nerve degeneration. The biggest risk factor for accelerated progression is an increased level of intraocular pressure (IOP) and reducing this is the only proven therapy in everyday use.

AMD affects approximately 10 million people worldwide and is one of the leading causes of vision loss in elderly patients over 60 years of age. The prevalence of AMD accounts for 20% of all posterior segment disorders in the 65-74 years age group and 35% in older age groups (Edelhauser et al. 2010) and is predicted to affect 288 million people by 2040 (del Amo et al. 2017). Cataract, DR, glaucoma and AMD will increase to nearly 70 million adults by 2050 (Joseph & Venkatraman 2017). Loss of vision will increase with the increase in the ageing population, which in turn will pose a challenge for the human health and economic growth (Delplace et al. 2015).

Inflammatory, angiogenic and fibrotic processes cause tissue damage and vision loss. These processes are also major contributors to the failure of current treatments for these diseases. Increased knowledge of the molecular mechanisms of blinding diseases (de Oliveira Dias et al. 2011; Rodrigues et al. 2009) has driven the development of therapeutic proteins including antibody-based medicines (Penedones et al. 2014). Vascular endothelial growth factor (VEGF) neutralising antibodies have considerably improved the treatment of exudative macular degeneration (wet AMD) and DR. A major challenge during both preclinical and clinical development is to determine the ocular clearance rates of new medicines. Even though the anti-VEGF antibody based medicines can be administered once a month and in some cases every other month (Stewart et al. 2012), much research is focused on developing medicines that will require less frequent dosing regimens.

Another factor in the development of longer acting formulations is the cost of the drugs and overall treatment costs, which is a function of dosing frequency. The expenditure to treat blinding ophthalmic diseases is considerable, with $ 51.4 billion spent in the US alone each year (2007). For example, ranibizumab (licensed) and bevacizumab (unlicensed) are widely used to treat AMD. Each injection of ranibizumab (Lucentis®) can cost $ 2,000, whereas bevacizumab (Avastin®) can cost only $ 50 for each intravitreal (IVT) dose (Raftery et al. 2007). Two multi-center randomised controlled clinical trials (IVAN and CATT) compared the use of ranibizumab and bevacizumab (Ahfat & Zaidi 2013; Chakravarthy et al. 2012; Martin et al. 2012). No difference was found in visual acuity outcome during 1- and 2-

year treatment periods respectively (Chakravarthy et al. 2012; Martin et al. 2012). Bevacizumab is normally provided as a solution in a glass vial containing 400 mg of the antibody at a concentration of 25 mg/mL. For ocular use, bevacizumab is often transferred under aseptic conditions into ready-to-use syringes for IVT injection by compounding pharmacies for local distribution. Many health systems cannot cope with the increasing demands for IVT injection, so bevacizumab is widely used (Elshout et al. 2014; Kwong & Mohamed 2014).

The eye-a complex organ

The anatomy of the eye and complex physiology of the retina means that the development of efficacious medicines is challenging. The eye is a specialised organ that enables light to be focused and processed into nerve impulses for interpretation by our brain. A huge range of pathology affects the eye, with either local triggers or manifestations of systemic disease such as diabetes mellitus. Furthermore, different parts of the eye can be affected to different degrees, with implications for drug delivery. The eye is broadly divided into two compartments called the anterior (front of the eye) and posterior (back of the eye) segment. Contact lens related infections occur in the cornea of the anterior segment, whereas macular degeneration is in the central retina of the posterior segment. Endophthalmitis, (infection within the eye) can cause blindness within a matter of hours. Optic nerve degeneration in open angle glaucoma may take many years before patients are aware that vision is compromised.

The least invasive routes for ocular drug administration are topical (e.g. eye drops) and systemic (e.g. tablets) formulations. The superficial nature of the eye enables local administration (usually eye drops), the main modality of treatment for anterior segment disease. One advantage of this is to bypass the liver, thus avoiding the need for higher systemic doses required with the oral route. The efficacy of drugs may also be assessed at a

local level. Parameters can be measured directly, for example the IOP in glaucoma, or through visual interpretation for signs of oedema in exudative macular degeneration.

Local applications do pose some disadvantages. Most treatments are self-administered and rely on a compliant patient, but many patients take their medication sporadically. This can be demonstrated by attaching detectors to bottles during glaucoma treatment used by patients (Kass *et al.* 1986). The reported rate of application from patients differed significantly to the measured rate (Kass *et al.* 1986). Consequently, even if drug delivery is optimised, efficacy may not be achieved. Topically administered drugs often display limited bioavailability (< 5%) due to many physical and biochemical barriers including the pre-corneal tear film, the structure and biophysiologic properties of the cornea, the limited volume that can be accommodated by the cul-de-sac, the lacrimal drainage system, reflex tearing and the aqueous outflow within the eye (Ranta & Urtti 2006; Peyman & Ganiban 1995; Rodríguez Villanueva et al. 2016). Newer methods of drug delivery include sustained release preparations that allow reduced frequency of drug administration (Rodríguez Villanueva et al. 2016; Mehta et al. 2017). Preservative free eye drops can be achieved with a new multidose bottle with an Airless Antibacterial Dispensing System (AADS, Pfizer Inc, USA) containing a valve system and an airless pump with a silver antibacterial coil (Ghate & Edelhauser 2008).

The patient population is also often elderly and susceptible to side effects. Despite lower doses needed than oral drugs, systemic toxicity can still be an issue. An elderly patient tends to have a lower body mass index, as well as decreased renal function. Furthermore, these patients are more likely to be on multiple medications that may interact. Even small quantities of drug absorbed systemically may have side effects, such as an increase in falls with topical β-blocker use (Glynn *et al*. 1991). Another example is the use of atropine. A 50 µL drop of 1% atropine contains 0.5 mg of drug. Treating both eyes with one dose (1.0 mg) can cause a tachycardia (Morton & Thomas 1958).

Significant ocular barriers that exist to prevent pathogen access also hinder drug delivery (Yellepeddi & Palakurthi 2016; Novack & Robin 2016). Transparency is necessary

for optical function, and therefore most of the inside of the eye lacks blood vessels. This is at the expense, however, of the host defence, which is weaker compared to rest of body, and if the barriers are breached, as in endophthalmitis, there are devastating effects. These barriers however are also key restrictors to delivering a drug to the area of need. Blinking and tear film turnover, designed to wash away foreign material and maintain a smooth clear anterior surface, also limits the residence time of a drug. Access to the deeper structures of the eye is hindered by a closely packed corneal epithelium and stroma with varying lipophilicity.

Delivery of a drug to the posterior segment has its own particular challenges. The vascular conjunctiva, sclera and choroid affect delivery, notwithstanding the tight junctions of the blood aqueous barrier of the non-pigmented ciliary body epithelium, and the endothelium of blood vessels that constitute the blood retina barrier (BRB). The BRB controls fluid and molecular movement between the ocular vascular beds and prevents leakage of macromolecules and harmful molecules into the retina (Kaur *et al.,* 2008). Due to the outer and inner BRB, the influx of drug into the retina and vitreous regions is limited, requiring the systemic administration of high doses to achieve therapeutic concentrations within the eye. As a result, drug is distributed and accumulated in all tissues in the body, causing unwanted side effects (Myles, *et al*., 2005). IVT injections are therefore required to administer drugs directly to the posterior segment to achieve reproducible and high doses. Although IVT injections are required to treat blinding conditions at the back of the eye, repeated administration poses potential complications including endophthalmitis, retinal detachment, traumatic cataract, intraocular hemorrhage and ocular infections (Jager *et al*., 2004). Particulate contaminants that may be present in a formulation also increases the potential for harmful effects to the posterior segment (Jager *et al*. 2004). In addition, only a little is known about vitreous dynamics, partly due to the changes in consistency and anatomy with age (Awwad *et al*., 2015; Bishop *et al*., 2004; Laude *et al*., 2010).

Understanding the nature of ocular barriers, and developing methods of bypassing or utilising them together with knowledge of the fluid dynamics within the eye are keys to

establishing successful ophthalmic pharmacotherapy. Experimental models act as platforms for drug development (Awwad, *et al*., 2017; Awwad *et al*., 2015) and translation to the clinic. This review aims to examine these barriers, ways of negotiating them, and methods of pharmacotherapy employed for different types of drugs. As the pathology and pharmacology differs anatomically we aim to discuss separately the anterior and posterior segment, and look at some of the future strategies of drug development on the horizon.

Anterior segment

Barriers

The anterior segment of the eye consists of the cornea, conjunctiva, iris, ciliary body and the lens. The common chronic anterior segment diseases are cataract, glaucoma and uveitis, with cataract accounting for 51% blindness (according on a 2010 survey (Joseph & Venkatraman 2017; Pascolini & Mariotti 2012)). The vast majority of pharmacotherapy is through topical application by the patients themselves, although other routes such as subconjunctival injection are also used. Tear film turnover is the main factor that limits topical drug residence time. Human tear volume is approximately 7 µL (Gaudana, *et al*. 2010). The volume of an eye drop of drug is up to 50 µL, and although the cul-de-sac may briefly expand to 30 µL (Nagataki & Mishima 1980; Gaudana, Ananthula, Parenky & Ashim K Mitra 2010), most drug is cleared by nasolacrimal drainage, and then to the systemic circulation directly after instillation. Increasing the drop size will therefore not deliver a greater amount of drug to the eye, but instead increase the chances of systemic side effects. The optimal size of drop to prevent systemic overflow is zero, which is obviously not achievable. Droppers have been created that consistently produce smaller volumes (Van Santvliet & Ludwig 2004; Kumar *et al*. 2011). Simpler strategies include nasolacrimal occlusion or closing the eyelid.

Lacrimation caused by irritant drugs, certain excipients, and pH deviation increase tear turnover and drug loss. Increase in tonicity can also have significant implications for increase in tearing. The normal tear turnover in human is 16%/min (Mishima *et al*., 1966).

Increased lacrimation due to drop instillation results in turnover being increased up to 80%/min. Therefore, the half-life of a drug is only 4 minutes even with a normal turnover. Blinking also increases drainage as eyelid muscle contraction encourages tear flow down the nasolacrimal duct. A significant increase in the drug residence time can be achieved simply by asking patients to close their eyes after drop instillation and apply pressure nasolacrimal duct (Flach 2008).

The tear film itself traditionally used to be thought of as a simple tri-layer structure, consisting of an oily surface layer that reduced evaporative loss, an aqueous middle layer that contained enzymes and other anti-bacterials (such as lactoferrin) and a mucin layer that provides lubrication and protection of the corneal surface. More recently that view has altered with the discovery of numerous glycosaminoglycans (GAGs), mucopolysaccharides and other molecules responsible for tear film integrity (Tiffany 2008). Furthermore, the tear film is dynamic as fluids are 'reshuffled' with blinking (Cher 2012). An unstable tear film is a result of dry eye syndrome and chronic eye irritation with changes in the level of lipid, protein and mucin profiles (Yellepeddi & Palakurthi 2016).

Understanding the tear film constituents and dynamics has led to the development of methods that increase drug residence time and bioavailability. Inserts provide sustained release of drug. Emulsions enable an increased drug load that may not be achievable in solution. Vehicles or ointments increase viscosity. Carriers of drug exist that bind to the tear film or ocular surface with greater adhesion than drug alone.

Bacterial ulceration of the cornea is a significant risk factor in people who regularly wear contact lenses. Poor hygiene combined and overnight use increases the risk of a bacterial infection (Stapleton *et al*. 2008). Aggressive dosing is required in the initial stages of therapy, with hourly or even half hourly drops to prevent ocular spread and loss of the eye. It is not uncommon for patients to be admitted to hospital for both day and night treatment (Teo *et al*. 2011). Ocular inserts (Table 1) are solid implants that sit in the cul-de-sac of the eyelids and slowly dissolve, releasing drug over a long period of time. The concept is constantly being explored and reported in literature (Saettone et al. 1994; Kumari

et al. 2010; Aburahma & Mahmoud 2011; Franca et al. 2014; Everaert et al. 2017; Rathod et al. 2017; Sharma et al. 2017). Pilocarpine, an IOP lowering treatment, was one of the first drugs to be formulated as an insert (Ocusert) (Langer 1983). Ocusert is a cul-de-sac sustained release insert composed of two membranes of ethylene vinyl acetate (EVA) copolymer surrounding a reservoir of pilocarpine allowing drug diffusion (40 µg/hour) for over a period of a week for the treatment of glaucoma (Barar et al. 2016; Peyman & Hosseini 2011; del Amo & Urtti 2008). An ocular insert that combined ciprofloxacin with sodium carboxymethylcellulose and polyvinyl alcohol (PVA) has shown significant promise. *In vitro* studies have shown that this insert can maintain levels within a therapeutic range for up to 48 hours (D. Jain *et al*., 2010). Good tissue compatibility has also been demonstrated in an *in vivo* rabbit model. Ocular inserts have also been clinically tested for patients with dry eye symptoms, with release of hydroxypropyl cellulose alleviating foreign body sensation significantly with blurring of vision being the most common side effect (in 8.7% patients) (Koffler *et al*., 2010).

Suspensions are commonly used to enable application of poorly water-soluble drugs such as the steroid prednisolone acetate. The suspension requires shaking to disperse drug particles in the bottle. However, drug distribution is still not uniform. Oil-in-water (o/w) emulsions are prepared to dissolve the drug in an oil phase and disperse it in the aqueous phase with a surfactant, which has been found to improve consistency (Koffler *et al*. 2010). Microemulsions, which are emulsions that are thermodynamically stable and form spontaneously, have also shown promise. A low concentration of surfactant maintains the drug suspension stability and may enhance penetrance by interacting with the corneal epithelial cells (Fialho & da Silva-Cunha 2004). A recent study found that a microemulsion of dexamethasone had an improved anti-inflammatory effect in a rabbit uveitic model compared to a marketed formulation of dexamethasone (Kesavan *et al*., 2012).

An alternative to formulating an emulsion for poorly water-soluble drugs is to combine it with a cyclodextrin (Kurkov & Loftsson 2013). Cyclodextrins are oligosaccharides consisting of a hydrophilic outer surface and a hydrophobic core (Loftsson & Stefansson,

1997). They are able to form inclusion complexes with 'guest' drug molecules, which sit within the core and the hydrophilic outside aids aqueous solubility. A dynamic equilibrium exists between the cyclodextrin drug complex and disassociated drug, enabling drug release (Kek et al. 2010). Cyclodextrins have been used preclinically to formulate eye drops (Loftsson & Brewster, 2011) with various drugs (Bary *et al*., 2000; Bozkir *et al*., 2012; Cappello *et al*., 2001; Jóhannsdóttir *et al*., 2015; Loftsson *et al*., 2012; Okamoto *et al*., 2010; Rodriguez-Aller *et al*., 2015; Siefert & Keipert, 1997). Several cyclodextrin based eye drops have been evaluated clinically, e.g. latanoprost and dexamethasone (Tanito *et al*. 2011; Gonzalez *et al*. 2007; Krag & Hessellund 2014; Shulman *et al*. 2015), while others have been registered in Europe for clinical use, e.g. chromaphenicol (Clorocil®), diclofenac (Voltaren Ophthalmic®) and indomethacin (Indocid®) (Davis & Brewster 2004). The percentage of cyclodextrin used for drug solubilisation was between 10-30% w/v for most of these formulations (Kearse *et al*., 2001).

Increasing the viscosity with a carrier increases residence time and in theory the drug bioavailability (Bourlais 1995). Ointments are often made from mineral oil, which can pose a challenge for the formulation of water-based treatments. The oily base may impair drug dissolution, reducing therapeutic efficacy (McCarthy 1975). The oil itself also interferes with tear film clarity, leading patients to complain of blurry vision or eyelashes being stuck together. Ointments still have an important therapeutic role in the setting of corneal exposure or thermal burns, where production of tear film constituents has been disrupted or where the ocular surface is damaged (Fish & Davidson 2010).

Another method of increasing the viscosity with less tear film disruption is to use a mucoadhesive component (polymer or excipient) such as polycarbophil (Agrahari et al. 2016) or carboxymethylcellulose (Reddy & Kim 2011). These substances are long chain polymers that bind to the mucous layer constituents on the ocular surface. Amongst the salts, lipids and proteins are numerous glycoproteins, such as mucin, that have charged carbohydrate groups and end in sialic acid groups. The polymer chains of mucoadhesives, which consist of both polar and non-polar groups, swell on contact with water, become

entangled and adhere to the mucin molecules (Khutoryanskiy 2010). The polymer length and the pH affect drug residence time and bioavailability. A longer chain polymer will have more viscosity, entanglement and greater adhesiveness to a certain extent. It will also restrict the ability to swell and result in less adhesion. Furthermore, there may be an increase in irritation and lacrimation. The pH is also important in determining how strongly a polymer binds as it governs whether hydrogen bond formation is able to take place (Grabovac *et al*., 2005). For many polymers, a more acidic pH results in greater hydrogen bonding between polymer and the mucin on the surface.

Hyaluronic acid (HA) has the additional property of shear thinning unlike other mucoadhesive polymers. With movement, the viscosity of HA decreases. Therefore, with blinking the polymer rearranges, but with an eye that is open there is greater stability (Rah 2011). HA is commonly used for maintaining anterior chamber volume during intraocular surgery and for the treatment of dry eye. Its potential for enhancing ocular delivery is still being evaluated, though has shown promise with drugs such as pilocarpine (Pahuja *et al*., 2012). HA stabilises and organises the extracellular matrix (ECM), regulates cell adhesion and motility and mediates cell proliferation and differentiation (Shu et al. 2004; Guter & Breunig 2017). The commercially available form, sodium hyaluronate is widely used in biomedical applications such as a scaffold material for wound healing and tissue engineering due to its biocompatible and biodegradable properties (Ha et al. 2006; Baino 2011).

Routes of drug absorption

From the tear film there are two main routes of drug absorption to the anterior segment:

i) The corneal route. The drug passes through the structural layers of the cornea to reach the anterior chamber, including the corneal epithelium, stroma, and endothelium.

ii) The non-corneal route. Drugs pass through the conjunctiva, Tenon's tissue, and sclera to reach the anterior chamber.

Corneal route

The cornea consists of three major layers with differential permeability to drug molecules. The epithelium and endothelium both consist of cells linked by tight junctions, which restrict the passage of large molecules, while the stroma is made up of closely packed collagen. It is the epithelium however that provides the most resistance to solute diffusion. Its influence on restricting large molecules may be demonstrated by comparing absorption of ^{14}C-dexamethasone with the epithelium intact to when it is debrided in an animal model (Cox *et al*. 1972a; Cox *et al*. 1972b) Only after epithelial debridement is ^{14}C-dexamethasone detected in the anterior chamber of rabbits after topical administration. Intercellular spaces with pore sizes of 60 A allow the passage of small ionic and hydrophilic molecules (<350 Da) via the paracellular route (Lee 1990). The transcellular route is the main mechanism of absorption of ocular drugs and other larger lipophilic molecules.

The lipophilicity of the cornea varies with the different layers. The epithelium and endothelium are relatively hydrophobic, whereas the corneal stroma is hydrophilic. Consequently, there is a parabolic relationship between the corneal permeability and the diffusion coefficient (Yoshida & Topliss 1996). With the stroma playing a lesser role in resistance, corneal penetrance increases with hydrophobicity with a decrease in penetrance in only the most hydrophobic of compounds. In conjunction with lipophilicity, pH is another key factor in determining the permeability of the cornea to a drug (Pahuja *et al*. 2012) There is a delicate balance therefore between aiming for a pH appropriate for corneal penetration and the physiological pH (7.4), which will result in the least tearing.

Certain drugs harness the differing lipophilicity of the cornea to their advantage for drug delivery. Latanoprost is one of the most common ocular drugs used for the treatment of glaucoma, a disease in which there is accelerated optic nerve degeneration in association with a raised IOP (Digiuni et al. 2012; Pek et al. 2016). Latanoprost is a prostaglandin analogue that reduces IOP by increasing the uveoscleral outflow, through targeting

receptors near the drainage angle. Although not fully understood, it is believed that it may cause ciliary muscle relaxation, or remodelling of the tissue matrix within the ciliary muscle.

Latanoprost is formulated as a lipophilic pro-drug ester, which is absorbed easily into the corneal epithelium. It is activated by esterases within the epithelium to the active hydrophilic moiety and passes through into the anterior chamber. The cornea therefore acts as a depot for the pro-drug with prolonged release after a single application. The elimination half-life in rabbit corneas has been found to be over an hour (Sjöquist *et al*. 1998). In humans IOP lowering begins between 2-4 hours after application, with the peak effect reached between 8-12 hours (Digiuni *et al*. 2012). This effectively means a once per day treatment, which helps with patient compliance.

The non-corneal route

Less is known about the permeability of the conjunctiva, Tenon's, and sclera, and the associated pharmacokinetics. Most papers that examine these different tissues report that the conjunctiva is more permeable to hydrophilic molecules than the cornea, though it is not clear that it is less permeable to hydrophobic molecules. Using a hollow glass cylinder fixed to the corneal surface to isolate cornea versus conjunctiva tissue Ahmed and Patton found the hydrophilic molecule inulin penetrated conjunctiva and sclera more easily than the cornea (Ahmed & Patton 1985).

Other conjunctival properties that increase drug absorption include a greater surface area (17 times that of the cornea in humans (Watsky *et al*. 1988)), and a larger pore size with greater permeability than the cornea (Lawrence & Miller 2004). However, factors that reduce absorption include mucous produced by goblet cells, and the presence of lymphatics and vasculature that enhance systemic loss of drug.

Changing the epithelium permeability directly may increase drug penetration. Surfactants are ionised substances, which can disrupt the plasma membrane of the epithelium. One surfactant in common use is the preservative benzalkonium chloride (BAC). Its ability to kill bacteria and prolong the shelf life of medicines makes it the preservative of

choice in many preparations. BAC can cause membrane disruption and emulsification of the lipid layer of the tear film, where the delivery of drug through the corneal layers may be significantly enhanced. This can be seen in studies with acyclovir ointment, a common treatment for herpes simplex keratitis. Acyclovir penetrance in *ex vivo* corneas of rabbits was increased by 3 times with a 0.005% BAC solution and by 10 times with a 0.01% BAC solution (Majumdar *et al*. 2008). A standard formulation is between 0.004 and 0.02%. However the effects of BAC are toxic that even at low concentrations the presence of BAC can cause cell death. A concentration of 0.0001% is sufficient to cause apoptosis. Higher concentrations cause necrosis. It is no surprise that patients complain of ocular surface irritation when using treatments that contain BAC. Ensuring ocular medications are pathogen-free is a mandatory part of formulating an ophthalmic preparation and much research has been performed to find other preservatives that have effective bactericidal properties but without the toxicity seen with BAC.

Iontophoresis is the application of electrical current to drive ionised substances into tissue (del Amo & Urtti 2008). It is a method of enhancing ocular drug delivery that has been in and out of vogue over many years since Wirtz reported its use for the treatment of infective corneal ulcers with zinc salts in 1908 (Wirtz 1908). The apparatus usually consists of a reservoir of drug connected to an electrode with the other electrode attached to the patient. It has been used with some success to enhance delivery of antibiotics such as gentamicin, steroids and antiviral treatments both through the cornea and sclera. Side effects such as tissue necrosis and patient discomfort have precluded its widespread use, however in some circumstances it may have a useful role (Güngör *et al*. 2010). Recent phase I/II trials have shown promise in the treatment of dry eye and uveitis (Patane et al. 2011; Cohen et al. 2012; Kang-Mieler et al. 2014),

Periocular injections

Drugs that are injected underneath the conjunctiva or Tenon's tissue effectively bypass the superficial tear film and conjunctival barriers. Another advantage of this route is the ability to

leave a depot of drug within the potential space between tissue layers. Furthermore, more posterior placement of the drug enables delivery to the posterior segment (discussed below). Periocular injections (Ghate et al. 2007) are particularly pertinent for drugs poorly soluble in water such as steroids. Sub-conjunctival, sub-Tenon's, peri-bulbar injections are commonly used in ophthalmology practice. Sub-conjunctival steroid is used for the treatment of refractory anterior uveitis. Injections of the antifibrotic agents 5-flurouracil and mitomycin C are also applied using this route to prevent scarring after trabeculectomy surgery. Sub-Tenon's and peribulbar injections are often the choice method of administering local anaesthetic. Less commonly used is the retrobulbar injection, which is associated with the small, albeit life-threatening risk of brain stem anaesthesia.

Posterior segment

The posterior segment of the eye refers to the posterior two-thirds of the eye, including the anterior hyaloid membrane and all the structures behind it such as the vitreous, retina choroid and optic nerve. The leading causes of vision impairment and irreversible blindness are posterior segment related diseases (Thrimawithana *et al*. 2011). Inflammation and fibrosis are also symptoms associated with posterior segment disorders and ocular tissue damage. The uniqueness of the cellular composition and anatomical structure of the retina means these biological processes are devastating and detrimental to vision. Inflammatory responses or hypoxic stimuli cause abnormal blood vessels to leak resulting in retinal thickening and edema, fibrovascular proliferation and fractional retinal detachment. To preserve the retinal structure and function, it is crucial to prevent primary vascular abnormality (Friedlander 2007).

Only a decade ago ocular treatments for these diseases were limited and were, at best, kept in check with laser therapy. With the advent of anti-VEGF treatment there have been significant improvements in stabilising, and sometimes improving disease states and vision (Jain *et al.* 2012). The delivery of anti-VEGF medicines to the posterior segment poses a particular challenge. The structures in the anterior segment serve as additional

barriers to those discussed above. Furthermore, the direction of aqueous flow in the eye (ciliary body to anterior chamber angle) is against the direction of drug delivery via a topical route. It is estimated that drugs applied in a conventional topical way are diluted by a factor of between 250000 and 1000000 by the time the vitreous is reached (Maurice, 2002). Instead the only modalities of treatment in everyday use are either periocular or IVT injections. Avoiding all barriers, the IVT route results in the greatest bioavailability, and for large molecules, such as proteins, is the only route in current clinical practice. However, each time an injection is performed there is a small but significant risk of a blinding complication. The risks of retinal detachment and infective endophthalmitis have been reported as 0.9% and 0.2% per injection respectively (Jager *et al*. 2004). Frequent (4-8 weeks) anti-VEGF treatment will result in a cumulative increase. Much research has been performed to improve transscleral delivery (Amrite *et al*. 2008), which would negate the need to breach the walls of the eye and to develop sustained release preparations, which would reduce the frequency of repeated IVT injections.

Periocular barriers

A drug must penetrate the tissue layers of the globe to reach the back of the eye at a therapeutic level. Various tissue barriers have varying tissue permeability. Unlike the cornea however, there is blood flow through the periocular tissues, and considerable drug is lost to the systemic circulation via venules and lymphatics. The Tenon's tissue and episclera are highly vascular with a network of capillary plexi. The reported rate of removal of drugs is between 5 and 80% (Edelhauser et al. 2010). This has implications not just for reaching the therapeutic concentration but also for preventing systemic toxicity.

Molecules that evade clearance by the subconjunctival circulation reach the sclera, the outer coating of the globe. The sclera is continuous with the cornea at the limbus and has a larger surface area. The sclera is hydrated, mainly composed of collagen fibres and proteoglycans embedded in an ECM, but with few protein binding sites. Its permeability is comparable to the corneal stroma, and aqueous intercellular media carry molecules through

pores between the collagen fibres. Molecular radius appears to play a bigger role in determining drug permeability than lipophilicity (Prausnitz & Noonan 1998), and molecules of linear shape, for example dextrans, are less able to permeate than globular proteins (Geroski & Edelhauser 2001). Electrical charge also contributes to permeation. Positively charged molecules penetrate the sclera poorly, believed to be due to binding to the negatively charged proteoglycan matrix (Kim *et al*. 2007) .

The choroid is below the sclera, and is a vascular network whose high flow rate results in considerable drug loss. The main function of the choroid is to supply the retina with nutrients and oxygen. Due to the retina being the most metabolically active tissue in the body (per unit mass), the choroid has a correspondingly high blood flow through it, again being the highest (per unit mass) in the body (Scheinman *et al*. 2011). The choroid contains an outer layer of large vessels, a middle layer of small vessels and an innermost capillary layer, the choriocapillaris. The choriocapillaris is fenestrated, which enhances metabolic exchange, but this highly dynamic equilibrium contributes to drug loss too.

The retinal pigment epithelium (RPE) is a single layered structure that acts as the metabolic interface between the photoreceptors and choroid. It forms the outer BRB, with tight junctions between cells preventing the passage of large molecules and cells across it. The inner BRB is formed by the endothelium of retinal arterioles, which are also linked with tight junctions. Both the choroid and the RPE are pigmented and rich in melanin. Melanin binds to free radicals and other molecules by electrostatic and Van der Waals forces, or simple charge transfer (Larsson 1993). Melanin bound drug can form a reservoir that can gradually release to the surrounding cells and as a result, prolong drug release (Urtti 2006; Gaudana, Ananthula, Parenky & Ashim K. Mitra 2010; Manzanares et al. 2016). The binding of drugs to melanin is especially important in transscleral drug delivery. The unbound drug is the driving force in drug permeation and the bound drug acts as a reservoir (Ranta & Urtti 2006). Significant retention of lipophilic compounds occurs within the Bruch's membrane and the choroid presumably due to the high levels of melanin (Cheruvu & Kompella 2006). However, the choroid-RPE is even more impermeable to hydrophilic molecules, being up to

20 times less permeable to hydrophilic beta-blockers than lipophilic ones (Pitkanen 2005). There do appear to be regional and species specific differences within the choroid-RPE (Durairaj *et al.* 2012). The peripheral choroid-RPE contains more melanin than central choroid-RPE. In humans, unlike monkeys or rabbits, there is also evidence that the sclera may contain more melanin than the central choroid-RPE (Durairaj *et al*. 2012). These differences should be considered when using animal models for drug development as it can contribute varying pharmacokinetic and clearance profiles.

Injection routes of administration

Sub-Tenon injections

Sub Tenon's injection of certain drugs has been shown to be efficacious for posterior segment disease. Inflammation is a key part of the pathophysiology of macular oedema following cataract surgery (Irvine Gass syndrome), diabetic macular oedema, and posterior uveitis. The steroid triamcinolone acetonide (TA) has been used as treatment for these conditions with variable success. Most commonly it is administered as an IVT injection, but is associated with the additional specific complications of cataract and raised IOP. Sub-Tenon's administration may carry a lower risk of complications. No difference in visual acuity outcomes for uveitic macular oedema was noted between IVT and sub-Tenon administration of TA (Choudhry & Ghosh 2007). There is also evidence that sub-Tenon injection leads to a significant increase of steroid in vitreous levels. Patients that received sub-Tenon's TA (40 mg/mL) preoperatively before macular hole surgery were found to have vitreous levels maintained between 17 and 31 ng/mL for 2 months (Kovacs *et al*. 2012). Systemic toxicity may be an issue with sub-Tenon's steroid injection. In this study plasma cortisol levels were also altered, indicating implications for patients with poor glucose control such as diabetics.

Other transscleral delivery systems are at different stages of development. Implants have been designed with an impervious casing for sub-Tenon's placement and openings directed towards the sclera (Pontes De Carvalho 2006). Using this method of delivery of the

chemotherapeutic agents carboplatin and topotecan clinical trials evaluating efficacy are currently underway for the treatment of retinoblastoma.

Intravitreal (IVT) injections

The delivery of most treatments for the posterior segment must be by IVT injection due to transscleral barriers. This is particularly pertinent for the delivery of large molecules such as anti-VEGF antibodies, although periocular delivery and even topical delivery continues to be explored (Chen *et al*. 2011). Due to the invasive nature and the associated risks of IVT injections, there is much effort to develop longer lasting therapies, which require a reduced dosing frequency.

Understanding the pharmacokinetics of drugs in the vitreous of humans is a significant challenge. The vitreous of humans is of a different consistency to other animals. It also undergoes considerable changes with age (Sebag 1989). As people grow older the vitreous loses viscosity, with lakes of fluid appearing within it (Bishop 2000). Collagen fibril links break down in some parts of the vitreous and fibrils aggregate in other parts (Bishop 2000; P N Bishop et al. 2004). At the weaker points the attachments can fall away and float around inside the eye. This lack of uniformity will affect drug distribution, but may preferentially result for example in anti-VEGF treatment being located over the macula.

The administration of humanised protein therapeutics (e.g. antibodies) intravitreally results in proteins diffusing more slowly in the vitreous than low molecular weight (MW) molecules. Therapeutic protein clearance times tend to be much longer than that of low MW molecules (days compared to hours) (Hayreh 1966; Cunha-Vaz 1997; Thrimawithana *et al*. 2011; Urtti 2006; Pitkanen 2005; Haghjou *et al.* 2013; Kwak & Amico 1992; Laude *et al.* 2010). An issue with therapeutic proteins is that the use of animals to evaluate pharmacokinetics will result in the development anti-drug antibodies (ADAs). The presence of ADAs will result in rapid clearance of the candidate protein and can also cause acute hypersensitivity or infusion reactions. ADAs can also bind to the active region of the therapeutic protein such as the receptor-binding site to neutralise the drug. Efficacy can

therefore be difficult to determine. ADAs unpredictively change drug pharmacokinetic properties, biological effects and toxicity profile (Vugmeyster *et al.* 2012; Brinks *et al.* 2011; Tamilvanan *et al.* 2010; Wang *et al.* 2012; Brinch *et al.* 2009). ADAs are an intractable problem in the development of protein therapeutics, especially new formulations with prolonged duration of action that are being developed.

Another factor whose contribution to drug distribution in the vitreous is difficult to quantify are eye movements. Saccades can result in sudden globe rotations of up to nine hundred degrees per second, approximately half the speed of an old washing machine on a spin cycle. These abrupt changes shake up the vitreous, and affect drug distribution. As the posterior segment is not a perfect sphere, with the lens causing a concave indentation, vortices are created with eye movements (Stocchino et al. 2007; Repetto et al. 2010).

Estimation of drug distribution and clearance is therefore difficult new *in vitro* models have recently been reported (Awwad *et al*. 2013; Awwad *et al*. 2015; Awwad *et al*. 2017; Repetto *et al*. 2005; Fogli *et al*. 2014; Patel *et al*. 2015). Therapeutic proteins do not readily permeate the retina and thus clear via aqueous outflow through the anterior chamber into the conjunctiva. A two-compartment model of the eye that mimics aqueous outflow mimics the human clearance times of therapeutic proteins (Awwad *et al*. 2015).

Some controversy exists in the treatment regimen frequency for certain pathologies. Exudative macular degeneration is a pathology that involves blood vessel growth and leakage from the choroid underneath the macula (CNV). Disruption of the retinal layers results in loss of visual function. A major factor to new blood vessel growth is VEGF that is released in association with oxidative stress. Anti-VEGF antibodies have revolutionised treatment outcomes, with patients showing stabilisation or improvement of vision together with leakage regression. What remains unclear is the frequency and time span of drug administration. Both the ANCHOR and MARINA trials examined visual outcomes after monthly dosing of ranibizumab, a humanised monoclonal antibody fragment (Fab) (Brown *et al*. 2006; Rosenfeld *et al*. 2006). Other trials such as the PRONTO or SUSTAIN trial have shown significant benefit from monthly injections of ranibizumab for 3 months only, then

injections as required (Holz *et al*. 2011; Lalwani *et al*. 2009). Comparative data between injections as required and monthly injections found little difference in outcome at one year in the CATT trial. The CATT and IVAN trials also compared the use of ranibizumab and bevacizumab, which is used unlicensed. Bevacizumab is a full IgG1 antibody registered for systemic use in cancer, but its use has been shown by the CATT (CATT Research Group et al. 2011) and IVAN (Chakravarthy *et al*. 2012) trials to be broadly similar to that of ranibizumab. Issues arise because bevacizumab has not been formulated for ocular use (Ng et al. 2012; L. Liu et al. 2011; Palmer et al. 2013). Presentation of bevacizumab is in a vial containing 25 mg/mL of antibody and the dose was established simply by what was in a 50 mL injection. However costs are dramatically reduced compared to ranibizumab, so bevacizumab is also widely used to treat conditions related to vascularistion (e.g. AMD).

Intravitreal (IVT) implants

A strategy to prolong drug action that has long been used clinically for low MW molecules is the IVT injection of a drug suspension of a poorly soluble drug. Although not yet possible with therapeutic proteins, this approach works with poorly soluble steroids. TA, as discussed earlier, consists of a suspension of steroid particles. An injection of 4.0 mg of TA has been shown to maintain elevated levels of steroid up to 3 months in non-vitrectomised eyes (Mason *et al.* 2004). The 4.0 mg dose is too large of a mass to dissolve in the eye, so TA dissolution occurs slowly over time with aqueous flow (Jermak et al. 2007; Zacharias et al. 2013; Yilmaz et al. 2011).

A growing field of research is the use of implants for the treatment of posterior segment disease (Figure 1, Table 2). These allow sustained release of drug negating the need for multiple injections. Taking advantage of the privileged immune state of the inside the eye, many implants have been used successfully without inciting the significant inflammatory reaction that would normally be found with implants used elsewhere in the body (Ratner 2002). Chronic diseases or those with a relapsing remitting course are particularly appropriate for sustained release implant therapy. The implants may be

formulated from biodegradable or non-biodegradable substances (Choonara et al. 2010; Thrimawithana et al. 2011; Thakur et al. 2014; Lee et al. 2010; Kang-Mieler et al. 2014; Christoforidis et al. 2012; Gilger et al. 2013; Cima et al. 2014; Bisht et al. 2017; Prata et al. 2017).

In immunocompromised patients, such as those with leukaemia or acquired immune deficiency syndrome (AIDS) the opportunistic infection CMV can cause retinal destruction (Pollard 1980). Patients may remain asymptomatic until advanced stages of retinal necrosis and haemorrhage. The advent of highly active antiretroviral therapy (HAART) has reduced the incidence of patients developing CMV retinitis, however individuals with specific immune deficiency to CMV may still develop retinitis. Effective treatment of CMV retinitis not only reduces the risk of vision loss, but also is associated with a decrease in mortality. Standard therapy may include ganciclovir (Martin et al. 1999; Pollard 1996), foscarnet (Berthe et al. 1994; López-Cortés et al. 2001), and cidofovir (Biron 2006; Ljungman et al. 2001).

The ganciclovir slow release implant (Vitrasert) was one of the first approved implants for IVT application (Sepahvandi et al. 2016). It releases ganciclovir at 1 mcg/hour from a PVA/EVA polymer based system. In a clinical trial it was found to be twice as effective in slowing retinitis progression than treatment with intravenous ganciclovir (Musch *et al*. 1997). One of the pitfalls of implant treatment to one eye only, however, is that is that the other eye is not protected, and in the implant treated group of patients the time to second eye involvement was significantly shorter. Combination therapy with both implant and oral valganciclovir (oral version of ganciclovir) is now advocated for sight threatening retinitis (Jabs 2008). Controversy exists as to whether implants should be removed from the eye after drug has been released, as its removal is associated with a risk of retinal detachment, haemorrhage and infection.

Treatment of macular oedema has also been successfully achieved with steroid implants. Macular oedema results from the leakage of fluid from vessels within the retina, which disrupts the retinal architecture, and causes vision loss. It is seen in association with uveitis, RVO and diabetic maculopathy. IVT injection of the steroid TA has shown benefit in

reducing oedema, however recurrence is a common feature of all diseases. Work on a dexamethasone pellet coated in PVA/EVA showed promise using a uveitic model of rabbits (Cheng *et al*. 1995). The Ozurdex® implant has recently been approved by the FDA for the treatment of macular oedema in association with non-infectious uveitis and RVO (Mehta et al. 2015; Barar et al. 2016). It consists of 0.7 mg of dexamethasone integrated into a poly(lactic–co-glycolic acid) (PLGA) polymer. Pharmacokinetic studies revealed that steroid continues to be released into the vitreous over a period of 4 months (Chang-Lin & Attar 2011). The polymer has the added advantage of being biodegradable, requiring no surgical removal. Other implants are at different stages of development (Table 2).

Future directions

Prolonging the duration of drug action to targets while maintaining drug stability and specificity are key goals of current research. Novel ways of solubilising drugs by conjugation with carriers, gene therapy and implants that are refillable or able to be directed remotely to the area of treatment are concepts in the process of development.

Dendrimers

Nanotechnology has been used to increase the drug residence time. Dendrimers are nano-sized, three-dimensional structures with a central core from which polymeric branches emerge (Patri *et al*. 2002). The hydrophobic drug is encapsulated in the internal cavity or complexed to the dendrimer. Its tree-like structure consists of a high surface density of functional groups, which make it possible to attach a wide variety of conjugates. Dendrimers can aid in controlled drug release due to their small size, high chemical versatility, drug loading capacity and ease in preparation (Rodríguez Villanueva et al. 2016; Yavuz et al. 2015). The poly amidoamine (PAMAM) dendrimers include functional carboxylic, hydroxyl and amine groups, and these increases with generation number.

Dendrimer drug complexes have shown potential as an application for prolonging treatment of CNV. A dendrimer complex of anti-VEGF antisense oligonucleotide was found to inhibit CNV in a laser induced rodent model when injected to the vitreous. The effective

lifespan of the dendrimer bound oligonucleotide was reported to be between 4-6 months, with effective protection against nucleases whilst also facilitating its delivery to the target site (Marano *et al.* 2005).

In a rabbit scarring model after glaucoma filtration surgery (GFS), dendrimer conjugates (dendrimer-glucosamine as an immunomodulator and dendrimer glucosamine 6-sulphate as an anti-angiogenic molecule) were found to be efficacious as an anti-scarring agent. Histopathological examination of the eyes showed minimal scar tissue formation and no inflammatory or neoangiogenic response, and success of GFS was promoted from 30 to 80% (Shaunak *et al*. 2004).

PAMAM dendrimers have also been found to be compatible with topical ocular dosage form formulations in terms of physicochemical properties (pH, osmolality and viscosity) (Vandamme & Brobeck 2005). Topical formulations of drugs such as pilocarpine nitrate (Vandamme & Brobeck 2005), carteolol (Spataro *et al*. 2010) and dexamethasone (Yavuz et al. 2015) have been reported. Puerarin-PAMAM dendrimer complex increased the corneal residence time of the drug thereby improving the efficacy and decreasing the frequency of dosing (Yao *et al.* 2010). This system also improved the availability of puerarin and delayed the half-life of drug in aqueous humor of rabbits from 0.48 to 1.30 hours (Wang *et al*. 2011).

Hydrogels

Hydrogels have received considerable interest in recent years due to their ability to prolong efficacy whilst being biocompatible and biodegradable. Hydrogels are an alternative to particulate associated formulations and have been used for the delivery of large MW molecules (Mitragotri *et al*. 2014). They are polymeric materials that do not dissolve in water under physiological conditions and swell considerably in aqueous medium. Many hydrogel systems that have been described do not require organic solvents during preparation (Shi et al. 2013; Stile et al. 1999; Vermonden et al. 2012). Hydrogels are networks of polymer main chains covalently linked together. This is known as crosslinking and sometimes the polymer

crosslinks can be strong non-covalent interactions. The crosslinking of polymer chains prevents complete dissolution of the polymer in a good solvent. Hence, hydrogels made of hydrophilic polymers can imbibe water into their network structure and swell. The high water content property of hydrogels makes them biocompatible and is being examined in tissue regeneration application. However, the high water content of hydrogels is a challenge for developing extended drug release. Hydrogels can be made with polymers that can undergo a phase transition in response to different external conditions such as pH, temperature, electric currents and ionic strength (Simões *et al*. 2012). Such hydrogels can be made to 'collapse' to entrap a drug after administration.

One thermosensitive material that shows gel-sol transition is poly(N-isopropylacrylamide) (pNIPAAM) (Yıldız et al. 2002; Silva & Oliveira 2007; Li et al. 2008; Klouda 2015; Drapala et al. 2011). It has been used in many drug delivery and tissue engineering studies (Li et al. 2008), with no signs of retinal toxicity (Turturro et al. 2011). PNIPAAM has a transition temperature of 32 °C and cross-linking the hydrogel with poly(ethylene glycol) diacrylate (PEGDA) improves drug release profile by forming homogenous pores (Zhang et al. 2009). This characteristic has been exploited to encapsulate and release protein for ocular delivery to the posterior segment.

Reservoir type devices

Another approach being explored recently is the use of refillable reservoir type devices. When the existing drug depletes, more drug can be refilled in the reservoir. An microelectromechanical system (MEMS) drug delivery device consisting of a pump, drug reservoir and transscleral cannula showed promise in *ex-vivo* porcine eyes (Li *et al*. 2008). Another MEMS device described in the literature has layers formed using lithography and master moulds made up of silicon wafers or acrylic. A hard-core base plate made up of polyetherether ketone is used to control the penetration depth of the needle, and prevent the puncture of the entire device with the force of needle. It is surgically implanted with the

reservoir placed beneath the conjunctiva, with the cannula inserted through the sclera and drug dispensing tip, terminating in either the anterior or posterior segment depending on the site of treatment required. When mechanically actuated by force applied by the patient's finger, a pressure gradient arises and the drug flows into the transscleral cannula. The one-way valve at the end of the cannula opens and results in release of a specific dose of the medication. This device was tested *in vivo* on rabbits using phenylephrine as a model drug (Lo *et al.* 2009). The Port Delivery System (PDS, ForSight VISION4, Inc.) is a refillable drug delivery device currently in phase 1 for preliminary safety for neovascular AMD (www.clinicaltrials.gov: NCT01186432) (Pearce *et al*. 2015).

Selective IVT drug delivery using a microrobotic device is a novel invention. Controlled electromagnetically, it acts as an IVT implant with a drug reservoir (Weidle *et al*. 2013). These microrobots can be placed in the lower vessel arcade without obstructing vision. Non-biodegradable, they are made biocompatible by coating with polypyrrole. It was demonstrated *in vitro* and *ex vivo* that the movement of this device could be wirelessly controlled in the vitreous. The group proposed an algorithm taking into account the complex optics of the eye that helps to localise the device based on 3-D structure and allows precise calculation of gradients and forces acting on the device.

Stem cell technology

Stem cells have been explored as a potential avenue for treatment of ocular diseases (Ramsden et al. 2013; Jeon & Oh 2015; Rao et al. 2017). Stem cells have the ability to grow into many different cell types and other kinds of cells can arise from differentiation (Vellonen et al. 2014). Stem cells are critical to the renewal and repair of tissue in the body. Pluripotent stem cells (embryonic stem cells, ESCs and induced pluripotent stem cells, iPSCs) are a rich source for the regeneration of damaged organs and tissues (Higuchi et al. 2017). Methods have been reported for the differentiation of human pluripotent stem cells (hPSCs) (Rezania et al. 2014; Burridge et al. 2014; Pagliuca et al. 2014; Gao et al. 2013; Bao et al. 2015). A

key challenge for the clinical use of stem cells is to optimise cell placement and the local host environment so that cell survival, differentiation and integration leads to the long-term restoration of tissue function (Limb & Daniels 2008). One of the major barriers to successful stem cell implantation and integration is to mediate the local inflammatory and fibrotic responses to the transplantation.

Stem cell treatments for corneal injuries are available clinically (Daniels et al. 2007; Daniels et al. 2006)**.** Recent progress in retinal stem cell research has been reported for the treatment of dry AMD. Though no treatment has been reported for the management of dry AMD, vitamins and anti-oxidants have been used to slow its progression. Stem cells could possibly help treat severe retinal degeneration involved in the condition to restore sight (Jeon & Oh 2015). Several trials are currently underway to treat AMD and retinitis pigmentosa using human embryonic, foetal and umbilical cord tissue-derived stem cells and bone marrow derived stem cells (Ramsden et al. 2013).

Though stem cell transplantation for retinal diseases has made considerable progress in the last decade, many issues however still need to be resolved before stem cell therapies can be routinely used in the clinic (Rao et al. 2017). Biological risk and technical difficulties associated with differentiation and culture procedures still need to be resolved (Jeon & Oh 2015). As understanding of retinal regeneration phenomena increases, there will be increased possibilities for cell therapies to regenerate retinal ocular tissues.

Gene therapy

Gene products have been reported to slow or prevent neovascularisation (Garoon & Stout 2016). Gene therapies (Rowe-Rendleman et al. 2014) require direct cellular delivery (del Amo et al. 2017) using a carrier system (Schön et al. 2015) where a key challenge is to release the gene drug from the carrier within the cell (Karimi et al. 2016), often further requiring the gene drug entering the nucleus. Vector loaded suspensions can be administered via a sub-retinal injection by pars plana vitrectomy with retinotomy and injection

into the subretinal space with a 41-gauge cannula (Garoon & Stout 2016). It is necessary for gene therapy that there be no toxicity or immunogenicity after the delivery of highly efficient genes to specific targeted cells (Bloquel et al. 2006). Both viral and non-viral vectors are available. Examples of viral vectors include adenoviruses, adeno-associated-virus (AAV), retroviruses and lentivirus vectors (Borrás 2003; Chaum & Hatton 2002; Mohan et al. 2005; Garoon & Stout 2016). Adenoviruses are the most commonly used vector targeted for a variety of chronic ocular diseases. Requiring sub-retinal injection, there are some AAV-based systems in clinical trials (Bainbridge et al. 2015; Weleber et al. 2016). The administration of adenoviruses allows for stable, long-term transgene expression in photoreceptors, RPE cells, ganglion cells and Müller cells (M. M. Liu et al. 2011). Viral vectors have been reported to display potential risks, such as mutagenesis and immunogenicity; resulting in hindrance to future development of these systems (Bloquel et al. 2006). An alternative solution are non-viral vectors, which display no toxicity and do not induce significant ocular inflammation (Bloquel et al. 2006). Reviews dedicated to gene therapy for ocular drug delivery can be found elsewhere (Bloquel et al. 2006; Garoon & Stout 2016; Oliveira et al. 2017; Boye et al. 2013; Bainbridge et al. 2006).

Neuroprotective agents

Ciliary neurotrophic factor (CNTF) is a cytokine belonging to the interleukin-6 (IL-6) family. CNTF promotes neurotransmitter synthesis, neurite outgrowth and photoreceptor survival (M. M. Liu et al. 2011). CNTF has been shown to be protective against ganglion cell death in models of oxidative stress and experimental glaucoma (Lipinski et al. 2015). Studies with recombinant adeno-associated virus (rAAV)-mediated gene therapy showed sustained expression of CNTF with the protection of photoreceptors (Bok et al. 2002; Liang et al. 2001; Schlichtenbrede et al. 2003). NT-501 (Neurotech Pharmaceuticals) is an implantable cell technology comprising of encapsulated human RPE cells (ARPE-19) genetically modified to secrete CNTF over an extended period of time for the treatment of glaucoma and retinitis

pigmentosa. In a clinical trial NT-501 was found to reduce photoreceptor degradation in patients with retinitis pigmentosa with improvement in objective visual acuity (Sieving et al. 2006). The implant consists of a scaffold of six strands of polyethylene terephthalate (PET) yarn and is sutured onto the sclera through a titanium loop (Thrimawithana et al. 2011). A semipermeable membrane allows the inward and outward diffusion of CNTF and prevents the attack of the host immune system. NT-501 represents a unique platform for the delivery of protein therapeutics (Sieving et al. 2006). NT-501 has completed phase II clinical trial for patients with atrophic macular degeneration (NCT00447954) and the implant was reported to be well tolerated (Girmens et al. 2012).

Conclusions

The eye is unique as a therapeutic target in the body. Whilst exhibiting a vast range of pathology, both local and systemic, the superficial nature enables effective local therapy. The privileged state of immune system inside the eye means there is greater tolerance of non-host materials, although with a significant infection risk each time the walls are breached. Ocular therapeutic development is therefore geared towards improving bioavailability of topical and periocular treatments, while efficacious sustained release implants are the cornerstone of development for therapies of the posterior segment.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al. 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander et al. 2015).

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Conflict of interest

The authors declares no conflicts of interest

References

Aburahma, M.H. & Mahmoud, A.A., 2011. Biodegradable ocular inserts for sustained delivery of brimonidine tartarate: preparation and in vitro/in vivo evaluation. *AAPS PharmSciTech*, 12(4), pp.1335–47.

Agrahari, V. et al., 2016. A comprehensive insight on ocular pharmacokinetics. *Drug Delivery and Translational Research*, 6(6), pp.735–754.

Ahfat, F.G. & Zaidi, F.H., 2013. Bevacizumab vs ranibizumab-an appraisal of the evidence from CATT and IVAN. *Eye (London, England)*, 27(3), pp.289–90.

Ahmed, I. & Patton, T.F., 1985. Importance of the noncorneal absorption route in topical ophthalmic drug delivery. *Invest Ophthalmol Vis Sci*, 26(4), pp.584–587.

Alexander, S.P. et al., 2015. The Concise Guide to PHARMACOLOGY 2015/16: Overview. *British Journal of Pharmacology*, 172(24), pp.5729–5743.

del Amo, E.M. et al., 2015. Intravitreal clearance and volume of distribution of compounds in rabbits: In silico prediction and pharmacokinetic simulations for drug development. *European Journal of Pharmaceutics and Biopharmaceutics*, 95, pp.215–226.

del Amo, E.M. et al., 2017. Pharmacokinetic aspects of retinal drug delivery. *Progress in Retinal and Eye Research*, 57, pp.134–185.

del Amo, E.M. & Urtti, A., 2008. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. *Drug discovery today*, 13(3–4), pp.135–43.

Amrite, A.C., Edelhauser, H.F. & Kompella, U.B., 2008. Modeling of corneal and retinal pharmacokinetics after periocular drug administration. *Investigative ophthalmology & visual science*, 49(1), pp.320–32.

Awwad, S. et al., 2013. Development of an in vitro pharmacokinetic model of the human eye. *Investigative Ophthalmology & Visual Science*, 54(15), p.5068.

Awwad, S. et al., 2017. Sustained release ophthalmic dexamethasone: In vitro in vivo correlations derived from the PK-Eye. *International journal of pharmaceutics*, 522(1–2), pp.119–127.

Awwad, S. et al., 2015. The PK-Eye: A Novel In Vitro Ocular Flow Model for Use in Preclinical Drug Development. *Journal of Pharmaceutical Sciences*, 104(10), pp.3330–3342.

Bainbridge, J.W.B. et al., 2015. Long-Term Effect of Gene Therapy on Leber's Congenital Amaurosis. *New England Journal of Medicine*, 372(20), pp.1887–1897.

Bainbridge, J.W.B., Tan, M.H. & Ali, R.R., 2006. Gene therapy progress and prospects: the eye. *Gene therapy*, 13, pp.1191–1197.

Baino, F., 2011. Towards an ideal biomaterial for vitreous replacement: Historical overview and future trends. *Acta biomaterialia*, 7(3), pp.921–35.

Bao, X. et al., 2015. Chemically-defined albumin-free differentiation of human pluripotent stem cells to endothelial progenitor cells. *Stem Cell Research*, 15(1), pp.122–129.

Barar, J. et al., 2016. Advanced drug delivery and targeting technologies for the ocular diseases. *BioImpacts*, 6(1), pp.49–67.

Bary, A.R., Tucker, I.G. & Davies, N.M., 2000. Considerations in the use of hydroxypropyl-??-cyclodextrin in the formulation of aqueous ophthalmic solutions of hydrocortisone. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(2), pp.237–244.

Berthe, P. et al., 1994. Toxicologic and pharmacokinetic analysis of intravitreal injections of foscarnet, either alone or in combination with ganciclovir. *Investigative Ophthalmology and Visual Science*, 35(3), pp.1038–1045.

Biron, K.K., 2006. Antiviral drugs for cytomegalovirus diseases. *Antiviral research*, 71(2–3), pp.154–63.

Bishop, P.N. et al., 2004. Age-related changes on the surface of vitreous collagen fibrils. *Invest Ophthalmol Vis Sci*, 45(4), pp.1041–1046.

Bishop, P.N. et al., 2004. Age-Related Changes on the Surface of Vitreous Collagen Fibrils. *Investigative Ophthalmology & Visual Science*, 45(4), pp.1041–1046.

Bishop, P.N., 2000. Structural macromolecules and supramolecular organisation of the vitreous gel. *Progress in retinal and eye research*, 19(3), pp.323–44.

Bisht, R., Jaiswal, J.K. & Rupenthal, I.D., 2017. Nanoparticle-loaded biodegradable light-responsive in situ forming injectable implants for effective peptide delivery to the posterior segment of the eye. *Medical Hypotheses*, 103, pp.5–9.

Bloquel, C. et al., 2006. Non-viral ocular gene therapy: Potential ocular therapeutic avenues. *Advanced Drug Delivery Reviews*, 58(11), pp.1224–1242.

Bok, D. et al., 2002. Effects of adeno-associated virus-vectored ciliary neurotrophic factor on

retinal structure and function in mice with a P216L rds/peripherin mutation. *Experimental eye research*, 74(6), pp.719–735.

Borrás, T., 2003. Recent developments in ocular gene therapy. *Experimental eye research*, 76(6), pp.643–52.

Bourlais, 1995. New ophthalmic drug delivery systems. *Drug Dev Ind Pharm*, pp.19–59.

Boye, S.E. et al., 2013. A Comprehensive Review of Retinal Gene Therapy. *Molecular Therapy*, 21(3), pp.509–519.

Bozkir, A., Denli, Z.F. & Basaran, B., 2012. Effect of hydroxypropyl-beta-cyclodextrin on the solubility, stability and in-vitro release of ciprofloxacin for ocular drug delivery. *Acta poloniae pharmaceutica*, 69(4), pp.719–24.

Brinch, K.S. et al., 2009. Influence of antidrug antibodies on plectasin efficacy and pharmacokinetics. *Antimicrobial agents and chemotherapy*, 53(11), pp.4794–800.

Brinks, V., Jiskoot, W. & Schellekens, H., 2011. Immunogenicity of therapeutic proteins: the use of animal models. *Pharmaceutical research*, 28(10), pp.2379–85.

Brown, D.M. et al., 2006. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*, 355(14), pp.1432–1444.

Burridge, P.W. et al., 2014. Chemically defined generation of human cardiomyocytes. *Nature Methods*, 11(8), pp.855–860.

Cappello, B. et al., 2001. Solubilization of tropicamide by hydroxypropyl-beta-cyclodextrin and water-soluble polymers: in vitro/in vivo studies. *International journal of pharmaceutics*, 213, pp.75–81.

CATT Research Group et al., 2011. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *The New England journal of medicine*, 364(20), pp.1897–908.

Chakravarthy, U. et al., 2012. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: One-year findings from the IVAN randomized trial. *Ophthalmology*, 119(7), pp.1399–1411.

Chang-Lin, J. & Attar, M., 2011. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Investigative Ophthalmology & Visual Science*, 52(1), pp.80–86.

Chaum, E. & Hatton, M.P., 2002. Gene therapy for genetic and acquired retinal diseases. *Survey of Ophthalmology*, 47(5), pp.449–469.

Chen, J.J. et al., 2011. Potential penetration of topical ranibizumab (Lucentis) in the rabbit eye. *Eye (Lond)*, 25(11), pp.1504–1511.

Cheng, C.K. et al., 1995. Intravitreal sustained-release dexamethasone device in the treatment of experimental uveitis. *Invest Ophthalmol Vis Sci*, 36(2), pp.442–453.

Cher, I., 2012. Fluids of the ocular surface: concepts, functions and physics. *Clin Exp Ophthalmol*, 40(6), pp.634–643.

Cheruvu, N.P.S. & Kompella, U.B., 2006. Bovine and Porcine Transscleral Solute Transport: Influence of Lipophilicity and the Choroid–Bruch's Layer. *Investigative Opthalmology & Visual Science*, 47(10), p.4513.

Chiang, P.P.C. et al., 2006. Global burden of disease and visual impairment. *Lancet*, p.365.

Choonara, Y.E. et al., 2010. A review of implantable intravitreal drug delivery technologies for the treatment of posterior segment eye diseases. *Journal of pharmaceutical sciences*, 99(5), pp.2219–39.

Choudhry, S. & Ghosh, S., 2007. Intravitreal and posterior subtenon triamcinolone acetonide in idiopathic bilateral uveitic macular oedema. *Clinical & experimental ophthalmology*, 35(8), pp.713–718.

Christoforidis, J.B. et al., 2012. Intravitreal devices for the treatment of vitreous inflammation. *Mediators of inflammation*, 2012, p.126463.

Cima, M.J. et al., 2014. Single compartment drug delivery. *Journal of controlled release : official journal of the Controlled Release Society*, 190, pp.157–71.

Cohen, A.E. et al., 2012. Evaluation of dexamethasone phosphate delivered by ocular iontophoresis for treating noninfectious anterior uveitis. *Ophthalmology*, 119(1), pp.66–73.

Cox, W. V, Kupferman, A. & Leibowitz, H.M., 1972a. Topically applied steroids in corneal disease. I. The role of inflammation in stromal absorption of dexamethasone. *Arch Ophthalmol*, 88(3), pp.308–313.

Cox, W. V, Kupferman, A. & Leibowitz, H.M., 1972b. Topically applied steroids in corneal disease. II. The role of drug vehicle in stromal absorption of dexamethasone. *Arch*

Ophthalmol, 88(5), pp.549–552.

Cunha-Vaz, J.G., 1997. The blood-ocular barriers: past, present, and future. *Documenta ophthalmologica*, 93(1–2), pp.149–57.

Daniels, J.T. et al., 2007. Limbal epithelial stem cell therapy. *Expert opinion on biological therapy*, 7(1), pp.1–3.

Daniels, J.T. et al., 2006. Stem cell therapy delivery: treading the regulatory tightrope. *Regenerative medicine*, 1(5), pp.715–9.

Davis, M.E. & Brewster, M.E., 2004. Cyclodextrin-based pharmaceutics: past, present and future. *Nature Reviews Drug Discovery*, 3(12), pp.1023–1035.

Delplace, V., Payne, S. & Shoichet, M., 2015. Delivery strategies for treatment of age-related ocular diseases: From a biological understanding to biomaterial solutions. *Journal of Controlled Release*, 219, pp.652–668.

Digiuni, M., Fogagnolo, P. & Rossetti, L., 2012. A review of the use of latanoprost for glaucoma since its launch. *Expert Opin Pharmacother*, 13(5), pp.723–745.

Drapala, P.W. et al., 2011. Role of Thermo-responsiveness and Poly(ethylene glycol) Diacrylate Cross-link Density on Protein Release from Poly(N-isopropylacrylamide) Hydrogels. *Journal of Biomaterials Science, Polymer Edition*, 22(1–3), pp.59–75.

Durairaj, C., Chastain, J.E. & Kompella, U.B., 2012. Intraocular distribution of melanin in human, monkey, rabbit, minipig and dog eyes. *Experimental Eye Research*, 98(C), pp.23–27.

Edelhauser, H.F. et al., 2010. Ophthalmic drug delivery systems for the treatment of retinal diseases: basic research to clinical applications. *Investigative ophthalmology & visual science*, 51(11), pp.5403–20.

Elshout, M. et al., 2014. The cost-utility of aflibercept for the treatment of age-related macular degeneration compared to bevacizumab and ranibizumab and the influence of model parameters. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 252(12), pp.1911–1920.

Everaert, A. et al., 2017. Optimisation of HPMC ophthalmic inserts with sustained release properties as a carrier for thermolabile therapeutics. *International Journal of Pharmaceutics*, 528(1–2), pp.395–405.

Fialho, S.L. & da Silva-Cunha, A., 2004. New vehicle based on a microemulsion for topical ocular administration of dexamethasone. *Clinical & experimental ophthalmology*, 32(6), pp.626–632.

Fish, R. & Davidson, R., 2010. Management of ocular thermal and chemical injuries, including amniotic membrane therapy. *Curr Opin Ophthalmol*, 21, pp.317–321.

Flach, A.J., 2008. The importance of eyelid closure and nasolacrimal occlusion following the ocular instillation of topical glaucoma medications, and the need for the universal inclusion of one of these techniques in all patient treatments and clinical studies. *Transactions of the American Ophthalmological Society*, 106, pp.138-45–8.

Fogli, G. et al., 2014. New eye phantom for ophthalmic surgery. *Journal of biomedical optics*, 19(6), p.68001.

Franca, J.R. et al., 2014. Bimatoprost-loaded ocular inserts as sustained release drug delivery systems for glaucoma treatment: in vitro and in vivo evaluation. *PloS one*, 9(4), p.e95461.

Friedlander, M., 2007. Fibrosis and diseases of the eye. *The Journal of clinical investigation*, 117(3), pp.576–586.

Gao, F. et al., 2013. Myostatin acts as an autocrine/paracrine negative regulator in myoblast differentiation from human induced pluripotent stem cells. *Biochemical and Biophysical Research Communications*, 431(2), pp.309–314.

Garoon, R.B. & Stout, J.T., 2016. Update on ocular gene therapy and advances in treatment of inherited retinal diseases and exudative macular degeneration. *Current Opinion in Ophthalmology*, 27(3), p.1.

Gaudana, R., Ananthula, H.K., Parenky, A. & Mitra, A.K., 2010. Ocular Drug Delivery. *The AAPS Journal*, 12(3), pp.348–360.

Gaudana, R., Ananthula, H.K., Parenky, A. & Mitra, A.K., 2010. Ocular drug delivery. *The AAPS journal*, 12(3), pp.348–60.

Geroski, D.H. & Edelhauser, H.F., 2001. Transscleral drug delivery for posterior segment disease. *Advanced Drug Delivery Reviews*, 52(1), pp.37–48.

Ghate, D. et al., 2007. Pharmacokinetics of intraocular drug delivery by periocular injections using ocular fluorophotometry. *Investigative ophthalmology & visual science*, 48(5), pp.2230–7.

Ghate, D. & Edelhauser, H.F., 2008. Barriers to glaucoma drug delivery. *Journal of glaucoma*, 17(2), pp.147–56.

Gilger, B.C. et al., 2013. Treatment of acute posterior uveitis in a porcine model by injection of triamcinolone acetonide into the suprachoroidal space using microneedles. *Investigative ophthalmology & visual science*, 54(4), pp.2483–92.

Girmens, J.-F., Sahel, J.-A. & Marozova, K., 2012. Dry age-related macular degeneration: A currently unmet clinical need. *Intractable & Rare Diseases Research*, 1(3), pp.103–114.

Glynn, R.J. et al., 1991. Falls in elderly patients with glaucoma. *Arch Ophthalmol*, 109(2), pp.205–210.

Gonzalez, J.R. et al., 2007. Comparison of the stability, efficacy, and adverse effect profile of the innovator 0.005% latanoprost ophthalmic solution and a novel cyclodextrin-containing formulation. *Journal of clinical pharmacology*, 47(1), pp.121–6.

Grabovac, V., Guggi, D. & Bernkop-Schnürch, A., 2005. Comparison of the mucoadhesive properties of various polymers. *Adv Drug Deliv Rev*, 57(11), pp.1713–1723.

Güngör, S. et al., 2010. Trans-scleral iontophoretic delivery of low molecular weight therapeutics. *Journal of Controlled Release*, 147(2), pp.225–231.

Guter, M. & Breunig, M., 2017. Hyaluronan as a promising excipient for ocular drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 113, pp.34–49.

Ha, D.I. et al., 2006. Preparation of thermo-responsive and injectable hydrogels based on hyaluronic acid and poly(N-isopropylacrylamide) and their drug release behaviors. *Macromolecular Research*, 14(1), pp.87–93.

Haghjou, N., Abdekhodaie, M.J. & Cheng, Y.-L., 2013. Retina-choroid-sclera permeability for ophthalmic drugs in the vitreous to blood direction: quantitative assessment. *Pharmaceutical research*, 30(1), pp.41–59.

Hayreh, S.S., 1966. Posterior Drainage of the Intraocular Fluid from the Vitreous. *Experimental eye research*, 5, pp.123–144.

Higuchi, A. et al., 2017. Polymeric design of cell culture materials that guide the differentiation of human pluripotent stem cells. *Progress in Polymer Science*, 65, pp.83–126.

Holz, F.G. et al., 2011. Safety and efficacy of a flexible dosing regimen of ranibizumab in

neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology*, 118(4), pp.663–71.

Jabs, D.A., 2008. AIDS and ophthalmology, 2008. *Archives of ophthalmology*, 126, pp.1143–1146.

Jager, R.D. et al., 2004. Risks of intravitreous injection: a comprehensive review. *Retina*, 24(5), pp.676–698.

Jain, D., Carvalho, E. & Banerjee, R., 2010. Biodegradable hybrid polymeric membranes for ocular drug delivery. *Acta Biomaterialia*, 6(4), pp.1370–1379.

Jain, G.K. et al., 2012. Therapeutic stratagems for vascular degenerative disorders of the posterior eye. *Drug Discovery Today*, pp.1–12.

Jeon, S. & Oh, I.H., 2015. Regeneration of the retina: Toward stem cell therapy for degenerative retinal diseases. *BMB Reports*, 48(4), pp.193–199.

Jermak, C.M. et al., 2007. Triamcinolone Acetonide in Ocular Therapeutics. *Survey of Ophthalmology*, 52(5), pp.503–522.

Jóhannsdóttir, S. et al., 2015. Development of a cyclodextrin-based aqueous cyclosporin A eye drop formulations. *International Journal of Pharmaceutics*, 493(1–2), pp.86–95.

Joseph, R.R. & Venkatraman, S.S., 2017. Drug delivery to the eye: what benefits do nanocarriers offer? *Nanomedicine (London, England)*, 12(6), pp.683–702.

Kang-Mieler, J.J., Osswald, C.R. & Mieler, W.F., 2014. Advances in ocular drug delivery: emphasis on the posterior segment. *Expert opinion on drug delivery*, 11(10), pp.1647–60.

Karimi, M. et al., 2016. Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. *Chemical Society reviews*, 45(5), pp.1457–501.

Kass, M.A. et al., 1986. Compliance with topical pilocarpine treatment. *Am J Ophthalmol*, 101(5), pp.515–523.

Kaur, C., Foulds, W.S. & Ling, E. a, 2008. Blood-retinal barrier in hypoxic ischaemic conditions: basic concepts, clinical features and management. *Progress in retinal and eye research*, 27(6), pp.622–47.

Kearse, E.C. et al., 2001. Influence of dehydroepiandrosterone on rabbit intraocular pressure. *Ophthalmic research*, 33(1), pp.42–7.

Kek, W.K. et al., 2010. In situ measurement of spectral changes in the anterior eye following application of ultraviolet-absorbing compounds. *European journal of pharmaceutics and biopharmaceutics*, 75(2), pp.200–5.

Kesavan, K. et al., 2012. Mucoadhesive Chitosan-Coated Cationic Microemulsion of Dexamethasone for Ocular Delivery: In Vitroand In VivoEvaluation. *Curr Eye Res*, pp.1–11.

Khutoryanskiy, V., 2010. Advances in Mucoadhesion and Mucoadhesive Polymers. *Macromol. Biosci.*, 11(6), pp.748–764.

Kim, S. et al., 2007. Transport Barriers in Transscleral Drug Delivery for Retinal Diseases. *Ophthalmic research*, 39(5), pp.244–254.

Klouda, L., 2015. Thermoresponsive hydrogels in biomedical applications A seven-year update. *European Journal of Pharmaceutics and Biopharmaceutics*, 97, pp.338–349.

Koffler, B., Mcdonald, M. & Nelinson, D., 2010. Improved Signs, Symptoms, and Quality of Life Associated With Dry Eye Syndrome: Hydroxypropyl Cellulose Ophthalmic Insert Patient Registry. *Eye & Contact Lens: Science & Clinical Practice*, 36(3), pp.170–176.

Kovacs, K. et al., 2012. Pharmacokinetic Study of Vitreous and Serum Concentrations of Triamcinolone Acetonide After Posterior Sub-Tenon's Injection. *Am J Ophthalmol*, 153(5), pp.939–948.

Krag, S. & Hessellund, A., 2014. Topical dexamethasone-cyclodextrin microparticle eye drops for uveitic macular oedema. *Acta ophthalmologica*, 92(8), pp.e689-90.

Kumar, S. et al., 2011. Reduction in drop size of ophthalmic topical drop preparations and the impact of treatment. *J Adv Pharm Technol Res*, 2(3), pp.192–194.

Kumari, A. et al., 2010. Ocular inserts — Advancement in therapy of eye diseases. *Journal of Advanced Pharmaceutical Technology & Research*, 1(3), pp.291–296.

Kurkov, S. V. & Loftsson, T., 2013. Cyclodextrins. *International Journal of Pharmaceutics*, 453(1), pp.167–180.

Kwak, H.W. & Amico, D.J.D., 1992. Evaluation of the Retinal Toxicity and Pharmacokinetics of Dexamethasone After Intravitreal Injection. *Arch Ophthalmol*, 110, pp.259–266.

Kwong, T.Q. & Mohamed, M., 2014. Anti-vascular endothelial growth factor therapies in ophthalmology: current use, controversies and the future. *British Journal of Clinical*

Pharmacology, 78(4), pp.699–706.

Lalwani, G.A. et al., 2009. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *American journal of ophthalmology*, 148(1), p.43–58.e1.

Langer, R., 1983. Implantable controlled release systems. *Pharmacol Ther*, 21(1), pp.35–51.

Larsson, B.S., 1993. Interaction between chemicals and melanin. *Pigment Cell Res*, 6(3), pp.127–133.

Laude, A. et al., 2010. Intravitreal therapy for neovascular age-related macular degeneration and inter-individual variations in vitreous pharmacokinetics. *Progress in retinal and eye research*, 29(6), pp.466–75.

Lawrence, M.S. & Miller, J.W., 2004. Ocular tissue permeabilities. *Int Ophthalmol Clin*, 44(3), pp.53–61.

Lee, S.S. et al., 2010. Biodegradable implants for sustained drug release in the eye. *Pharmaceutical research*, 27(10), pp.2043–53.

Lee, V.H.L., 1990. Mechanisms and facilitation of corneal drug penetration. *Journal of Controlled Release*, 11, pp.79–90.

Li, X., Wu, W. & Liu, W., 2008. Synthesis and properties of thermo-responsive guar gum/poly(N-isopropylacrylamide) interpenetrating polymer network hydrogels. *Carbohydrate Polymers*, 71(3), pp.394–402.

Liang, F.Q. et al., 2001. AAV-mediated delivery of ciliary neurotrophic factor prolongs photoreceptor survival in the rhodopsin knockout mouse. *Mol Ther*, 3(2), p.241–8.

Limb, G.A. & Daniels, J.T., 2008. Ocular regeneration by stem cells: present status and future prospects. *British medical bulletin*, 85, pp.47–61.

Lipinski, D.M. et al., 2015. CNTF Gene Therapy Confers Lifelong Neuroprotection in a Mouse Model of Human Retinitis Pigmentosa. *Molecular therapy : the journal of the American Society of Gene Therapy*, 23(8), pp.1308–19.

Liu, L. et al., 2011. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: Effects of long-term storage and product mishandling. *Investigative Ophthalmology and Visual Science*, 52(2), pp.1023–1034.

Liu, M.M., Tuo, J. & Chan, C.-C., 2011. Gene therapy for ocular diseases. *The British journal*

of ophthalmology, 95(5), pp.604–612.

Ljungman, P. et al., 2001. Cidofovir for cytomegalovirus infection and disease in allogeneic stem cell transplant recipients. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood*, 97(2), pp.388–92.

Lo, R. et al., 2009. A passive MEMS drug delivery pump for treatment of ocular diseases. *Biomed Microdevices*, 11(5), pp.959–970.

Loftsson, T. & Brewster, M.E., 2011. Pharmaceutical applications of cyclodextrins: Effects on drug permeation through biological membranes. *Journal of Pharmacy and Pharmacology*, 63(9), pp.1119–1135.

Loftsson, T., Jansook, P. & Stefánsson, E., 2012. Topical drug delivery to the eye: Dorzolamide. *Acta Ophthalmologica*, 90(7), pp.603–608.

Loftsson, T. & Stefansson, E., 1997. Effect of Cyclodextrins on Topical Drug Delivery to the Eye. *Drug Dev Ind Pharm*, pp.473–481.

López-Cortés, L. et al., 2001. Intravitreal pharmacokinetics and retinal concentrations of ganciclovir and foscarnet after intravitreal administration in rabbits. *Investigative ophthalmology & visual science*, 42(5), pp.1024–1028.

Majumdar, S., Hippalgaonkar, K. & Repka, M.A., 2008. Effect of chitosan, benzalkonium chloride and ethylenediaminetetraacetic acid on permeation of acyclovir across isolated rabbit cornea. *Int J Pharm*, 348(1–2), pp.175–178.

Manzanares, J.A., Rimpelä, A.K. & Urtti, A., 2016. Interpretation of Ocular Melanin Drug Binding Assays. Alternatives to the Model of Multiple Classes of Independent Sites. *Molecular Pharmaceutics*, 13(4), pp.1251–1257.

Marano, R.J. et al., 2005. Dendrimer delivery of an anti-VEGF oligonucleotide into the eye: a long-term study into inhibition of laser-induced CNV, distribution, uptake and toxicity. *Gene Ther*, 12(21), pp.1544–1550.

Martin, D.F. et al., 1999. Oral Ganciclovir for Patients with Cytomegalovirus Retinitis Treated with a Ganciclovir Implant. *New England Journal of Medicine*, 340(14), pp.1063–1070.

Martin, D.F. et al., 2012. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology*, 119(7), pp.1388–1398.

Mason, J.O., Somaiya, M.D. & Singh, R.J., 2004. Intravitreal concentration and clearance of triamcinolone acetonide in nonvitrectomized human eyes. *Retina (Philadelphia, Pa)*, 24(6), pp.900–904.

McCarthy, T.J., 1975. The effect of vehicle composition on the release of chloramphenicol from creams and eye ointments. *S Afr Med J*, 49(31), pp.1259–1262.

Mehta, H., Gillies, M. & Fraser-Bell, S., 2015. Perspective on the role of Ozurdex (dexamethasone intravitreal implant) in the management of diabetic macular oedema. *Therapeutic advances in chronic disease*, 6(5), pp.234–45.

Mehta, P. et al., 2017. Approaches in topical ocular drug delivery and developments in the use of contact lenses as drug-delivery devices. *Therapeutic delivery*, 8(7), pp.521–541.

Mishima, S. et al., 1966. Determination of tear volume and tear flow. *Invest Ophthalmol*, 5(3), pp.264–276.

Mitragotri, S., Burke, P.A. & Langer, R., 2014. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. *Nature reviews. Drug discovery*, 13(9), pp.655–72.

Mohan, R.R. et al., 2005. Gene therapy in the cornea. *Progress in Retinal and Eye Research*, 24(5), pp.537–599.

Morton, H.J. & Thomas, E.T., 1958. Effect of atropine on the heart-rate. *Lancet*, 2(7060), pp.1313–1315.

Musch, D.C. et al., 1997. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. *The New England journal of medicine*, 337(2), pp.83–90.

Myles, M., Neumann, D. & Hill, J., 2005. Recent progress in ocular drug delivery for posterior segment disease: emphasis on transscleral iontophoresis. *Advanced drug delivery reviews*, 57(14), pp.2063–79.

Nagataki, S. & Mishima, S., 1980. Pharmacokinetics of instilled drugs in the human eye. *Int Ophthalmol Clin*, 20(3), pp.33–49.

Ng, D.S. et al., 2012. Intravitreal bevacizumab: Safety of multiple doses from a single vial for consecutive patients. *Hong Kong Medical Journal*, 18(6), pp.488–495.

Novack, G.D. & Robin, A.L., 2016. Ocular pharmacology. *Journal of clinical pharmacology*,

56(5), pp.517–27.

Okamoto, N. et al., 2010. Preparation of ophthalmic formulations containing cilostazol as an anti-glaucoma agent and improvement in its permeability through the rabbit cornea. *Journal of oleo science*, 59(8), pp.423–30.

Oliveira, A. V., Rosa da Costa, A.M. & Silva, G.A., 2017. Non-viral strategies for ocular gene delivery. *Materials Science and Engineering C*, 77, pp.1275–1289.

de Oliveira Dias, J.R. et al., 2011. Cytokines in neovascular age-related macular degeneration: fundamentals of targeted combination therapy. *The British journal of ophthalmology*, 95(12), pp.1631–7.

Pagliuca, F.W. et al., 2014. Generation of functional human pancreatic β cells in vitro. *Cell*, 159(2), pp.428–439.

Pahuja, P., Arora, S. & Pawar, P., 2012. Ocular drug delivery system: a reference to natural polymers. *Expert Opin Drug Deliv*, 9(7), pp.837–861.

Palmer, J.M., Amoaku, W.M. & Kamali, F., 2013. Quality of bevacizumab compounded for intravitreal administration. *Eye (London, England)*, 27(9), pp.1090–1097.

Pascolini, D. & Mariotti, S.P., 2012. Global estimates of visual impairment: 2010. *British Journal of Ophthalmology*, 96(5), pp.614–618.

Patane, M.A. et al., 2011. Ocular iontophoresis of EGP-437 (dexamethasone phosphate) in dry eye patients: results of a randomized clinical trial. *Clin Ophthalmol*, 5, pp.633–643.

Patel, S. et al., 2015. Evaluation of protein drug stability with vitreous humor in a novel ex-vivo intraocular model. *European journal of pharmaceutics and biopharmaceutics*, 95, pp.407–417.

Patri, A.K., Majoros, I.J. & Baker, J.R., 2002. Dendritic polymer macromolecular carriers for drug delivery. *Curr Opin Chem Biol*, 6(4), pp.466–471.

Pearce, W., Hsu, J. & Yeh, S., 2015. Advances in drug delivery to the posterior segment. *Current opinion in ophthalmology*, 26(3), pp.233–9.

Pek, Y.S. et al., 2016. Long-Term Subconjunctival Delivery of Brimonidine Tartrate for Glaucoma Treatment Using a Microspheres/Carrier System. *Advanced Healthcare Materials*, 5(21), pp.2823–2831.

Penedones, A. et al., 2014. Safety monitoring of ophthalmic biologics: a systematic review of

pre- and postmarketing safety data. *Journal of ocular pharmacology and therapeutics*, 30(9), pp.729–751.

Peyman, G.A. & Hosseini, K., 2011. Combination therapies in ophthalmology: Implications for intravitreal delivery. *Journal of Ophthalmic and Vision Research*, 6(1), pp.36–46.

Peyman, G. & Ganiban, G., 1995. Delivery systems for intraocular routes. *Advanced drug delivery reviews*, 16(504), pp.107–123.

Pitkanen, L., 2005. Permeability of Retinal Pigment Epithelium: Effects of Permeant Molecular Weight and Lipophilicity. *Investigative Ophthalmology & Visual Science*, 46(2), pp.641–646.

Pollard, R., 1996. CMV retinitis: ganciclovir/monoclonal antibody. *Antiviral research*, 29, pp.73–75.

Pollard, R.B., 1980. Cytomegalovirus Retinitis in Immunosuppressed Hosts: I. Natural History and Effects of Treatment with Adenine Arabinoside. *Annals of Internal Medicine*, 93(5), pp.655–664.

Pontes De Carvalho, R., 2006. Delivery from Episcleral Exoplants. *Invest Ophthalmol Visl Sci*, 47(10), pp.4532–4539.

Prata, A.I., Coimbra, P. & Pina, M.E., 2017. Preparation of dexamethasone ophthalmic implants: a comparative study of in vitro release profiles. *Pharmaceutical Development and Technology*, 1(0), pp.1–20.

Prausnitz, M.R. & Noonan, J.S., 1998. Permeability of cornea, sclera, and conjunctiva: a literature analysis for drug delivery to the eye. *J Pharm Sci*, 87(12), pp.1479–1488.

Quigley, H.A. & Broman, A.T., 2006. The number of people with glaucoma worldwide in 2010 and 2020. *The British journal of ophthalmology*, 90(3), pp.262–7.

Raftery, J. et al., 2007. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. *The British journal of ophthalmology*, 91(9), pp.1244–6.

Rah, M.J.R.O., 2011. A review of hyaluronan and its ophthalmic applications. *Optometry*, 82(1), pp.38–43.

Ramsden, C.M. et al., 2013. Stem cells in retinal regeneration: past, present and future. *Development*, 140, pp.2576–85.

Ranta, V. & Urtti, A., 2006. Transscleral drug delivery to the posterior eye: prospects of

pharmacokinetic modeling. *Advanced drug delivery reviews*, 58(11), pp.1164–81.

Rao, R.C., Dedania, V.S. & Johnson, M.W., 2017. Stem Cells for Retinal Disease: A Perspective on the Promise and Perils. *American Journal of Ophthalmology*, 179, pp.32–38.

Rathod, L. V, Kapadia, R. & Sawant, K.K., 2017. A novel nanoparticles impregnated ocular insert for enhanced bioavailability to posterior segment of eye: In vitro , in vivo and stability studies. *Materials Science & Engineering C*, 71, pp.529–540.

Ratner, B.D., 2002. Reducing capsular thickness and enhancing angiogenesis around implant drug release systems. *J Control Release*, 78(1–3), pp.211–218.

Reddy, R. & Kim, S.J., 2011. Critical appraisal of ophthalmic ketorolac in treatment of pain and inflammation following cataract surgery. *Clinical ophthalmology (Auckland, N.Z.)*, 5, pp.751–758.

Repetto, R., Siggers, J.H. & Stocchino, a, 2010. Mathematical model of flow in the vitreous humor induced by saccadic eye rotations: effect of geometry. *Biomechanics and modeling in mechanobiology*, 9(1), pp.65–76.

Repetto, R., Stocchino, A. & Cafferata, C., 2005. Experimental investigation of vitreous humour motion within a human eye model. *Physics in medicine and biology*, 50(19), pp.4729–43.

Rezania, A. et al., 2014. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. *Nature Biotechnology*, 32(11), pp.1121–1133.

Rodrigues, E.B. et al., 2009. Therapeutic monoclonal antibodies in ophthalmology. *Progress in retinal and eye research*, 28(2), pp.117–44.

Rodriguez-Aller, M. et al., 2015. New prostaglandin analog formulation for glaucoma treatment containing cyclodextrins for improved stability, solubility and ocular tolerance. *European Journal of Pharmaceutics and Biopharmaceutics*, 95, pp.203–214.

Rodríguez Villanueva, J., Navarro, M.G. & Rodríguez Villanueva, L., 2016. Dendrimers as a promising tool in ocular therapeutics: Latest advances and perspectives. *International journal of pharmaceutics*, 511(1), pp.359–66.

Rosenfeld, P.J. et al., 2006. Ranibizumab for Neovascular Age-Related Macular Degeneration. *The New England Journal of Medicine*, 355(14), pp.1419–1431.

Rowe-Rendleman, C.L. et al., 2014. Drug and gene delivery to the back of the eye: from bench to bedside. *Investigative ophthalmology & visual science*, 55(4), pp.2714–30.

Saettone, M.F. et al., 1994. Mucoadhesive ophthalmic vehicles: evaluation of polymeric low-viscosity formulations. *Journal of ocular pharmacology*, 10(1), pp.83–92.

Van Santvliet, L. & Ludwig, A., 2004. Determinants of eye drop size. *Surv Ophthalmol*, 49(2), pp.197–213.

Scheinman, R.I., Vooturi, S.K. & Kompella, U.B., 2011. Druggable targets and therapeutic agents for disorders of the back of the eye. In U. B. Kompella & H. F. Edelhauser, eds. *Drug product development for the back of the eye*. Springer, p. 596.

Schlichtenbrede, F.C. et al., 2003. Intraocular gene delivery of ciliary neurotrophic factor results in significant loss of retinal function in normal mice and in the Prph2Rd2/Rd2 model of retinal degeneration. *Gene therapy*, 10(6), pp.523–7.

Schön, C., Biel, M. & Michalakis, S., 2015. Retinal gene delivery by adeno-associated virus (AAV) vectors: Strategies and applications. *European journal of pharmaceutics and biopharmaceutics*, 95(Pt B), pp.343–52.

Sebag, J., 1989. Development and aging of the vitreous. In *The Vitreous. Structure, function and pathobiology*. Springer, pp. 73–95.

Sepahvandi, A., Eskandari, M. & Moztarzadeh, F., 2016. Drug Delivery Systems to the Posterior Segment of the Eye: Implants and Nanoparticles. *BioNanoScience*, 6(4), pp.276–283.

Sharma, R. et al., 2017. Comparison of electrospun and solvent cast polylactic acid (PLA)/ poly(vinyl alcohol) (PVA) inserts as potential ocular drug delivery vehicles. *Materials Science & Engineering C*, 77, pp.895–903.

Shaunak, S. et al., 2004. Polyvalent dendrimer glucosamine conjugates prevent scar tissue formation. *Nat Biotechnol*, 22(8), pp.977–984.

Shi, Y. et al., 2013. Preparation and characterization of a hydrogel carrier to deliver gatifloxacin and its application as a therapeutic contact lens for bacterial keratitis therapy. *Biomedical materials (Bristol, England)*, 8(5), p.55007.

Shu, X.Z. et al., 2004. In situ crosslinkable hyaluronan hydrogels for tissue engineering. *Biomaterials*, 25(7–8), pp.1339–1348.

Shulman, S. et al., 2015. Topical dexamethasone-cyclodextrin nanoparticle eye drops for non-infectious Uveitic macular oedema and vitritis - a pilot study. *Acta ophthalmologica*, 93(5), pp.411–415.

Siefert, B. & Keipert, S., 1997. Influence of Alpha-Cyclodextrin and Hydroxyalkylated β-Cyclodextrin Derivatives on the In Vitro Corneal Uptake and Permeation of Aqueous Pilocarpine-HCl Solutions. *Journal of Pharmaceutical Sciences*, 86(6), pp.716–720.

Sieving, P.A. et al., 2006. Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proceedings of the National Academy of Sciences of the United States of America*, 103(10), pp.3896–901.

Silva, R. & Oliveira, M.G. De, 2007. Effect of the cross-linking degree on the morphology of poly(NIPAAm-co-AAc) hydrogels. *Polymer*, 48(14), pp.4114–4122.

Simões, S., Figueiras, A. & Veiga, F., 2012. Modular Hydrogels for Drug Delivery. *Journal of Biomaterials and Nanobiotechnology*, 3(2), pp.185–199.

Sjöquist, B. et al., 1998. The pharmacokinetics of a new antiglaucoma drug, latanoprost, in the rabbit. *Drug Metab Dispos*, 26(8), pp.745–754.

Southan, C. et al., 2016. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. *Nucleic acids research*, 44(D1), pp.D1054-68.

Spataro, G. et al., 2010. Designing dendrimers for ocular drug delivery. *Eur J Med Chem*, 45(1), pp.326–334.

Stapleton, F. et al., 2008. The incidence of contact lens-related microbial keratitis in Australia. *Ophthalmology*, 115(10), pp.1655–1662.

Stewart, M.W. et al., 2012. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina (Philadelphia, Pa.)*, 32(3), pp.434–57.

Stile, R.A., Burghardt, W.R. & Healy, K.E., 1999. Synthesis and characterization of injectable poly (N-isopropylacrylamide)-based hydrogels that support tissue formation in vitro. *Macromolecules*, 32(22), pp.7370–7379.

Stocchino, A., Repetto, R. & Cafferata, C., 2007. Eye rotation induced dynamics of a Newtonian fluid within the vitreous cavity: the effect of the chamber shape. *Physics in*

medicine and biology, 52(7), pp.2021–34.

Tamilvanan, S. et al., 2010. Clinical concerns of immunogenicity produced at cellular levels by biopharmaceuticals following their parenteral administration into human body. *Journal of drug targeting*, 18(7), pp.489–98.

Tanito, M. et al., 2011. Topical dexamethasone-cyclodextrin microparticle eye drops for diabetic macular edema. *Investigative Ophthalmology and Visual Science*, 52(11), pp.7944–7948.

Taylor, H.R., 2009. Glaucoma: where to now? *Ophthalmology*, 116(5), pp.821–2.

Teo, L. et al., 2011. A survey of contact lens complications in Singapore. *Eye Contact Lens*, 37(1), pp.16–19.

Thakur, S.S. et al., 2014. Intravitreal drug delivery in retinal disease: are we out of our depth? *Expert opinion on drug delivery*, 11(10), pp.1575–90.

Tham, Y.-C. et al., 2014. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*, 121(11), pp.2081–90.

Thrimawithana, T., Young, S. & Bunt, C., 2011. Drug delivery to the posterior segment of the eye. *Drug discovery today*, 16(5–6), pp.270–7.

Tiffany, J.M., 2008. The normal tear film. *Dev Ophthalmol*, 41, pp.1–20.

Turturro, S.B. et al., 2011. The effects of cross-linked thermo-responsive PNIPAAm-based hydrogel injection on retinal function. *Biomaterials*, 32(14), pp.3620–3626.

Urtti, A., 2006. Challenges and obstacles of ocular pharmacokinetics and drug delivery. *Advanced drug delivery reviews*, 58(11), pp.1131–5.

Vandamme, T.F. & Brobeck, L., 2005. Poly(amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. *J Control Release*, 102(1), pp.23–38.

Vellonen, K.S. et al., 2014. A critical assessment of in vitro tissue models for ADME and drug delivery. *Journal of Controlled Release*, 190, pp.94–114.

Vermonden, T., Censi, R. & Hennink, W.E., 2012. Hydrogels for Protein Delivery. *Chemical Reviews*, 112(5), pp.2853–2888.

Vugmeyster, Y. et al., 2012. Pharmacokinetics and toxicology of therapeutic proteins: Advances and challenges. *World journal of biological chemistry*, 3(4), pp.73–92.

Waite, D. et al., 2017. Posterior drug delivery via periocular route: challenges and opportunities. *Therapeutic delivery*, 8(8), pp.685–699.

Wang, W. et al., 2012. Immunogenicity of protein aggregates-concerns and realities. *International journal of pharmaceutics*, 431(1–2), pp.1–11.

Wang, W.Y. et al., 2011. Determination of puerarin in rabbit aqueous humor by liquid chromatography tandem mass spectrometry using microdialysis sampling after topical administration of puerarin PAMAM dendrimer complex. *J Pharm Biomed Anal*, 56(4), pp.825–829.

Watsky, M.A., Jablonski, M.M. & Edelhauser, H.F., 1988. Comparison of conjunctival and corneal surface areas in rabbit and human. *Curr Eye Res*, 7(5), pp.483–486.

Weidle, U.H. et al., 2013. The intriguing options of multispecific antibody formats for treatment of cancer. *Cancer Genomics and Proteomics*, 10(1), pp.1–18.

Weleber, R.G. et al., 2016. Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy. *Ophthalmology*, 123(7), pp.1606–1620.

Wirtz, R., 1908. Die ionentherapie in der Augenheilkunde. *Klin Mbl Augenheilk*.

Yao, W. et al., 2010. Preparation and characterization of puerarin-dendrimer complexes as an ocular drug delivery system. *Drug Dev Ind Pharm*, 36(9), pp.1027–1035.

Yavuz, B. et al., 2015. In Vitro/In Vivo Evaluation of Dexamethasone--PAMAM Dendrimer Complexes for Retinal Drug Delivery. *Journal of pharmaceutical sciences*, 104(11), pp.3814–23.

Yellepeddi, V.K. & Palakurthi, S., 2016. Recent Advances in Topical Ocular Drug Delivery. *Journal of Ocular Pharmacology and Therapeutics*, 32(2), pp.67–82.

Yilmaz, T., Cordero-Coma, M. & Federici, T.J., 2011. Pharmacokinetics of triamcinolone acetonide for the treatment of macular edema. *Expert opinion on drug metabolism & toxicology*, 7(10), pp.1327–35.

Yıldız, B., Işık, B. & Kış, M., 2002. Synthesis and characterization of thermoresponsive isopropylacrylamide–acrylamide hydrogels. *European Polymer Journal*, 38(7),

pp.1343–1347.

Yoshida, F. & Topliss, J.G., 1996. Unified model for the corneal permeability of related and diverse compounds with respect to their physicochemical properties. *J Pharm Sci*, 85(8), pp.819–823.

Zacharias, L.C. et al., 2013. Assessment of the differences in pharmacokinetics and pharmacodynamics between four distinct formulations of triamcinolone acetonide. *Retina (Philadelphia, Pa.)*, 33(3), pp.522–31.

Zhang, Z. et al., 2009. Reversible gelation of rod-like viruses grafted with thermoresponsive polymers. *Langmuir : the ACS journal of surfaces and colloids*, 25(4), pp.2437–2442.

Table 1: U.S. Food and Drug Administration (FDA) approved and current clinical trial drugs for treatment of anterior segment diseases

Name and company	Drug delivery platform	Drug and excipients	Indications	Status
Acuvail™ (Allergan)	Eye drops	Solution of ketorolac tromethamine (0.45%) in carboxymethylcellulose (pH 6.8)	Reduction of pain and inflammation post cataract surgery	Approved
Azasite® (InSite Vision)	Eye drops	Solution of azithromycin (1.0%) in polycarbophil (Durasite®)	Bacterial conjunctivitis	Approved
Azasite Plus™ (InSite Vision)	Eye drops	Solution of azithromycin (1.0%)/dexamethasone (0.1%) (ISV-502) in Durasite®	Blepharoconjunctivitis	Phase III completed
Bromsite™ (InSite Vision)	Eye drops	Solution of bromfenac sodium (0.075%)	Reduction of pain and inflammation post cataract surgery	Approved
Betoptic-S™ (Alcon)	Eye drops	Suspension of betaxolol (0.25%) in polystyrene-divinylbenzene) sulfonic acid, carbomer and BAC (0.01%)	Open angle glaucoma	Approved
Cationorm® (Santen Pharma)	Eye drops	Cationic emulsion	Dry eye	Approved
DexaSite™ (InSite Vision)	Eye drops	Solution of dexamethasone (0.1%) (ISV-305) in Durasite®	Reduction of pain and inflammation post cataract surgery; and non-bacterial blepharitis	Phase III
Durezol™ (Alcon)	Eye drops	Emulsion of difluprednate (0.05%) in castor oil, glycerine, boric acid, polysorbate 80 and sorbic acid (0.1%)	Anterior uveitis	Approved
EGP-437 (Eyegate Pharma)	Iontophoresis	Solution of dexamethasone phosphate in EyeGate® II Drug Delivery System (EGDS)	Anterior uveitis	Phase III
Indocollirio® (Bausch & Lomb)	Eye drops	Suspension of indomethacin (0.1%) and hydroxypropyl-b-cyclodextrin (IND-CD)	Mydriasis during cataract surgery or conjunctivitis	Approved
Lacrisert® (Aton Pharma)	Ocular insert	Sterile, rod-shaped HPMC insert	Dry eye	Approved
Lumigan® (Allergan)	Eye drops	Solution of bimatoprost (0.03%) in BAC (0.005%)	Glaucoma	Approved
Mydriasert (Thea Pharma)	Ocular insert	Tropricamide (0.28 mg) and phenylephrine hydrochloride (5.4 mg) in ammoniomethacrylate copolymer, glycerol and ethylcellulose	Induced pre-operative mydriasis	Approved
Ocusert® (Alza)	Ocular insert	Pilocarpine with EVA and alginic acid	Glaucoma	Approved
Prolensa™ (Bausch & Lomb)	Eye drops	Solution of bromfenac (0.07%)	Postoperative inflammation	Approved

Propine™ (Allergan)	Eye drops	Solution of dipivefrin-HCl (0.1%) with BAC (0.02%)	IOP control in open angle glaucoma	Approved
Restasis™ (Allergan)	Eye drops	Cationic emulsion of cyclosporine (0.05%) in castor oil, glycerine, polysorbate 80 and carbomer	Dry eye	Approved
TobraDex® (Alcon)	Eye drops	Suspension of tobramycin/dexamethasone in xanthan gum	Blepharitis	Approved
Timoptic-XE™ (Aton Pharma)	Eye drops	*In situ* gel solution of timolol maleate (0.25 or 0.5%) in gellan gum, mannitol, tromethamine and BAC (0.012%)	Glaucoma	Approved
Travatan™ (Alcon)	Eye drops	Solution of travaprost (0.004%) in BAC (0.015%)	Glaucoma	Approved
Xalatan™ (Pfizer)	Eye drops	Solution of latanoprost (0.005%) in BAC (0.015%)	Glaucoma	Approved
Zirgan™ (Bausch & Lomb)	Ophthalmic gel	Ophthalmic gel with ganciclovir (0.15%) with carbopol and BAC (0.0075%)	Acute herpetic keratitis	Approved

Abbreviations: BAC: benzalkonim chloride, HPMC: hydroxypropylmethylcellulose. **Note:** All drug therapies mentioned above was also cross-checked with www.clinicaltrials.gov.uk and its official company site

Table 2: U.S. Food and Drug Administration (FDA) approved and current clinical trial drugs for treatment of posterior segment diseases

Name and company	Drug delivery platform	Drug and excipients	Indications and ongoining trials	Status
Brimonidine (Allergan)	IVT implant	Brimonidine (0.4 mg) with PLGA	Dry AMD with GA	Phase II
Cortiject®/NOVA63035 (Novagali Pharma)	IVT	Dexamethasone emulsion (preservative and solvent-free)	DME	Phase I/II
Durasert™ (pSivida Corp)	IVT implant	Latanoprost with EVA/PVA	Ocular hypertension and glaucoma	Phase I/II
I-vation® (Surmodics Inc)	Reservoir IVT implant	TA (0.925 mg) with PMMA/EVA	DME	Phase IIb
IBI-20089 (Icon Biosciences Inc)	IVT	TA (6.0 mg or 13.8 mg) and benzyl benzoate with lucentis (0.5 mg)	AMD CNV	Phase I Phase II
Iluvien™ (Alimera Sciences, Inc.)	25-gauge IVT implant	FA (0.19 mg) with polyimide/PVA	DME AMD with GA Posterior uveitis	Approved Phase II Phase III
NT-501/Renexus (Neurotech Pharma)	IVT implant	CNTF with PET and ARPE-19 cells	Glaucoma RP	Phase I
NT-503 (Neurotech Pharma)	IVT implant IVT injection	Anti-VEGF receptor protein	Recurrent CNV with wet AMD	Phase I Phase II
NT-506 (Neurotech Pharma)	IVT implant	Anti-PDGF/Anti-VEGF	Wet AMD	Preclinical
Ozurdex® (Allergan)	IVT implant	Dexamethasone (0.7 mg) with PLGA	DME, CRVO, uveitis	Approved
Posurdex (Allergan)	IVT implant	Dexamethasone	Posterior uveitis DME	Phase III Phase III
Retisert® (Bausch & Lomb)	Reservoir IVT implant	FA (0.59 mg) with silicone/PVA	Non-infectious uveitis	Approved
Vitrasert® (pSivida Corp)	Reservoir IVT implant	Ganciclovir with EVA/ PVA	CMV retinitis	Approved

Abbrevitations: AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; CMV: cytomegalovirus; CNTF: ciliary neutrophic factor; CRVO: central retinal vein occlusion; EVA: ethylene-vinyl acetate; FA: fluocinolone acetonide; GA: geographic atrophy; IVT: Intravitreal; PDGF: platelet-derived growth factor; PET: polyethylene terephthalate; PLGA: poly(lactide-co-glycolide); PMMA: poly(methyl methacrylate); PVA: poly(vinyl alcohol); RP: retinitis pigmentosa; TA: Triamcinolone acetonide, VEGF: vascular endothelial growth factor. **Note:** All drug therapies mentioned above was also cross-checked with www.clinicaltrials.gov.uk and its official company site

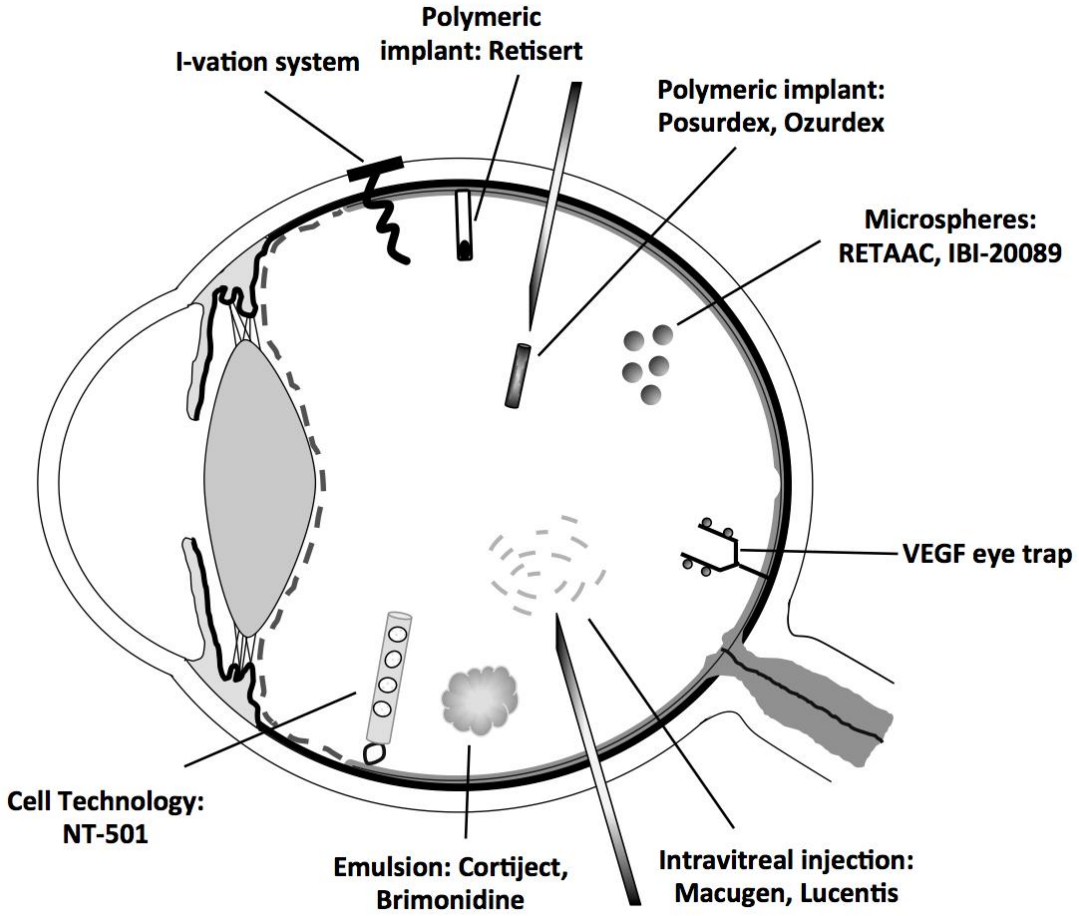

Figure 1: Some of the drug delivery technologies indicated for treatment of posterior segment diseases