INTRODUCTION

Drug delivery has the potential to have a tremendous impact on treatment of retinal diseases. There are a large number of drugs that are reasonably effective to treat retinal conditions, but those drugs are limited by delivery issues such as the need to have the molecule cross the blood–eye barrier, be present for long times, or the need to mitigate side-effects. The challenges of having drugs at a physiologically relevant concentration for extended periods or in a localized delivery system are challenges that can be solved with drug delivery technology, whether it is using cellular delivery systems, microelectromechanical (MEMs)-based devices, polymer matrices, or gene delivery systems.

A BRIEF HISTORY OF THE FIELD OF DRUG DELIVERY

The most common form of administration of a medication is the pill. There is evidence of the use of pills at least as early as ancient Egypt in the Ebers Papyrus (1500 BC). They consist, generally, of a medication mixed with a number of excipients or additives such as sugars and starches to protect and stabilize the formulation. The basic concept is that one swallows the pill, it dissolves in the stomach, and the medication is absorbed in the intestines to the circulation. This approach works well for many drugs, but not for those which can break down in the stomach. Insulin is usually presented as a case in point which must be injected because it cannot survive the environment of the stomach. Insulin is injected into the fatty tissue and is then absorbed into the systemic circulation.

Systemic administration of medications by either route can be problematic for certain tissues, particularly those with strong barrier characteristics or those which are poorly vascularized. Early versions of local delivery systems to the eye involve ointments which were described in ancient Mesopotamia. Pilocarpine drops have been used for at least 100 years to lower intraocular pressure (IOP) and treat glaucoma.

Drug delivery systems are a broad area that includes targeted systems as well as systems that provide controlled release of the drug. One of the earliest targeted systems was the liposome, which has been shown to build up in tumors due to the enhanced permeation effect. Liposomes were discovered in the 1960s and the first US Food and Drug Administration (FDA) approval came with Doxil, the liposomal-encapsulated formulation of doxorubicin, an anticancer agent in the 1990s. More recent variants on targeted systems have focused on adding molecules on the outside of liposomes or other nanoparticles that can allow them to target the tissue of interest. Targeted systems may allow the systemic delivery of a molecule that is released in the ocular tissues. However, in and of themselves, targeted systems do not provide sustained delivery of drugs. They can be engineered to do so, but if one looks at the half-life of doxorubicin, it is still on the order of hours as opposed to days or weeks. This does not mean that targeting cannot be combined with sustained delivery, but they are two components to consider.

Sustained delivery is better termed controlled delivery. The fundamental difference is that controlled delivery is dictated by the device and not the environment around the device. This is fundamental to the drug delivery. One does not want to administer a device to a patient and have different patients get the drug over different time courses, particularly in an unexpected way. One of the first controlled delivery systems was actually in the eye, the Ocusert system to deliver pilocarpine for glaucoma. The Ocusert system is a reservoir system that relies on the transport of the drug through a membrane. Membranes are effective for small molecules (less than 600 Da), but are not suitable for delivering larger molecules such as antibodies, growth factors, and proteins more broadly.

The watershed in the drug delivery world occurred in 1976. Robert Langer and Judah Folkman showed that large molecules could be delivered over days and weeks from polymer matrices, and they showed that the release profile could be tailored based on the matrix. The concept was not warmly received and there were huge questions about the mechanism and plausibility of the approach, but the drug delivery field has grown from being nonexistent in the USA in the 1980s to 11.5 billion dollars in 1996, to an estimated 85 billion dollars in 2010. The economic impact is a reflection of a number of factors, including the ability to provide new patent protection for off-patent medications, but it also reflects the impact on human health.

Several of the applications of drug delivery technology have been in the eye, as discussed in this chapter, but we have barely begun to realize the potential. Drug delivery provides the means to improve patient compliance, increase efficacy, and reduce side-effects of ocular medications.

DRUG DELIVERY

Formulating sustained-delivery systems

There are five broad approaches for the sustained delivery of drugs (Fig. 38.1). The first approach involves attaching molecules to the drug to increase its residence time. Poly(ethylene glycol) or PEG is the workhorse of this approach. PEGylating or attaching PEG molecules can increase the circulation time of a drug in the bloodstream by creating a highly hydrated
The third approach involves mixing the drug with polymers which entrap the drug in a matrix. The drug typically phase separates on the micro- or nanoscale from the polymer, leading to veins of the drug in the polymer matrix. The tortuosity of the veins plays a tremendous role in the release of the drug. With nondegradable polymers, the drug delivery profile is dictated by diffusion. With degradable polymers, the drug delivery profile is dictated by a combination of diffusion and degradation events that occur over time.

The second broad approach is to encapsulate the drug of interest in a reservoir system that includes a membrane that allows the drug to diffuse through the device and into the surrounding tissue. This approach lies at the basis of drug delivery systems, including the Ocusert implant delivering pilocarpine. Diffusion-based systems work for limited, typically small, molecules with molecular weights less than 600 Da. There are great benefits to the membrane-based systems, such as the ability to deliver many drugs over very long timescales, but there are risks, including the rupture of the membrane, leading to spontaneous delivery of the entire reservoir.

The third approach involves mixing the drug with polymers which entrap the drug in a matrix. The drug typically phase separates on the micro- or nanoscale from the polymer, leading to veins of the drug in the polymer matrix. The tortuosity of the veins plays a tremendous role in the release of the drug. With nondegradable polymers, the drug delivery profile is dictated by diffusion. With degradable polymers, the drug delivery profile is dictated by a combination of diffusion and degradation events that occur over time. The challenges in the matrix-based approaches involve achieving good mixing of the drug in the matrix to form tortuous pathways as well as promoting interactions between the drug and matrix. The closer the two associate
with each other, the more likely one will achieve very long (weeks to months to years) release. Thinking about this interaction becomes part of the process of formulating drug delivery systems.

The fourth approach involves osmotic systems. In these systems the diffusion of water into the matrix leads to swelling and drives the release of the drug via diffusion. Typically, osmotic systems lead to relatively fast release of drugs with a significant burst effect. Investigators are developing asymmetric membranes to control the delivery in a more uniform manner over time, but osmotic systems have not been used extensively other than as components to drive pump technologies which do have robust, long-term delivery.

Pump systems, the fifth approach, permit tight control of drug delivery over time for a wide range of medications. Pumps can either be continuous and passive or actively directed to deliver medications, and in some cases, pumps are refillable. The major limitation of pumps has been their size. Historically, they have been bulky and require more extensive implantation and placement than some of the other materials which are more amenable to delivery via small needles.

In thinking about which approach makes the most sense in formulating a drug delivery system, one needs to consider the following: the size, nature, and stability of the drug, the length of time one wants to deliver the drug, and the amount of the drug one wants to deliver over time. Regarding size, small molecules (<600 Da) can diffuse through polymers such as silicone. Larger molecules, macromolecules such as proteins, are not able to diffuse through polymers on a useful timescale for most applications. If one is hoping to deliver larger molecules, one will need to consider the methods outside of the membrane approach.

The nature of the drug refers to its charge and solubility. Most of the popular biodegradable polymers are extremely hydrophobic. If the drug of interest is very hydrophilic, it can be challenging to encapsulate the hydrophilic drug in the hydrophobic polymer matrix. One of the classic methods to overcome this challenge is to use excipients that interact with both the drug and the polymer. Fu et al. showed how excipients could greatly improve loading and delivery of glial cell line-derived neurotrophic factor (GDNF) through the use of excipients. Likewise, charged molecules can interact poorly in uncharged or similarly charged polymer systems. Poly(lactic-co-glycolic acid) (PLGA) can be synthesized with a carboxyl group on the end that carries a negative charge depending on the pH. This can improve the encapsulation of positively charged molecules.

The stability of the drug is crucial. Delivery of a drug that has lost its bioactivity is fruitless. Large molecules, in particular, are susceptible to losing bioactivity via cleavage or conformational changes during encapsulation or storage. The techniques used to encapsulate molecules play a tremendous role in preserving their bioactivity. When water-soluble molecules are exposed to fewer organic solvents and less energy during processing, it is more likely that the bioactivity will be preserved; however, it is always critical to check bioactivity upon release. One of the exciting findings in the matrix-based approaches has been that, for many drugs, if the drug is active upon encapsulation, the activity can be maintained for long times with drugs which are released years after encapsulation.

Beyond the drug, one needs to consider the amount of the drug one needs to deliver and the time course. Matrix-based formulations have been shown to deliver medications for years, but they rely on relatively high polymer-to-drug ratios, which makes them more suitable for applications where one can either deliver a large volume of material (which is unlikely in the eye) or where one has a relatively potent medication. As we will see in the examples below, many of the commonly used drugs are effective at low concentrations, but it is an important consideration. Membrane and pump systems can both deliver larger amounts of drugs over time, but the volume they deliver determines the necessary reservoir size and overall device dimensions. The time course is the second critical component. Membrane and pump approaches can both lead to very constant delivery depending on the geometry of the devices. Careful formulation can lead to very constant delivery over time from matrix-based formulations, but they are prone to burst release due to drug adsorbed on or near the surface of the materials.

There are clear benefits and challenges to all of these approaches, and multiple approaches may achieve the same desired effect. The key is to know one’s drug and desired delivery profile and then to determine which approaches are likely to be the most effective. One must then consider the route of administration to narrow down the approach finally to the one that is the most likely to be effective. If one wants to inject a material through a 33-gauge needle into the intravitreal space, one will have a very different set of potential approaches than if one is looking for an implant to sit in or near the tear duct. The examples outlined in this chapter will help to provide specific, real-world examples of how the formulation challenges can be approached successfully to develop therapeutically viable treatments.

**Delivering drugs in a targeted manner**

One simple way to achieve targeted drug delivery is to place the device in the area where one wants to deliver the drug. For a number of ocular conditions, this probably makes the most sense. If one wants long-term, local delivery of a drug that one is already injecting intravitreally every 4–6 weeks like the antivasocendothelial growth factor (VEGF) medications, being able to deliver the same drug with the same injection method but for several months or years would be very attractive. Injecting a device or matrix into the intravitreal space is a reasonable way to provide local delivery.

For some compounds, though, one may want either to deliver them systemically or to deliver them to a particular cell type in the eye and not to all cell types. A good example of this would be the delivery of a specific agent for a specific cell type, such as the retinal pigment epithelium (RPE). The most common forms of targeting have involved creating particles, typically nanoparticles, from either liposomes or other polymers that are covered in PEG arms to reduce their aggregation and promote transport, and attaching molecules to the particles that bind to receptors or molecules on the cells of interest. Antibodies, liposomes, and aptamers have all been used to facilitate targeting.

The key issues to consider in designing a targeting molecule are the specificity and affinity of the targeting moiety to the molecule of interest on the cell. Poor affinity or specificity will lead to poor targeting. Once one has identified targeting molecules with appropriate affinity and specificity, one needs to insure the stability of targeting molecule in vivo. Larger molecules, such as antibodies, have the potential to be denatured or enzymatically cleaved in vivo, which has motivated the
The role of devices in drug delivery

The term “devices” can include everything from membrane-based depots to microparticles, implants, hydrogels, and MEMs-based systems. In the novel delivery systems, a number of devices will be discussed along with their advantages and limitations.

Devices that are based on pumps and other microfluidic delivery systems have the potential to facilitate extremely well-controlled delivery of drugs over long times and, in some cases, may be refilled. The initial implantation of a device may be more involved than a simple injection of a drug, but that one-time invasiveness may be countered if a drug can be delivered for exceptionally long times in a controlled manner or if the device can be refilled and permit far fewer invasive injections.

The remaining classes of device rarely exhibit the ability to be refilled, with the one potential exception of affinity-based systems which are in the very early stage of preclinical testing. However, if one designs the geometry properly, many of the implant systems can be administered in a minimally invasive manner, and with careful formulation many implants achieve very well-controlled delivery of the drugs of interest.

GENE DELIVERY

Gene therapy has the potential to replace or restore function in the retina as well as produce growth factors which protect the eye. It is very challenging, though, to get the genetic material both to the cells and into the genome without breakdown of the material. There have been many studies looking at the transfection efficiency of deoxyribonucleic acid (DNA) through routes of administration, including drops, subconjunctival, intravitreal, and subretinal injections, and in all cases the transfection efficiency has been low to the retina and the subsequent protein expression is typically small and over a short duration.

To facilitate more effective delivery of DNA and subsequent protein expression, a number of vectors have been pursued. The two basic approaches involve viral and nonviral delivery of constructs to the retina. Viruses have adapted over millions of years to deliver genes to cells efficiently, and viral delivery is generally efficient. Viral delivery does raise safety concerns and there were substantial complications and deaths in early viral-based gene therapy trials. Nonviral gene delivery has sought to provide safer alternatives, but the challenge lies in getting efficient delivery and incorporation of the genetic material.

Viral systems

There are three major classes of virus that have been used for transduction: retroviruses, lentiviruses, and adenoviruses. Retroviral vectors only infect dividing cells, making them relatively unattractive for ocular applications. Lentiviral vectors are designed to infect nondividing cells in the G0 or G1 phase of the cell cycle. There are significant safety concerns with both retroviral and lentiviral vectors because they have the potential to insert into the genome. Of the three major classes, adenoviruses have drawn tremendous interest for gene therapy because they do not incorporate into the genome, which is thought to reduce their oncogenic potential, and they are extremely effective at transducing cells. However, adenoviruses have been found to be very immunogenic, and one of the early clinical trials using an adenovirus had to be halted when an 18-year-old died due to a systemic inflammatory response syndrome.

Adenovirus-based vectors have continued to be pursued in the eye because of the local delivery and immune-privileged nature. GenVec has used an adenovirus to deliver the gene for pigment epithelium-derived factor (PEDF) for the treatment of neovascular AMD in a phase I trial. The adenovirus-based delivery system was well tolerated by patients with only transient, mild inflammation in some patients which was managed with topical medications. There was no control group in this phase I trial, but the size of the choroidal neovascular lesions was smaller in the high-dose group. Much of the follow-on research has focused on repeated administrations, longer-term expression of PEDF, and using inducible promoters to direct expression of the protein of interest.

A variant on the adenovirus, first found as a contaminant of adenoviruses, the adeno-associated virus (AAV), has proven to be an effective alternative. Like adenoviruses, AAV vectors do not integrate into the genome. Furthermore, they do not elicit a strong immune response. One of the first major successes for gene therapy with AAV vectors has been the treatment of Leber congenital amaurosis, a severe form of retinal degeneration that leads to vision loss in early childhood. A replication-deficient AAV vector was used to deliver a gene for isomerohydrolase activity (AAV-hRPE65v2). The vector was injected subretinally, and vision gains were found in younger patients.

Nonviral systems

Viruses are extraordinarily effective at delivering genetic material to cells, but there are safety concerns, and the size of the vector limits the amount of genetic material that can be delivered. Nonviral vectors have been pursued to address these issues.

There are five basic steps that have to be achieved to transfect a cell (Fig. 38.2). The genetic material must get to the cell, into the cell, out of the endosome, to the nucleus, and into the nucleus. Viruses have evolved a complex set of tools to achieve this. For example, the adenovirus has a targeting moiety for the cell of interest and leverages the pH drop in the endosome by having the capsid undergo a conformational change which opens the endosome. It is thought to bind to dynein, a molecular motor that moves along the microtubules to travel to the nucleus.

Nonviral systems have been designed to address one or more of these issues, and the more recent systems have been designed to address several or all of these critical steps for transfection. Liposomes were among the earliest transfection agents. Liposomes are capable of shielding DNA from enzymatic breakdown until the material gets to the cell, but their fusion with the cell membranes is not efficient. However, in 1987, the use of cationic liposomes was first identified as a means to facilitate high rates of transfection. The cationic component of the system facilitates interactions with the negatively charged cell membranes and the subsequent cell fusion which delivers the DNA...
While using nonviral vectors for engineering cells in vivo in the DRUG DELIVERY CELLULAR DELIVERY FOR SUSTAINED term transfection, but the field is moving forward rapidly. It is likely to be a very different landscape in the next decade. The challenges involved in getting genes from outside cells to the nucleus.

Positively charged polymers like polylysine and polyethyleneimine (PEI) were very early in the nonviral vector development timeline. PEI, one of the major cationic polymers, was first shown to be an effective polymer for gene delivery in 1995. It does two critical things. First, it is a positively charged polymer that complexes with negatively charged DNA to create positively charged nanoparticles which stick to the anionic membranes of cells. Second, it is a proton sponge, meaning that as the pH is lowered in the endosome, the amines on the polymer take up the hydrogen ions and the polymer protonates. It does this to the point that it swells and bursts the endosome. The polymer, however, has no specific method for getting the DNA to or into the nucleus. PEI tends to be most effective in dividing cells where the organization of the mitotic spindles facilitates movement of the particles to the nucleus. PEI has been used in animal models for transfection of retinal cells. The particles were taken up primarily by what appear to be Müller glial cells but no quantification is discussed so it is not possible to assess what sort of efficiency was achieved.

In light of the complexities of getting DNA to the nucleus, more recent research has focused on developing multicomponent systems that incorporate protection of DNA with endosomal escape mechanisms and nuclear targeting moieties. The challenges of specific transfection of retinal cells in the eye with nonviral vectors are significant, and it is likely that careful engineering of the vector will be needed for successful, long-term transfection, but the field is moving forward rapidly. It is likely to be a very different landscape in the next decade.

## CELLULAR DELIVERY FOR SUSTAINED DRUG DELIVERY

### Engineering cells for delivery

While using nonviral vectors for engineering cells in vivo in the retina may not be efficient, nonviral vectors can be very attractive for ex vivo engineering of cells where one can sort for the cells which produce the factor of interest. Viral vectors may also be more attractive because the safety of the cells can be well assessed before introduction in vivo.

The attraction of using cells for the delivery of therapeutic agents is that cells can deliver a molecule for very long periods of time, potentially years. Furthermore, cells have the potential to integrate into the retina and deliver molecules in layers that may not be easily reached by standard drug delivery of gene therapy approaches. For example, it can be challenging to deliver genes to the retina and to get robust expression of the molecule of interest via intravitreal injections. However, there are studies showing that certain cells may be able to migrate and integrate with the retina following intravitreal administration and produce molecules such as GDNF and brain-derived neurotrophic factor (BDNF) to preserve retinal cells in a number of models of retinal degeneration.

### Engineered cells for delivery

Engineering materials for immunological protection

While the eye is immune-privileged, the presence of disease can alter this privilege, and long-term survival of transplanted cells is not guaranteed. Since the primary purpose of the engineered cells is to deliver their molecular payload, encapsulating them to protect them from the host while allowing their molecules to reach the retina makes a great deal of sense. It also facilitates their removal should complications arise.

As noted in the section on sustained delivery systems, solid polymer membranes do not allow large molecules (> 600 Da) to diffuse through. Most of the growth factors noted above are significantly greater than 600 Da. The solution, then, is to engineer the materials with higher-molecular-weight cutoffs that allow the growth factors through but still block the transport of antibodies and other larger molecules.

Alginate gels and variants on alginate gels have been one of the most used materials to encapsulate cells for this purpose since the early 1980s. Alginate is an attractive material in that it does not adsorb proteins, facilitating their transport, but the molecular weight of the transported molecules can be controlled by the crosslinking density. Because alginate gels are cross-linked water-swollen gels, the encapsulated cells are able to remain hydrated and transport of nutrients and waste is maintained. Other materials, primarily synthetic hydrogels, have become popular because the permeability can be tightly controlled through crosslinking agents and density, membrane thickness, and the use of multiple layers. Kristi Anseth’s group has shown that functionalizing hydrogels with moieties that interact with cells can still maintain the long-term delivery of the protein of interest while leading to higher and longer-term cell viability, the ultimate goal of these encapsulation systems.

### ROUTES OF DELIVERY TO THE RETINA

#### Traditional routes of administration

**Oral delivery**

Oral delivery is the most preferred route of delivery of medications by patients. Drugs such as timolol maleate can be given orally and do have an ocular effect, namely the lowering of...
lens market is expanding. Million people in the USA wear contact lenses and the contact device. To use the insert systems and older patients did not like the comfortable especially if it twisted, and it could fall out. Follow-on designs sought to make the insert remain in the eye, IOP. There was a fundamental problem was that patients had to be taught how to use the insert systems and older patients did not like the device.

**Topical delivery**

A large range of medications are delivered topically either as solutions or as gels. Because a large portion of the drop or gel is cleared from the tear film quickly, topical delivery leads to significant (typically 80%) systemic absorption of the drug. There is also relatively limited adsorption of the drug to the ocular tissues. There are a number of models of pharmacokinetics of topically delivered medications, and the drug chemistry, particularly the hydrophobic versus hydrophilic nature of the drug, plays a role, but overall, there is very little drug delivered to the vitreous and the retina. This makes topical administration challenging for retinal diseases.

There have been clinical trials in Europe looking at delivery of nerve growth factor (NGF) for neuroprotection of the retina, and in particular, there are trials looking at topical administration of NGF for glaucoma. Three glaucoma patients who were losing vision received drops containing murine NGF four times daily for 3 months. There are no data from the human or animal studies regarding the concentration of NGF that reaches the back of the eye, but some patients undergoing this treatment exhibited some signs of improvements in their electroretinograms.

**Injections**

When oral medications and drops are not effective, injections are typically considered. Subconjunctival injections are one of the least invasive injections but there are several barriers between the subconjunctival space and the retina, although a number of molecules can diffuse in low concentrations to the retina with this approach, depending on their size and chemistry. Intravitreal injections, though more invasive, provide a means to put molecules near the retina. The vitreous is also capable of acting as a sink for many molecules, absorbing them and slowly releasing them, which can increase the residence time of these molecules in the intravitreal space. Subtenon injections have shown more interest with the thought that the drug will be delivered over a prolonged period through this route.

**Novel approaches for administration**

**Devices**

**Inserts**

The Ocusert system is one of the best-known and most widely studied membrane-based drug delivery systems. The device consists of two membranes of poly(ethylene-co-vinyl acetate) and a ring of the same material filled with pilocarpine to lower IOP. The insert was designed to deliver the drug for 7 days when placed in the cul de sac of the eye. The system worked to manage IOP, but patients found that the device could be uncomfortable especially if it twisted, and it could fall out. While follow-on designs sought to make the insert remain in the eye, a fundamental problem was that patients had to be taught how to use the insert systems and older patients did not like the device.

The landscape for inserts may be changing. Approximately 40 million people in the USA wear contact lenses and the contact lens market is expanding. Modifying contact lenses makes sense in that many patients are familiar with them and their use. Soft contact lenses, those primarily used at this point, are hydrogels, water-soluble polymers that are crosslinked to form networks, and hydrogels are a potential material for controlled drug delivery. It should be noted, however, that when drug delivery researchers start looking at contact lenses or modified lenses as the solution to patient- and clinician-friendly inserts, they often forget that most patients remove their contact lenses at night. If one wants to use contact lenses as a depot for drug delivery, one either needs to account for the actual time patients wear the lenses or design a wearable long-term lens.

While hydrogels can be used as a drug delivery vehicle, water-soluble drugs, such as those likely to cross the conjunctiva most effectively, tend to elute very quickly from the highly hydrated polymer networks on the order of minutes or hours. Timolol maleate, a water-soluble drug for lowering IOP, has been shown to be able to be delivered from contact lenses consisting of polymers of N,N-diethylacrylamide and methacrylic acid for approximately 24 hours. A study of 3 patients using contact lenses delivering timolol showed the lenses controlled IOP as well as drops. While this is promising, timolol, like pilocarpine, does not have to reach the retina. It only needs to be in a reasonable concentration near the ciliary body to affect aqueous production.

Getting molecules into lenses or inserts that then are delivered to the retina requires crossing many physical barriers in the eye. Liposomes, surfactants, and penetrating agents may facilitate transport through these barriers, but a formulation that achieves this safely has yet to be demonstrated.

**MEMs devices**

Using a MEMs-based approach is exciting in that one can actively control the drug release by dictating the rate of electrolysis. An active delivery system allows the clinician to change the rate of delivery based on assessments. None of the other systems presented up to this point permits active control of the delivery of the drug. MEMS-based systems also have the potential for the delivery of multiple drugs with minor modifications, which increases the potential impact of these devices on treating retinal disease.

**Replenish external scleral fixed refillable device**

Implanting a reservoir system in the subconjunctival space opens the door to well-controlled long-term delivery of both small and large molecules without the need for repeated intravitreal injections. The MEMs device uses electrolysis to create bubbles that push the drug out of the reservoir of the implantable device, and there is a port that facilitates loading of the drug into the system. Implantation of the device is similar to a glaucoma drainage device in complexity and it can be reloaded several times and has been well tolerated in initial rabbit studies.

**Iontophoresis system**

EyeGate Pharma has developed a delivery system composed of an annular scleral iontophoresis reservoir which is filled with drug (Fig. 38.3). A potential is applied between an electrode on the forehead of the patient and the device to drive the charged drug into the anterior and posterior segments of the eye over 2-4 minutes. This device is currently in clinical trials, including a study to assess the safety and efficacy of a dexamethasone phosphate iontophoresis formulated solution (EGP-437) at two different dose levels for dry eye (NCT01129856), and a trial of four iontophoretic doses of EGP-437 in patients with noninfectious
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anterior-segment uveitis (NCT00694135). While the system has not yet been tested for diseases of the retina, it may be an alternative to different retinal pathologies due to the good penetration in human sclera of drugs like bevacizumab.86

Implants

Vitrasert ganciclovir implant

There are several implants either in or through clinical trials which deliver drugs to the retina for long periods of time, up to several years. The Vitrasert implant was approved by the FDA in 1996 for the treatment of cytomegalovirus (CMV) retinitis.87 The implant delivers ganciclovir, an antiviral drug, from an implant of poly(vinyl alcohol) and poly(ethylene vinyl acetate), one of the early workhorses of the controlled-release field.8 The implant delivers the medication for approximately 32 weeks and has been shown to halt the progression of CMV.88,89 One of the challenges with a nondegradable implant is removal, and to deal with this, the implant is sutured to the eye wall once inserted.90 Figure 38.4 shows a comparison of the sizes of the Iluvien, Retisert, and Vitrasert implants.

Retisert fluocinolone implant

Retisert is an implant the size of a grain of rice that delivers fluocinolone acetonide intravitreally for 30 months for uveitis and was approved in 1995.91 It has also been studied in trials for diabetic retinopathy.91 The implant consists of a blend of the drug with poly(vinyl alcohol) and methylcellulose in a tablet geometry that is secured with a suture once inserted into the vitreal space through a scleral incision, similarly to the Vitrasert implant. The implant is very effective at treating uveitis, but there are side-effects, including an increase in IOP associated with the steroid delivery and formation of cataracts.92

Iluvien fluocinolone implant

The Iluvien implant is composed of the same materials and drug as the Retisert implant but is designed with a very different geometry (a narrow cylinder 3.5 × 0.37 mm) that can be injected into the intravitreal space through a 25-gauge needle.93 The implant and injector are shown in Fig. 38.5. The system delivers a lower level of fluocinolone than the Retisert implant and in clinical trials for diabetic macular edema, there have been fewer complications. In the lowest dose format (0.2 µg/day), no elevation in IOP has been seen in a phase II trial.93 Five of 17 subjects with the higher-dose (0.5 µg/day) system required IOP-lowering drops and one patient required a glaucoma drainage device.93 A total of 34% of the low-dose patients and 71% of the high-dose patients showed progression of cataracts, and 14% and 29% in each group had surgery.93 Some improvements in visual function were seen, and all patients showed reduction in foveal thickness.

Ozurdex dexamethasone implant

Ozurdex (Allergan) is a dexamethasone implant that delivers the steroid intravitreally for 6 months.94,95 The implant consists of poly(lactic-co-glycolic acid), a degradable polyester and dexamethasone. It is inserted into the intravitreal space with a single-use applicator through a 22-gauge needle. The implant and applicator are shown in Fig. 38.6. The implant is not tethered in
immortalized RPE cells engineered to deliver CNTF in an encapsulated format, and it is inserted into the vitreous cavity and sutured to the eye wall. A schematic is shown in Fig. 38.8. The implant was studied in a phase I trial for retinitis pigmentosa, it was well tolerated by patients, and some patients showed improvements in visual acuity.

The implant (designated NT-501) was then studied in phase II trials for early- and late-stage retinitis pigmentosa. The retinal thickness was higher for those receiving the implant over a year, and Neurotech, the company developing the implant, has been given a fast-track designation by the FDA for the treatment of visual loss from retinitis pigmentosa.

ECT technology anti-VEGF implant
Neurotech is also developing an anti-VEGF ECT implant for the treatment of age-related macular degeneration (NT-503). Like the CNTF implant, the anti-VEGF implant uses human cells encapsulated to protect them from the immune system but allowing the release of the secreted molecule. At this time, Neurotech is in preclinical models with this implant and hopes to start phase I trials in the near future.

Injectables
Micro- and nanoparticles
The majority of micro- and nanoparticles used in the eye are based on the degradable polyesters poly(lactic acid) (PLA) and PLGA. These polymers degrade by hydrolysis and the rate of degradation is controlled by the ratio of lactic acid to glycolic acid. The I-vation triamcinolone implant
Surmodics has developed the I-vation implant, a helical screw coated with triamcinolone acetonide that delivers the drug intravitreally for 36 months. The implant is designed to be inserted through the sclera once a hole has been made with a 25-gauge needle. The implant and a schematic are shown in Fig. 38.7. The helical design increases the surface area from which the drug is released. One of the striking features of the implant is that the drug is entirely within the coating on the helical structure and not within the bulk of the device. Like the Retisert device, long-term usage is associated with an increase in IOP and cataracts.

Encapsulated cell technology (ECT) ciliary neurotropic factor (CNTF) implant
CNTF can be delivered from a rice-sized implant via ECT for an estimated time of 2 years or more. The implant contains immortalized RPE cells engineered to deliver CNTF in an encapsulated format, and it is inserted into the vitreous cavity and sutured to the eye wall. A schematic is shown in Fig. 38.8. The implant was studied in a phase I trial for retinitis pigmentosa, it was well tolerated by patients, and some patients showed improvements in visual acuity. The implant (designated NT-501) was then studied in phase II trials for early- and late-stage retinitis pigmentosa. The retinal thickness was higher for those receiving the implant over a year, and Neurotech, the company developing the implant, has been given a fast-track designation by the FDA for the treatment of visual loss from retinitis pigmentosa.

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Injectables
Micro- and nanoparticles
The majority of micro- and nanoparticles used in the eye are based on the degradable polyesters poly(lactic acid) (PLA) and PLGA. These polymers degrade by hydrolysis and the rate of degradation is controlled by the ratio of lactic acid to glycolic acid.
Micro- and nanoparticles based on PLA and PLGA have been used for many years to deliver a range of drugs from small molecules to large proteins. One of the biggest challenges associated with these polymers in spherical form is that they tend to release the drug in multiple phases (typically triphasic) beginning with a burst phase. However, by adding the appropriate excipients that interact with both the polymer and the drug, such as GDNF, one can achieve reduced burst and relatively constant delivery over very long times up to several months from microparticles. GDNF microspheres based on this approach have been used in vivo in the DBA/2J mouse model of retinal ganglion cell (RGC) degeneration. The spheres delivering GDNF were injected intravitreally and led to significantly higher numbers of fluorogold-labeled RGCs as compared to the blank spheres or untreated animals. The same formulation was shown to preserve RGC and function in the pig following a model of acute ocular ischemia and found that GDNF microspheres led to the preservation of a greater number of RGCs as well as improved function over time as measured by multifocal electroretinogram.

A number of drugs have been formulated into microspheres for intravitreal and subconjunctival administration. PLGA microparticles delivering celecoxib have been administered subconjunctivally to reduce the concentration of VEGF in the retina and vascular leakage in a diabetic rat model. Likewise, microparticles delivering the corticosteroid, budesonide, have been injected subconjunctivally in rats to alter VEGF expression. Nanoparticles delivering carboplatin for a mouse model of retinal neoblastoma showed a reduction in tumors. Nanoparticles delivering dexamethasone showed a reduction in choroidal neovascularization in a laser-induced rat model. Intravitreal administration of microspheres delivering BDNF showed neuroprotective effects in a rat model of retinal ischemia.

The difference between nanoparticles and microparticles in this format is really just one of size. The size does have effects, including obvious things like increasing the surface area of the delivery vehicle as the particle size shrinks, which tends to lead to faster release of the drug. Size also has an effect on the concentration of particles which can be administered through a small-gauge needle. Since one of the greatest attractions of the micro- and nanoparticle formulations is that they can be suspended in saline and injected using standard techniques, it is critical to be able to inject them at reasonable concentrations through fine-bore needles. When one is performing an intravitreal injection, in particular, there is very little volume that can be added safely, so one would like to be able to inject as much of the drug delivery system and as little saline as possible.

With careful formulation, and a few predictive models, one can develop injectable formulations that facilitate long-term delivery (typically over several months) of the drug of interest at drug-loading efficiencies and with release kinetics that are suitable for long-term therapy for retinal diseases.

**Nanoscale systems**

Novagali Pharma is developing an emulsion-based delivery system called Eyeject for the sustained delivery of drugs to the intravitreal space. The system is currently in a phase I trial delivering corticosteroid prodrug for the treatment of diabetic macular edema (clinical trial identifier NCT00665106). The system involves combining the prodrug such as lipophilic ester of dexamethasone with an oil such as mineral or vegetable oil, a surfactant, and glycerol. The combination of these components leads to the formation of an emulsion that can be injected intravitreally and deliver the prodrug for 1–6 months.

**Ocular uptake of systemically delivered nanoparticles**

Size plays a critical role in whether nanoparticles can be delivered systemically and be found in the retina. While there is a blood–retina barrier, in one study, a small concentration of 20 nm gold nanoparticles was found in the retina in mice following intravenous administration; 100 nm gold nanoparticles were not found. In another study, PLA-based nanoparticles encapsulating rhodamine (100–200 nm) were not found in normal rat retinas, but a few were seen in a rat model of experimental autoimmune uveoretinitis where the blood–retinal barrier is compromised. Generally, few nanoparticles of any size make it to the retina. The vast majority are likely picked up by the reticuloendothelial system and cleared.

**Nanocomposites for topical delivery**

Eye drops are far preferred by patients and clinicians to more invasive injections, and a great deal of research has focused on methods to make drops a viable system for delivery of drugs to the posterior segment of the eye. Nanocomposites typically involve liposomes or other nanoscaled particles to deliver the drug. One of the primary objectives of nanocomposite research has been to increase the residence time of the solution on the eye to facilitate transport of the drug. The charge or lack thereof on the nanoparticles plays a critical role in their behavior. Neutrally charged liposomes delivering pilocarpine were shown to lead a drop in IOP for twice as long as free drug alone, suggesting that the liposomes increased the residence of the drug following administration. Providing more direct evidence, rhodamine-loaded colloidal solutions of nanoparticles were administered as drops in the eye. Neutral particles showed greater delivery of rhodamine than negatively charged particles.

The question, though, is whether these nanocomposite systems can lead to drug delivery in the back of the eye. Hironaka et al. investigated the delivery of coumarin-6 to the retina via nanocomposites of liposomes containing coumarin-6 as eye drops in mice. Coumarin-6 was found in the inner plexiform layer over the first 60 minutes postadministration. The group found that there was better delivery with smaller liposomes, and coating with mucoadhesive molecules increased the delivery of coumarin-6. The mechanism for delivery was not clear in this work, but the group hypothesized that conjunctival adsorption played a role. What is also not clear from this work is how much of the dose was absorbed and how much went into the systemic circulation. The group extended this work to rabbits and monkeys with similar results.

It is impressive that any measurable amount of a molecule can reach the retina via topical administration. Whether enough drug could be delivered to be effective without substantial systemic or ocular side-effects remains to be seen, but the possibility does exist that nanocomposites could be formulated to permit delivery to the back of the eye.
PHARMACOKINETICS IN THE EYE

The delivery of a drug is dictated not only by the delivery device but also by the transport parameters in the tissue of interest. When in vitro release studies are conducted, they are almost always conducted under unlimited or infinite sink conditions, meaning the sink into which the drug is delivered is not limited and does not put a boundary condition on the rate of delivery. In the eye there are several barriers to delivery as well as tissues and fluids that can act as drug sinks and delivery systems. Both the behavior of the drug delivery system and the transport of the drug in the eye need to be considered when predicting and understanding the kinetics of delivery to the retina.

Barriers to delivery

The major barriers to delivery of molecules in the eye depending on route of administration include the conjunctiva, the sclera, the choriocapillaris, the RPE, the external limiting membrane, the internal limiting membrane, and the blood–retinal barrier. The conjunctiva is permeable to molecules up to ~26 kDa, the sclera is permeable to molecules up to 150 kDa, the choriocapillaris up to 55 kDa, the RPE up to 30 kDa, the external limiting membrane up to 70 kDa, the internal limiting membrane up to 150 kDa, and the blood–retinal barrier is not even permeable to 3 kDa dextran.121

Modeling delivery

Impact of drug chemistry

There are good models for predicting drug release from nondegradable systems.99 There are also good models for the release of drugs from degradable polymers that are highly predictive and based on a combination of diffusion and degradation behaviors.122 The one limitation of this model is that it does not consider the interaction between the polymer matrix and the drug. This interaction is crucial for understanding release of many of the molecules of interest for the retina from polymer matrices. While size plays an important role in delivery, the drug chemistry is also critical. A good example of a place where the chemistry has a striking effect is in the delivery of NGF, BDNF, and neurotrophin-3. These molecules are from the same family of growth factors and are essentially identical in structure with minor changes in their amino acid residues123 and yet their delivery profiles from identically processed matrices can be extremely different.124–126

More models that consider the drug–polymer interactions are being developed129–131 which can be combined with the diffusion and degradation-based models to predict release of drugs from matrices. This, however, is only the first step.

One must also consider how the drugs are absorbed by the surrounding tissues in vivo. Depending on the drug chemistry, several of the tissues of the eye can absorb the drug and, potentially, prolong the delivery.132 When performing pharmacokinetic experiments, it is useful to look at not only the vitreous and aqueous concentrations, but if possible, to consider whether the lens, iris, and other tissues are acting as sinks for the drug.

Impact of depot placement

One will get a very different delivery profile of a drug to the retina if the depot is placed in the intravitreal, subconjunctival, or subtenon space. What is becoming exciting is that more and more assessments of pharmacokinetics for the major drugs in the eye are being published, leading to more data regarding the diffusivities of the drugs through the major barriers in the eye. Often, simple compartment models based on traditional diffusion can be used to predict surprisingly well the potential pharmacokinetics of a drug delivery system placed in the subconjunctival versus intravitreal space.133–136 The availability of this data increases the probability of efficiently designing delivery systems for treating the retina.

REFERENCES

3. Vogel WH, Berke A. Brief history of vision and ocular medicine. Amsterdam: Kugler; 2009.


