CHAPTER 2

Drug Delivery Systems in Ophthalmic Applications

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I. INTRODUCTION

Ophthalmic drug delivery systems are essential to improve duration, targeting and compliance. For chronic diseases such as glaucoma, macular degeneration and diabetic retinopathy, administration routes can include oral, parenteral, topical, subconjunctival, intracameral, intravitreal, sub-Tenon’s, intrascleral, and subretinal. Most drug delivery systems are either reservoir or matrix type. Reservoir systems provide more precise rate control but usually are more complex to implant and remove. Erodible matrix systems depend on drug dissolution and release and excipient erosion for rate control.

Topical reservoir inserts (e.g. Ocusert®) have existed for some time with limited delivery success. Most successful have been enhancements of topical delivery by improvements to standard drop forms through use of gelling agents. Materials such as gellan or xanthan have been
successfully commercialized, with many others on the horizon.

Many styles of intravitreal systems are being developed. These systems have been designed to release drugs for multiple year periods. The pioneer commercialized device was Vitrasert® (Bausch & Lomb), which released ganciclovir for cytomegalovirus (CMV) retinitis therapy. A variation of that device is the Retisert® which has been commercialized for sustained delivery of fluocinolone acetonide in uveitis patients. Additional erodible and non-erodible devices are in various stages of clinical trials; namely Posurdex® (dexamethasone), Medidur™ (fluocinolone acetonide), I-Vation™ (triamcinolone acetonide) and NT-501 (ciliary neurotrophic factor). Transscleral delivery via subconjunctival or sub-Tenon’s capsule routes is also advancing. Other routes such as subretinal, suprachoroidal and intrascle-ral remain in research stages and have not yet advanced clinically.

A. Historical Perspectives

The application of drug delivery principles in ophthalmology is not new, but in fact has roots in ancient practice. Between 20 BC and AD 50, Greeks and Romans formulated ophthalmic solutions with perceived beneficial agents by dissolving them in water, egg white or milk to produce what was termed “collyria” (Olejnick, 1993). During the Middle Ages preparations derived from solutions of Atropa belladonna or “Deadly Nightshade” (the natural source of atropine) were used to induce ophthalmic dilation as a means to cosmetically alter the appearance of the eye (King, 1984). Mixtures of myrrh, saffron, and frankincense with yellow arsenic dissolved in quantities of coriander water were not uncommon during this era as a method for treating most ophthalmic diseases. During this period it was even thought that oil applied to the eye could help treat cataract. The dangers of such practices were not well known, and even into modern times, uncontrolled application of solutions to the eye continued until greater controls were established with the advent of pharmacies. The practice of compounding ophthalmic solutions in pharmacies evolved during the periods prior to World War II and well into the 1940s. Still, some of the quality controls recognized today in the United States were not established until 1953 when sterile (i.e. “unadulterated”) dosage forms were mandated by the Food and Drug Administration (FDA) with subsequent adoption of sterility guidance in 1955 from the United States Pharmacopoeia (USP, 1955).

The paradigm to completely dissolve drug substances for use in the eye was eventually changed with the application of suspension dose forms. Solid drug particles were first suspended in the 1950s, owing to the availability of cortisone acetate. For the first time, clinical studies revealed that sufficiently reducing the particle size of the drug allowed it to be instilled on the ocular surface without significant safety concerns or unacceptable foreign body sensation. Drug suspensions represented the earliest form of what would now be considered a “sustained” delivery formulation. Better understanding of the solubility properties of drug molecules and a growing armamentarium of safe excipients allowed for increasing development of useful suspensions. For example, one approach utilized the binding to insoluble cationic polystyrene divinylben- zene sulfonic acid resin particles to retard aqueous delivery of betaxolol, resulting in a more comfortable form of the drug now recognized as Betoptic S® (Jani et al., 1994).

In parallel with the evolution of suspension technologies, it was recognized that even larger solid systems might have application following the invention and development of polymers that could be used to form hydrophilic contact lenses. It had been observed that hydrogel co-polymer compositions with hydroxethylmethacrylate were capable of being loaded with drugs by soaking them in drug laden aqueous solutions. This application was first reported in the early 1970s in reports which examined
uptake and release of agents such as fluorescein from Bionite and Soflens lenses (Waltman and Kaufman, 1970; Maddox and Bernstein, 1972). Studies showed significant differences in uptake and release rates for the two types of lenses. Focus quickly turned to lens studies using pilocarpine, the predominant available glaucoma drug during that era. Several studies reported improvements in reduction of intraocular pressure and corneal drug flux using presoaked lenses containing lower pilocarpine concentrations than standard drops (Podos et al., 1972; Kaufman et al., 1971, Krohn, 1978; Krohn and Breitfeller, 1975). Many years of research using different drug soaked contact lenses followed these early studies. Still, the common feature of these lenses was that only minor prolongations of drug release could be achieved, most dumping their contents within a day. This should not have been totally unexpected as these systems were designed to allow free diffusion of water through the porous matrix without additional mechanisms for retarding the solutes within the water.

Concurrent with the development of contact lens materials, other ophthalmically acceptable biocompatible materials were under investigation. For example, polyvinylalcohol (PVA) disks for delivery of drugs to the eye were proposed as early as 1966 for use by astronauts while in space (Yakovlev and Lenkevich, 1966). At that time experimental studies with pilocarpine-loaded PVA disks exhibited sustained miosis and intraocular pressure (IOP) reduction in human subjects. This was further elaborated with studies reporting that PVA films containing pilocarpine, antibiotics, or antimeatabolites increased drug concentration in the tear film and prolonged the delivery times (Maichuk, 1967, 1975a,b). Subsequent studies showed that bioavailability, miotic activity in rabbits, and intraocular pressure control in human glaucoma subjects were all enhanced over a 24 hour period with PVA/pilocarpine–polyacrylic acid salt disks of 4 mm diameter and 0.4 mm thickness prepared from cast films (Saettone et al., 1984).

The explosive search for biomaterials culminated in a seminal development in ophthalmology with the commercialization of an ethylene vinyl acetate (EVA) membrane device known as Ocusert® in 1974 (Ness, 1974; Friederich, 1974; Zaffaroni et al., 1979). Engineered to provide uniform controlled rates of pilocarpine delivery (20 or 40 µg/hour rate over 7 days), the Ocusert required two outer layers of rate controlling EVA, and an inner layer of pilocarpine in an alginate gel, the latter rate necessitating the addition of a flux enhancer, di-(ethylhexyl)phthalate. While the device functioned quite effectively in a specific niche of difficult to manage glaucoma patients, it was not universally adopted due to unsatisfactory control of IOP in some patients, difficulty inserting the device, ejection of the device from the eye, irritation or tolerance difficulties, and unenthusiastic acceptance by ophthalmologists who were called upon to devote more time to the training of patients (Pollack et al., 1976; Sihvola and Puustjarvi, 1980; Akerblom et al., 1980).

The eventual failure of Ocusert in the marketplace brought clarity to the field in recognizing that the development of drug delivery systems for ophthalmic use was not simply a matter of in vitro engineering of rates and durations. Both patient and physcian factors were as critical, if not more so, in the successful application of the technologies. For more than 30 years since the introduction of the Ocusert, these factors continue to confound scientists in their quest to develop a second successful topical ocular system which can deliver drug for significantly more than a day. Numerous designs of insert type systems have been proposed since the introduction of Ocusert (Cohen et al., 1979; Miyata et al., 1979; Katz, 1982; Haddad and Loucas, 1983; Darougar and Weiner, 1994; Benjamin, 1999; Darougar, 2001; Hsiue et al., 2001; Sasaki et al., 2003; Pijls et al., 2004; Barbu et al., 2005; Huang...
2. DRUG DELIVERY SYSTEMS IN OPHTHALMIC APPLICATIONS

et al., 2005; Leahy and Labombard, 2005; Pijls et al., 2005; Samanta and Ghosal, 2005) but none has successfully overcome the daunting physiologic or compliance barriers.

The difficulty in developing a topical, long-term release system is a probable reason that more attention has recently been given to the delivery of drugs from other administration sites in the eye. However, key driving factors also include development and acceptance of invasive surgical interventions (i.e. invasion of the vitreous) as well as the eventual introduction of medications for therapy of posterior segment diseases such as macular degeneration and diabetic retinopathy. While the factors of retention and tear flow are avoided, new challenges are presented from deposition of a system in an internal tissue.

B. Defining Drug Delivery Systems and Their Mission

The requirement for a drug delivery system can be invoked for more than one endpoint. The three critical applications of drug delivery in ophthalmology are (1) duration; (2) targeting; and (3) compliance. Within these categories, the following questions clarify the need for consideration of an ophthalmic drug delivery system.

Duration and drug pattern:

- What duration of drug delivery is needed at the receptor for more effective treatment of disease?
- Does continuous drug at the receptor result in efficacy equivalent to pulse dosing?

Targeting:

- What tissue or cellular structure contains the target drug receptor?
- What area of coverage is needed for treatment?
- What concentration is needed for efficacy?

- Does the delivery method result in a therapeutic concentration of drug in the target tissue?
- How long does the therapeutic concentration stay in the target tissue?

Compliance:

- What makes it difficult for the patient to take their medication?
- What difficulty does the physician have in administering the medication to the patient?
- What economic factors inhibit physicians and patients from accepting the dose form?

1. Duration and Drug Pattern

As with all drug delivery systems, the mechanism by which drug is presented to the tissue is of prime importance. For the moment, if we assume drug reaches the appropriate target site when delivered from a designated site of administration, a key focus should be on receptor activation. Knowing the level of in vivo drug needed to initiate a receptor response, as well as how long the response occurs are critical studies which need to be conducted. This information gives us the initial clues essential to determine what type of delivery system might be needed and an understanding of which duration and pattern of drug release are required to maintain an efficacious effect. However, efficacy is not the only consideration as both the pattern of drug release and the duration can dramatically affect toxicological responses. This is illustrated in Figure 2.1. Using standard dosage forms, tissues will be exposed to a pattern of alternating drug concentrations, depending on the dosing interval. This pulse dosing pattern may be quite different from patient to patient depending on individual compliance factors. It is possible to prolong the level of drug seen by the tissue using a “sustained” dose form in which the alternating wave pattern is drawn out over time. Usually, drug delivery scientists set goals of developing “controlled” dose forms, in
which the wave is eliminated, thus removing the potential for brief periods of either toxic levels and/or ineffective levels. While this goal is often appropriate, it should not be assumed that at a given rate a continuous level of drug is maximal for the receptor activity over time. As there can be refractory responses of receptors, either related to induction of receptor synthesis or through a change in receptor activity, pulsed dose regimens are not always a bad thing. Nonetheless, it is within the realm of the scientist to check the hypothesis that continuous delivery produces a continuous response.

A practical approach that can be taken is through the use of experimental devices designed for such investigations, namely constant infusion systems or Alzet® minipumps, which deliver set rates of drug effusion over periods of days to weeks. For example, such pumps have been used to show that 0.01% fluorescein solution infused on the ocular surface of horses at a rate of 0.14 mL/h for 72h resulted in assayed tear film concentrations of approximately 20% of the applied dose (Myrna and Herring, 2006). Kwon et al. (2005) have shown that continuous pumping of artificial tears or 0.1% fluorometholone facilitated recovery in a rabbit chemical burn model. In experiments we have conducted to determine the potential of continuously delivered prostaglandin analogs to continuously depress the intraocular pressure of rabbits, minipumps provided good evidence that an eventual commercial device which can mimic this type of kinetic pattern is a worthwhile goal (Figure 2.2).

2. Targeting

Drug delivery systems have additional utility beyond improvements in duration of drug action. Indeed, another application may include improving the ability of drug to reach a target tissue. Penetration enhancement and tissue selectivity can be goals for the design of delivery systems. This could include facilitation of gene or short interfering RNA (siRNA) transfer into tissue, avoiding general toxicities by virtue of targeted receptor ligand binding (such as antibody or other targeting moieties) and/or passive targeting to areas of vascular leakage (e.g. as practiced through the use of liposome entrapped photodynamic therapy agents). The ability of a system to deliver a drug payload only to the tissue requiring it is usually a tall order, but nonetheless a meaningful objective. The area of tissue coverage that needs to be targeted will vary, depending on the severity of the condition. For example, retinal vein occlusion may occur either locally or centrally, the latter mandating a system that would deliver more general pan-retinal concentration...
than the former. For therapy of glaucomas, potential objectives may be either in IOP response, targeting anterior tissues such as trabecular meshwork or iris–ciliary body, or neuroprotection, targeting posterior tissues such as the lamina cribrosa. Delivery systems would be very different in these instances, depending on the goal.

Understanding something about the receptor location and tissue barriers are important elements to the system design. For instance, conjunctival placement of dose forms is perceived as an easily accessible site and thought to be a logical choice for slow releasing drugs. However, it would be faulty thinking to view it as a universal site since the distribution of drug from that position may not be sufficient to reach a wide range of tissues, particularly posterior ones. Small local devices or depots may provide only local and limited levels to adjacent tissues, but distal regions will typically see minor levels, if any, due to gradient and clearance effects around the device or depot.

3. Compliance

Drug delivery may have extremely important implications in the quality of life for patients. By providing dosing regimens that patients can remember or comply with, overall improvements in the efficacy of the therapy should eventually be realized. Since many ocular disease patients are older, difficulty in the administration or removal of a system are key considerations. In fact, the difficulties that patients experience may drive development of new systems toward physician administered strategies. Table 2.1 illustrates the goals that should be achieved to best improve compliance, whether the system is patient or physician administered. Dosing intervals listed should optimize the probability for compliance.

A variety of factors influence the likelihood that a physician will adopt a new delivery system. A survey asked general ophthalmologists and glaucoma specialists to rate attributes of a drug delivery system that have the greatest influence on the likelihood they will adopt a new delivery system (Table 2.2). Patient safety, compliance, cost and wide applicability are all major factors. While not as high a priority, the business perspective (i.e. reimbursement) also has impact. It is interesting to observe that while compliance is a top consideration for physicians, it is not necessarily the only issue. This was highlighted when the same physicians were polled on their likelihood to adopt an intravitreal delivery system as therapy for glaucoma patients (Table 2.3). A lukewarm or adverse response to this mode of administration was recorded even with the knowledge it would dramatically improve the compliance for the patient. Obviously opinions concerning safety factors played a much bigger role.

The following chapter will deal with the extensive efforts that have been made to address the above questions of duration, targeting and compliance through delivery system development, the progress and understanding achieved to date, and the future direction which may eventually solve some of the most intimidating ophthalmic challenges.

<table>
<thead>
<tr>
<th>Ophthalmic mode of administration</th>
<th>Current state of the art</th>
<th>Objective to improve beyond state of the art</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient administered</td>
<td>From 1–4 times daily</td>
<td>QD or once weekly</td>
</tr>
<tr>
<td>In office administration</td>
<td>Days to weeks</td>
<td>Greater than 3 months</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>Months to years</td>
<td>Months to years, minimally invasive</td>
</tr>
</tbody>
</table>
II. MECHANICS OF DELIVERY SYSTEMS AND THEIR ADMINISTRATION

A. Sites for Delivery System Administration

Currently, commercialized ocular drug delivery systems have been limited to administration by topical and intravitreal routes. However, both clinical and non-clinical studies are ongoing to evaluate systems administered by subconjunctival, sub-Tenon’s capsule, intrascleral, subretinal, and suprachoroidal routes as well as improvements to topical application by using unique fornix devices or punctal placement (Figure 2.3). Systemic delivery using oral tablets is still a viable alternative to ocular administration, although unique delivery systems may not be as essential since it is usually easier for patients to comply with normal oral medication schedules, even if given more than once a day.

TABLE 2.2 A survey of ophthalmologists and glaucoma specialists asked to rate how much the following attributes would impact the likelihood they will adopt a new delivery system for administering glaucoma medication

<table>
<thead>
<tr>
<th>Attributes of a new drug delivery system*</th>
<th>Total (n = 117)</th>
<th>Ophthalmologists (n = 82)</th>
<th>Glaucoma Specialists (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to use in a wide patient population</td>
<td>11.5</td>
<td>11.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Continuous release of medication over time</td>
<td>8.6</td>
<td>8.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Cost to patient</td>
<td>11.1</td>
<td>11.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Covered by patient’s insurance</td>
<td>8.3</td>
<td>8.4</td>
<td>7.8</td>
</tr>
<tr>
<td>Extends dosing frequency of glaucoma medication</td>
<td>7.4</td>
<td>7.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Improves patient compliance</td>
<td>13.4</td>
<td>12.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Low risk of infection</td>
<td>6.9</td>
<td>7.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Patient convenience</td>
<td>8.4</td>
<td>8.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Requires a surgical procedure to implant</td>
<td>3.1</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Safety</td>
<td>11.8</td>
<td>12.7</td>
<td>9.7</td>
</tr>
<tr>
<td>Tolerability/comfort of delivery device</td>
<td>9.0</td>
<td>9.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Other</td>
<td>0.6</td>
<td>0.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Those polled were told to assign a total of 100 points to the list of attributes, giving more points to the attributes considered more important, and less to those considered being less important. If an attribute did not matter, the instruction was to assign it 0 points.

TABLE 2.3 Survey of physicians asked the question “How likely are you to prescribe an intravitreal drug delivery device to your glaucoma patients?”

<table>
<thead>
<tr>
<th>Likelihood to prescribe an intravitreal drug delivery device</th>
<th>Total (n = 117)</th>
<th>Ophthalmologists (n = 82)</th>
<th>Glaucoma specialists (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely unlikely</td>
<td>11.1%</td>
<td>14.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Very unlikely</td>
<td>17.1%</td>
<td>22.0%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Somewhat unlikely</td>
<td>14.5%</td>
<td>15.9%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Neither unlikely nor likely</td>
<td>10.3%</td>
<td>8.5%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Somewhat likely</td>
<td>28.2%</td>
<td>24.4%</td>
<td>37.1%</td>
</tr>
<tr>
<td>Very likely</td>
<td>16.2%</td>
<td>13.4%</td>
<td>22.9%</td>
</tr>
<tr>
<td>Extremely likely</td>
<td>2.6%</td>
<td>1.2%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>
B. Delivery System Design

Delivery systems can be designed as either a reservoir or a matrix (Figure 2.4). Reservoir systems are non-eroding devices that give the best control of drug release rate by virtue of a specific physical rate control feature connected with the internal drug reservoir. This feature can be as simple as an opening in the device, a porous screen or a coating through which the drug diffusion is retarded. It is easiest to achieve a zero order constant rate of drug release using a reservoir system as there is only the one variable of the rate controlling region impacting the drug release. Vitraser® (Bausch & Lomb), Retisert® (Bausch & Lomb) and Ocuser® (Alza) are all reservoir type devices that have...
rate controlling membranes surrounding a central core of drug. To construct non-eroding systems, there are a number of useful compatible biomaterials such as polyimides, polysulfone, polyvinylalcohol, polyvinylidene fluoride, ethylene vinyl acetate, siloxane polymers, and various methacrylate and ethylacrylate polymers. Alternatively, in a matrix system, drug is co-mixed with the rate controlling biomaterial. A matrix device can be made to produce a zero order drug release rate, for example, if the biomaterial is non-eroding. Release is then governed by the dissolution rate of the drug. However, in such a device, the drug concentration must be high enough such that, when it dissolves away from the matrix, it leaves enough of a fenestrated channel in the device for aqueous diffusion to reach internally located drug particles. In this non-eroding system, the strength or integrity of the device could be compromised as diffused drug leaves behind a series of interconnected voids through the device. If the biomaterial in the matrix device is erodible then the device will exhibit more complex kinetics of drug release due to the erosion factor of the biomaterial which can contribute independently of the drug dissolution and diffusion. Further, the biomaterials can erode, either by a bulk mechanism (i.e. small chunks of polymer breaking off) or through a surface mechanism (i.e. smooth and even erosion). Poly-lactide, poly-glycolide, and polycaprolactone polymers are the most common materials employed and will degrade by bulk erosion. Known best for their use in bioabsorbable sutures, these polymers can be engineered to provide a range of delivery durations up to months, depending on the co-polymer ratios. Surface eroding polymers include certain polyanhydrides and polyorthoesters which have either been commercialized or studied in human disease applications.

Generally, for ocular delivery, the selection of a particular system depends upon the length of time it is anticipated that the disease site needs to be treated. If the duration of treatment is days, weeks or a few months, it is probably best to use a bioerodible device which can provide therapy for intermediate durations, and can be made to disappear prior to the subsequent dose. On the other hand, if the duration of disease site treatment is anticipated to be for a year or greater, a non-eroding device may be the only way to deliver the high drug-loading dose needed to provide continuous and uniform drug release for multi-year delivery.

But it is not always a simple matter to actually create a minimally invasive solid system if the delivery period is long and the potency of the drug is low. To illustrate this point let’s assume we are interested in delivering a drug whose optimum efficacy is established at a 1 mg/day rate and where we would like to deliver it for 6 months or 180 days. The requirement therefore would be a total of 180 mg drug. Yet this is not the final weight of the total drug delivery system. Indeed for most delivery systems, the maximum loading of drug is typically in the 40–50% range, whereby the remainder is made up of materials needed to form the delivery system itself (i.e. polymers or excipients). In this example, if we say that 40% is our maximum drug load, the remaining 60% of the system, or 270 mg, is made up of the polymers or excipients. In total, therefore, the weight of the delivery system is 450 mg (i.e. 180 mg drug +270 mg polymer). Now let’s assume our interest is to administer the device through a 21 gauge needle, which is probably larger than optimum, but reasonable for this exercise. A 21 gauge needle is 0.8 mm in diameter. Through geometric, density and physical calculations we’ve determined roughly that a 0.8 mm diameter will yield approximately 4 millimeters length for every milligram of polymer/drug system delivered. A simple computation therefore shows us that 450 mg multiplied by 4 mm/mg is equal to 180 cm, or in other words a 6 ft long device! It is not hard to conclude that it is critical to have drugs with potencies in the µg/day range,
preferably even less per day, to accommodate the spaces we have in the eye.

Additional aspects of ophthalmic drug delivery systems have been presented in previous review articles (Weiner, 1994; Kumar, 2000; Chowhan et al., 2002; Edlund and Albertsson, 2002; Divvuri et al., 2003; Davis et al., 2004; Yasukawa et al., 2005; Hughes et al., 2005; Heller, 2005; Ludwig, 2005; Sultana et al., 2006a; Ghate and Edelhauser, 2006).

III. DELIVERY SYSTEMS FOR OCULAR DISEASE

A. Oral and Parenteral Dose Forms

Oral administration is generally the patient’s most-preferred route, given the simplicity. However, it may not be the first choice of ophthalmic drug companies, as oral delivery of drugs exposes the entire body to potential serious adverse effects, particularly germane when considering therapy options for a non-life threatening ocular disease. A further impediment to developing a parenteral dose form is the consideration of the blood–retinal barrier, and that it may be necessary to increase the oral dose substantially in order to achieve efficacy. This is also true for drugs that undergo a substantial first pass effect, and thus the need for higher concentrations could result in higher toxic metabolites which may limit further development. Nonetheless, for certain chronically administered drugs, such as those being developed as neuroprotectives, or those intended to treat chronic conditions where vision may still be good (such as dry AMD and retinopathies), the use of an oral system makes sense. Such is the case for ongoing studies on memantine (Hare et al., 2004).

Systemic parenteral administration of drugs can overcome the problem of the first pass effect; however, the distribution of the drug still exposes the entire body to potential serious adverse effects and, like oral drug delivery, may necessitate high doses to penetrate the blood–retinal barrier. A significant barrier to development is that repetitive parenteral administration is inconvenient and expensive for patients and may lead to non-compliance. Because of the pulsed nature of parenteral administration each injection may briefly expose the tissue to potentially toxic levels of drug, and later before the next injection, to ineffective concentrations. The problems associated with pulsed dosing may be mitigated with drug delivery devices such as dermal patches, subdermal devices, or by use of bioabsorbable implants. While there are currently no such products in development, it remains a future option pending discovery of efficacious drugs.

B. Topical Delivery Systems

Typically after instillation of an eye drop, less than 5% of the applied drug penetrates the cornea and reaches intraocular tissues. The major fraction of the instilled dose is usually absorbed systemically via the naso-lacrimal duct or through the conjunctiva. For certain anterior applications, this may be enough to initiate a response, as exemplified by the choice of intraocular pressure lowering medications currently available. However, to reach the posterior segment, the intraocular levels achieved are often below minimal effective concentrations. In either case, attempts to improve the delivery from a topical route continue.

1. Anterior Objective

Aqueous gel forming ingredients, being predominantly comprised of water, are very porous to movement of solutes and thus would not be expected to dramatically increase the duration of drug delivery. Nonetheless, while dramatic duration increases have not been a hallmark of gel formulations, such products have offered some of the best potential to improve residence time on the ocular surface during
the day and/or to enhance anterior drug levels. Historically, polyacrylic polymers (carbomers) formulated to a gel consistency have been commercially used to reduce frequency of instillation as was originally developed for Pilopine HS® Ophthalmic Gel. Carbomer-based formulations continue to be advanced, such as those utilizing the DuraSite® vehicle (InSite Vision) which has been developed with several drug compounds, the latest being azithromycin, the active agent in AzaSite™ (Abelson et al., 2006). Other valuable gel forming materials have since been identified, particularly for delivery of timolol maleate. Two extended duration timolol maleate products, one containing gellan as a gel forming ingredient (Timoptic XE®) (Mazuel and Friteyre, 1989) and the other with xanthan (Timolol Maleate Ophthalmic Gel Forming Solution) (Bawa et al., 2001) have been approved for commercial use. Gellan gum has also shown utility for enhancing carbonic anhydrase release as well as fluoroquinolone antibiotics (Sultana et al., 2006b; Balasubramaniam and Pandit, 2003), carteolol (El-Kamel et al., 2006) and indomethacin (Balasubramaniam et al., 2003).

One of the most familiar commercial ophthalmic gel materials is hyaluronate. Since hyaluronate requires refrigeration to protect it from loss of viscosity, it has not been an immediate choice for developing topical drug formulations. Nonetheless, research has shown some utility of this material to improve delivery rates of drugs (Liao et al., 2005). In one report 5-FU release was compared from Healon®, Healon 5® and Healon GV® OVD gels (Wong et al., 2006). Over the course of 2–3 hours, release rates were higher with the H-GV and H-5 formulations compared to Healon alone. Delivery was first order as expected, showing higher initial rates prior to leveling off. Rates ranged from 2 to 100 µL/minute depending on the in vitro flow method used to analyze the drug (i.e. either 50 or 200 µL flow chambers). Dexamethasone release kinetics (either 4 mg/mL or 20 mg/mL) has been studied using Healon or Healon 5 (Spitzer et al., 2006). No more than 2 days of delivery were observed, but it was shown that at levels of about 1 mM, proliferation (BrdU incorporation) in ARPE19 and human tenon fibroblast cells was inhibited. In an attempt to circumvent the commercial issue of viscosity loss at room temperature, some are working on developing an applicator containing a small aliquot of lyophilized hyaluronate (Suverkrup et al., 2006).

Poloxamers are often used to form gels, particularly Pluronic® solutions (Wei et al., 2002; Lin and Sung, 2003; Xia, 2004). It has been found that 0.1% concentrations of fluorescein isothiocyanate (FITC)-labeled dextran formulated into 25% solutions of poloxamer 407 (BASF, Germany) will release the marker from the gel over a 6 hour period (Vehanen et al., 2006). When injected via parabulbar administration in rats, fluorescence disappeared between 12 and 24 hours following injection. Other studies have looked at release of growth factors (Kim et al., 2002a) and of ciprofloxacin (Yoo et al., 2005). While topical application of poloxamers may have an appropriate safety window to allow their use, in contrast when injected intravitreally, Pluronic concentrations ranging from 20 to 30% caused serious reduction or elimination of the electroretinogram (ERG) signals after 8 days with inflammatory infiltrate on the hyaloid as well as cataract and some IOP increase (Su et al., 2006).

In situ gelling can also be produced using alginate which undergoes a transition in the presence of divalent cations. Pre-corneal retention of gatifloxacin from alginate/hydroxypropylmethylcellulose (HPMC) gels has been shown to be enhanced compared to the solutions of alginate or HPMC alone (Liu et al., 2006a). Similar results were found using an alginate/Pluronic gel for enhancing pilocarpine delivery (Lin et al., 2004). Carageenan, another polysaccharide derived from algae, has also been employed similarly (Bonferoni et al., 2004).
There is a large body of work on using collagen to extend delivery of drugs, particularly as delivered from early commercial collagen “shields” such as the Bio-Cor (Bausch & Lomb, Clearwater, FL), Medilens (Chiron IntraOptics, Irvine, CA) and Soft Shield (Oasis, Glendora, CA). These shields naturally dissolve over a 12 to 72 hour period depending on the amount of cross-linkage. In a majority of investigations, preexisting shields were impregnated with agent over various periods of time (Friedberg et al., 1991). Diffusion into and out of the shield does not typically surpass 2–3 hours. Yet a wealth of studies have looked at diffusion from collagen for anti-infectives such as gatifloxacin and moxifloxacin (Kleinmann et al., 2006, 2005; Hariprasad et al., 2005), gentamicin (Silbiger and Stern, 1992; Bloomfield et al., 1978; Baziuk et al., 1992), tobramycin (Assil et al., 1992; Poland and Kaufman, 1988; Unterman et al., 1990), amphotericin B (Pleyer et al., 1992), penicillin and erythromycin (Punch et al., 1987), anti-inflammatories like dexamethasone (Hwang et al., 1989; Aquavella et al., 1988) and prednisolone (Sawusch et al., 1989), antimetabolites such as 5-fluorouracil and trifluorothymidine (Finkelstein et al., 1991; Gussler et al., 1990), glaucoma agents like pilocarpine (Sun et al., 1996; Aquavella et al., 1988) or metipranolol (Kaufman, 1989), tissue plasminogen activator (Murray et al., 1992) and cyclosporin (Reidy et al., 1990). Efforts continue to engineer collagen to release drug for longer periods of time. For example, a recent report (DeVore et al., 2006) has demonstrated some potential to improve drug release using a soluble collagen that gels in situ within 2 minutes and releases sufficient tracer to detect trans-scleral residence over a 22 hour period with residuals up to 56 days. The addition of nanoparticles to collagen also has potential to extend the delivery time (Weiner et al., 1985; Said et al., 2001).

Chitosan, a linear polysaccharide derived from the deacetylation of chitin extracted from insect or crustacean exoskeletons, is a more recent subject of investigation. Because of its strong positive charge in neutral pH ranges, it has shown good mucoadhesive properties for topical ophthalmic use (Alonso and Sanchez, 2003). Using formulations that combined chitosan and hydroxypropyl-beta-cyclodextrin (HPBCD), improvement in IOP lowering was achieved in Dutch Belted rabbits when incorporating either ethacrynic acid or a compound termed SA 9000 in these formulations (Arnold et al., 2006). IOP lowering improved from 8 to 24% when the ethacrynic acid was complexed with the HPBCD and mixed into 5% chitosan. The SA 9000 overall was less effective than ethacrynic acid, but was enhanced by the HPBCD/chitosan formulation (15% IOP lowering). In another study, increases in subconjunctival tissue levels of fluorescent tracer were observed when delivered from a topical chitosan emulsion (Yamaguchi et al., 2006). Chitosan has also been formed into hydrogels as a hybrid polymer with N-isopropylacrylamide or 2-hydroxyethyl methacrylate (Verestiuc et al., 2006).

There is greater recent attention to development of unique packaging to deliver microdroplets to the surface of the eye, either as a way of improving compliance by the patient or for claims of improving the total drug delivered posteriorly. A horizontal spray-type device is being developed as a means to improve compliance in delivering Xalatan vehicle (Rotberg et al., 2006). In an open label crossover study of 90 patients, dosing with the conventional Xalatan bottle was compared to the spray device and physicians qualitatively assessed the ability of patients to get the dose to the eye in four successive doses spaced at 30 minute intervals. Higher frequency of successful dosing with the spray device was reported at each of the intervals with statistical significance. Diestelhorst et al. (2006) have reported on a misting device that was adapted from the Respimat® Soft Mist™ inhaler technology. The device is held horizontally and it contains a funnel that fits on the eye and has
a cartridge which is activated by digitally depressing a button. Using a Fluorotron™, deposition of a mist (<5 micron droplets) of fluorescein was evaluated and compared to standard drops in 20 patients over a 4 hour period. While the actual dose of the fluorescein from the spray was approximately 2.7-fold less than the standard drop, when corrected for the disparity of the dosing concentration, data indicated moderate enhancement in cornea and anterior chamber fluorescence. Other designs involving ophthalmic spray or nebulizer devices have been reported (Carlsson and Hedman, 2003; Kahn, 2005).

While it was previously discussed that contact lenses have been known for some time to release drugs for only short periods of time, more advanced developments have renewed the interest in this approach as a possible commercial method to improve duration of drug release. By the incorporation of nanoparticles within the lens materials, longer durations of release can be achieved, possibly as long as 1–2 weeks without significantly affecting refractive properties (Gulsen and Chauhan, 2004, 2005a,b). While this type of approach offers potential hope in the future for a workable system, it should not be assumed that drug release will be the same from every diopter or type of lens. Changes in thickness, surface area, charge or density of the lens will impact the drug delivery rate from it. Change in polymer hydrophobicity or hydration will also dramatically impact delivery rate. Significant differences, for example, might be expected between polyhydroxyethylmethacrylate (PHEMA) and polymethylmethacrylate (PMMA) lenses.

The punctum has also been considered as a potential site for the delivery of agents to the tear film (Cohan and Diamond, 2001; Prescott, 2006; Odrich, 2005). As with fornix-based systems, inserts within the punctum are known to be extruded and lost, and long-term compliance for all patients may be difficult to achieve without proper sizing prior to therapy. Such inserts also have only a small volume in which drug can be incorporated and may be limited in the type of drugs which can be integrated.

2. Posterior Objective

Efforts to enhance penetration to the back of the eye from anterior application have been accomplished either using unique drug design, permeation enhancing formulations or longer residence topical formulations (Kaur and Smitha, 2002; Kaur and Kanwar, 2003; Koevary, 2003). Studies have demonstrated that there is potential for many drugs to reach the posterior tissues from topical application, but the disease state itself may influence the actual level established (Maurice, 2002; Mallick et al., 1984). Certainly, there are many glaucoma agents that were designed to penetrate the cornea in sufficient concentration and reach anterior chamber tissues to effect intraocular pressure control. In some of them the potential for “neuroprotective” effect has also been suggested based on measured vitreous or retinal levels (Hollo et al., 2006; Whitson et al., 2002; Dickinson et al., 2002; Acheampong et al., 2002; Mizuno et al., 2001). In the future, promising pro-drugs may have greater penetration to the back of the eye by virtue of their engineered design (Lee and Li, 1989; Duvvuri et al., 2003). Use of “soft” drugs has been known for some time to facilitate penetration without increasing systemic levels of the active drug. In this approach, compounds are chemically engineered as pro-drugs which are activated after transport and have lesser capacity to be systemically absorbed. Another recent pro-drug is nepafenac, which has shown potential for effecting therapy of posterior neovascularization from topical administration (Kern et al., 2005; Takahashi et al., 2003).

Of the excipients promoted for their potential ability to increase permeability of topical drugs, cyclodextrin is promising (Kaur, 2004). Significant improvement in dexamethasone penetration was observed when formulated with cyclodextrins and
applied topically. Aqueous humor levels increased about 28-fold from controls when cyclodextrin was used to complex the dexamethasone. Levels in the retina more than doubled (Kim et al., 2002a; Loftsson and Stefansson, 2002). Other studies have looked to cyclodextrin complexes to enhance disulfiram or diethyldithiocarbamate penetration for prevention of cataract (Wang et al., 2004a,b).

Nanoparticles are often mentioned for their potential to improve tissue penetration (Patravale et al., 2004). Many types of particle compositions have been employed with ophthalmic drugs to improve efficiency of topical delivery (Rabinovich-Guillatt et al., 2004). Materials reported on include, but are not limited to, polycaprolactone-based systems (Barbault-Foucher et al., 2002; Crawford et al., 2005), cationic polyethyleneimine (Liu et al., 2006b), neutral polyethylene glycol-lysine peptide (Naash, 2006), niosomes (Mainardes et al., 2005; Guinedi et al., 2005), polycrystalline-based formulations (De et al., 2001, 2003), chitosan and polyphosphoesters (Prow et al., 2006; deCampos et al., 2004), hyaluronate (Diebold et al., 2006), cationic PEGylated lipids and amino acids (Sugisaki et al., 2005; Tang et al., 2006), Epuraqit (Pignatello et al., 2002), dendrimers using glucosamine 6-sulfate (Shaunak, 2006), or poly(amoideamine) (Vandamme and Broeck, 2005), polylactic-glycolic acid (PLGA) (Giannavola et al., 2003), and inorganics like quantum dots (Jayagopal et al., 2006), iron oxide (Calzi et al., 2006), and nanogold (Bakri et al., 2006). Most reports show at least 1.5- to 2-fold improvements in tissue penetration using the nanosystems.

There are a wide range of other excipients which have been reported and may function as penetration enhancers, such as azone (Chen, 2003); however, chronic safety for these needs to be established.

It is possible to facilitate the movement of molecules from the anterior to the posterior segment of the eye by means of physical augmentation using iontophoresis. Several designs have been reported (Eljarrat-Binstock and Domb, 2006; Parkinson et al., 2004; Myles et al., 2005; Halal et al., 2004). In one style, a small flexible topical device (shaped to the outer eye like a contact lens) is inserted in the cul-de-sac and emits a low current, which drives ionic drugs from the front of the eye to the back. A second design comprises an eyepiece through which drug is infused from a syringe reservoir. Reports have examined the ability of iontophoresis to facilitate ocular delivery of acetylsalicylic acid (Kralinger et al., 2003), gentamicin (Eljarrat-Binstock et al., 2004; Frucht et al., 2004), dexamethasone (Szle et al., 2002), combretastatin A4 (Vollmer et al., 2002a), diclofenac (Fischer et al., 2002), amikacin (Vollmer et al., 2002b), methylprednisolone (Behar-Cohen et al., 2002), DNA and dyes (Nickerson et al., 2003), carboplatin (Voigt et al., 2001), and ganciclovir (Chapon et al., 1999). Depending on current intensity and duration of exposure to the current, the effects have been variable. Improvements in penetration are reported to range anywhere from 10 to 50%. Consistent reproducible drug delivery at a safe current level is not always possible. Additionally, many drugs, which are uncharged or have a high molecular weight (e.g. >8000 daltons), will resist moving with the applied current. In the case of small solubilized molecules, the vitreal turnover will be short (i.e. a day or two) and thus iontophoresis would likely need to be applied frequently in order to maintain an effective concentration at the target tissue. Iontophoretic kits designed for patient use are not yet available and frequent visits to the doctor for iontophoresis therapy may lead to poor patient compliance due to cost and inconvenience. Improvements in iontophoresis have been attempted by better formulations and solutions used in conjunction with the devices. However, the techniques are infrequently compared to controls with other less complex technologies and still the methods have not yet solved key issues such as patient friendliness and frequency of application.
Another physical approach which is undergoing investigation is ultrasound. Ultrasound devices have been constructed to examine enhancement in drug penetration through the eye. Improvements in corneal permeability of several glaucoma agents were reported by using 1 second bursts of 20kHz ultrasound (Zderic et al., 2002).

C. Subconjunctival Delivery

It has been determined that both anterior and vitreous levels of drugs can be established from subconjunctival injection (Lee and Li, 1989; Hosoya et al., 2005) making it a common route of administration for anti-infective compounds (Kayarkar and Dinakaran, 2001; Colleaux and Hamilton, 2000). Anterior sites may be easily accessed by this route. For example, subconjunctival administration of vascular endothelial growth factor (VEGF) trap has been shown to suppress adjacent corneal vascularization (Cao et al., 2004). The uveoscleral outflow pathway may serve as the mode by which retinal and uveal tissue levels have been established following subconjunctival placement of fluorescence-labeled dextran (Kim et al., 2002a). However, the subconjunctival route may only provide a limited capability for delivering sufficient level of drugs from implanted devices. In studies in rats, Kim et al. (2002b) measured tissue levels of fluorescence tracer that had been incorporated into subconjunctival implants constructed of polyvinyl alcohol, hydroxypropylcellulose, or silicone. Only implants with the highest rate of release imparted measurable levels in the choroid and subretinal space. In an attempt to quantitate the movement of implanted compounds from the subconjunctival space dynamic three-dimensional magnetic resonance imaging has been used to trace gadolinium-diethylenetriaminopentaacetic acid (DTPA) distribution from subconjunctival polymer implants (Kim et al., 2004). Unfortunately, only a small fraction of the total dose (0.12%) was detectable in the vitreous with no levels seen in other posterior segment tissues. In support of this data, it was also found that non-degrading nano- and micro-particles containing fluorescence marker were not able to sustain a detectable level in the posterior tissues following subconjunctival administration (Amrite et al., 2003). Nonetheless, a number of animal efficacy models have shown that subconjunctival implants might still provide sufficient levels of drugs to be of value. Using a silicone-based cyclosporin episcleral matrix, implant delivery of drug was effective in a canine model of keratoconjunctivitis sicca over a 6 month follow-up period (Kim et al., 2005). Cytochalasin or 2-methoxyestradiol implants given by subconjunctival administration inhibited choroidal neovascularization (CNV) better in a VEGF induced model in rats than sham implants (Kim et al., 2003; Robinson et al., 2003). Antimetabolites such as 5-fluorouracil (Wang et al., 1996; Einmahl et al., 2001; Bernatchez et al., 1994), or daunorubicin (Rabowsky et al., 1996) have been incorporated into bioerodible implants made from polylactide-co-glycolide or polyorthoester materials as a means to better maintain surgically created blebs (Berdugo-Polak et al., 2005). Similarly, cyclosporin A implants placed in the subconjunctival space can effect prolongation of corneal allografts (Xie et al., 2001; Apel et al., 1995).

It may be possible to take advantage of the subconjunctival space to deliver posterior drug levels by using slowly dissolving drugs alone or in combination with semisolid mediums. For example, retinal levels of Celecoxib have been detected following a subconjunctival suspension depot suggesting its potential use in therapy of posterior vascular leakage (Ayalasomayajula and Kompella, 2003, 2004). Carboplatin has also been incorporated into a fibrin sealant, which prolonged delivery of the drug and upon injection was efficacious in treating retinoblastoma in transgenic mice (Van Quill et al., 2005; Pardue et al., 2004). Kompella and colleagues (Amrite et al., 2006) used...
isolated sclera in a diffusion chamber to study whether a larger molecule, lens epithelium-derived growth factor (LEDGF), reaches the retina from subconjunctival administration. Fluorescent tagged protein and mass spectroscopy were used to quantitate levels. Amounts were detected in retinal pigment epithelium, outer and inner nuclear layers and ganglion cell layer, indicating transscleral movement of the protein. Polylactic acid (PLA) microspheres of budesonide, a steroid to reduce VEGF expression, were given by subconjunctival route (Escobar et al., 2006). The formulation did not elevate IOP when given by this route.

D. Lens-Based Systems

The lens is not as often considered a prime site for drug delivery systems. Certainly any drug induced interference in refractive properties of the lens optic would not be tolerated. Still there have been some efforts to design various intraocular lenses with embedded drugs. The concepts for incorporation of drugs into hydrophilic polymers for implantation into the lens capsule have been disclosed (Aiache et al., 2004). Siqueira et al. (2005) have incorporated dexamethasone into a PMMA intraocular lens (IOL) which contained a biodegradable dexamethasone drug release system. The lens was implanted into the posterior chamber of rabbits and levels of drug were detectable in both aqueous and vitreous humor. The effect of drug incorporation into hydrophilic acrylic intraocular lenses on adherence of lens epithelial cells was studied (Matsushima et al., 2005). Lenses impregnated with either diclofenac, tranilast, mitomycin C, colchicine, 5-fluorouracil, or ethylene diamine tetraacetic acid (EDTA) exhibited less epithelial cell adhesion.

E. Sub-Tenon’s Capsule Administration

The sub-Tenon’s space extends posteriorly from the subconjunctival region and will exhibit similar characteristics. Like studies on subconjunctival dosing, the administration of antibiotics by the sub-Tenon’s capsule approach has also been known for some time (Christy and Lall, 1986; Golden, 1971). However, the real potential for transscleral posterior delivery of drugs has come to light only recently. An advantage of this route is that the vitreous is not penetrated, so adverse effects such as retinal detachment and endophthalmitis are far less likely to occur when compared to an intravitreal injection. The sub-Tenon’s capsule route has been used to deliver anesthetics (LaMarnierre et al., 2002; Farmery et al., 2003; Mathew et al., 2003), corticosteroids (Helm and Holland, 1995; Verma et al., 2004; Venkatesh et al., 2004; Cardillo et al., 2005), anti-angiogenics (Slakter et al., 2003; Smith et al., 2003; Cheng et al., 2001; Jockovich et al., 2005), anti-cancer agents (Lim et al., 1998; Velez et al., 2002; Mulvihill et al., 2003) and botulinum toxin (Kao and Chao, 2003). For drug suspensions like anecortave acetate, injections by this route have been demonstrated to have duration of up to 6 months in monkeys and man (Slakter et al., 2003). It should be noted that it has not yet been demonstrated that posterior juxtatarscleral injections can deliver an effective pan-retinal dose of drug. Therefore, such injections might be restricted to local treatment of lesions. Drug distribution may be dependent on a number of factors including solubility and scleral thickness. It has been shown in an isolated tissue model that elevated pressures can affect scleral permeability although this is not related to significant changes in scleral thickness or hydration (Lee et al., 2004; Geroski et al., 2006). Using fluorescein movement from a posterior sub-Tenon’s capsule injection, it has been determined that increasing the volume while maintaining the same amount of drug results in larger peak areas in choroid/retina and slightly longer duration (Kao et al., 2005). Intravitreal administration of a 100 µL volume of 12% octreotide resulted in retina and choroid levels in the 30 µg/g range, while sub-Tenon’s capsule administration
produced retinal levels only in the range of 1µg/g after 8 days (Margaron et al., 2006). Total concentrations leveled off between 60 and 90 days.

Because of the potential for fibrous encapsulation and inflammatory reactions to device materials, not all fabricated systems may be appropriate for sub-Tenon’s capsule implantation. Fernandez et al. (2002) have examined a series of biomaterials implanted in the space under the Tenon’s capsule between the extraocular muscles Biomaterials which were tested included hydrophobic polydimethylsilane (PDMS; Baerveldt, AMO), expanded polytetrafluoroethylene (ePTFE; Mitex), hydrophilic polyhydroxyethylmethacrylate-methylmethacrylate (pHEMA-MMA 26 and 34; Corneal SA), and hydrophobic polyethyleneacrylate-polyethyl methacrylate (PEA-PEMA; Acry-soft, Alcon). Interestingly, the study showed that the hydrophilic materials had the least tendency for inflammation and fibrosis. Correspondingly, it is well known that silicone devices such as scleral buckles will become fully encapsulated when placed in this space.

A pioneer system for delivery of drug via the posterior transscleral approach using a unidirectional silicone-based juxtascleral device was reported by Yaacobi and co-workers (Yaacobi 2002a,b, 2003, 2006; Yaacobi et al., 2003). This device is loaded with a solid dose of anecortave acetate which has been shown in rabbits to deliver drug to the macula for 2 years or longer. The device was fashioned to follow along the lateral border of the superior rectus muscle while positioning a drug reservoir directly above the macula (Olson et al., 2003). Concentrations of the active metabolite of anecortave acetate were observed in both choroid and retina of the rabbit above the 0.1µM efficacy level over the 2 years observed.

A series of similar devices has been described in which cyclosporin A and 2-methoxyestradiol drug cores are enclosed in various laminate-type holder devices which impart semi-permeable membranes (Robinson et al., 2003). In vitro drug release over months was demonstrated.

A non-eroding episcleral implant has also been used to study transport of bevacizumab to the posterior pole (Kato et al., 2004). Zero order release of drug was reported over the 4 week observation period.

A refillable transscleral sub-Tenon’s capsule device has been described for delivery of iohexol and carboplatin (Krause et al., 2005). The device was also studied for delivery of sodium fluorescein in ethylene vinyl acetate copolymers (deCarvalho et al., 2006). Levels of the fluorescein were detectable out to 6 months.

In a proliferative vitreoretinopathy (PVR) model in which 75% of animals develop tractional retinal detachments, the sub-Tenon’s capsule implantation of an ethylene vinyl acetate copolymer loaded with 10% 5-fluorouracil was able to completely prevent the detachments (Gaynon, 2005).

Eroding microspheres of PLGA (50/50) have been used to deliver anti-VEGF aptamer via the transscleral route. Inhibition of VEGF induced blood–retinal barrier breakdown was observed after two weeks (Carrasquillo et al., 2003).

Pulsatile release systems are not as often studied. But as described earlier, depending on disease state, efficacy may be optimized by this type of intermittent dosing. In one report transscleral pulsatile delivery of FITC conjugated IgG was examined using a polypropylene device attached to the bare scleral surface of rabbits (Rigas et al., 2002). Choroidal and retinal levels were measured for 120 hours. The peak was determined to be at 24 hours with greatest lateral diffusion at 48 hours and residual levels out to 5 days.

F. Suprachoroidal Delivery

Investigation of the suprachoroidal space as a sustained depot administration site is relatively new. Techniques reported are still early and longer-term effects are
not yet known. In one approach a micro-cannulation method can be used to access the suprachoroidal space (Olsen et al., 2006). Full incision was made through the sclera exposing the posterior surface of the choroid. A 175 micron cannula containing a fiber optic is led along the border of the choroid. Using wide-field fundus imaging, the location of the cannula tip was visualized. Triamcinolone (TA) suspension was infused through the cannula. Tissue levels in choroid and retina were measured for 120 days after a high dosage of TA (3 mg). Blood levels were observed up to 14 days with low dosage (0.75 mg) and 40 days at higher dosages (3 mg). A long-term cyclosporin A (CsA) implant has also been studied in the suprachoroidal space in horses (Gilger et al., 2006). Data through 3 months suggested that the CsA delivery should continue for up to 3 years at the current rate with levels in retina and choroid around 0.1 µg/mg tissue. Drug levels in the opposite quadrant from the device were not reported.

G. Intravitreal Administration

Intravitreal administration is the most common approach used to deliver posterior levels of drugs in humans. Drugs introduced by this route include anti-infectives (Hanscom, 2004), tissue plasminogen activator (Ghazi et al., 2003; Sharma and D’Amico, 2004), pegaptanib (Eyetech study group, 2002, 2003; Gragoudas, 2004; D’Amico and Bird, 2004), ranibizumab (Heier, 2004; Chang et al., 2004), P2Y2 receptor agonist (Tornambe et al., 2003), adenoviral vector for pigment epithelium derived factor (Rasmussen et al., 2001; Campochiaro et al., 2004) and triamcinolone (Klais and Spaide, 2004; Andrade et al., 2004; Jonas, 2004a,b; Gillies et al., 2004; Massin et al., 2004). Depending upon whether the dosage form is a solution or suspension and of higher molecular weight, intravitreal injections can deliver drug to the retina for periods up to 6 weeks. To date, many of the developed products require pulse-dosed multiple injections throughout the year, and thus the disadvantages include high cost, non-compliance, and potential for side effects such as endophthalmitis, hemorrhage and retinal detachment. Suspended drug particles could also end up in the visual field.

An important objective for intravitreal delivery is a minimally invasive intrusion through the pars plana to reduce trauma and risk of endophthalmitis. Self-sealing injection through 25 gauge needle or smaller is desired if possible. A wide array of drug delivery systems which meet this criterion are possible and would encompass bioabsorbable threads, micro- and nano-particles and thin non-eroding systems which contain a potent drug. PLGA microspheres are most frequently examined for their potential to deliver drugs in the vitreous. Release kinetics of PLGA microsphere formulations containing 10–15% concentrations of pegaptanib have been reported (Cook et al., 2006). PLGA microspheres were also used to deliver small pigment epithelium-derived factor (Pedf) peptides to protect the ganglion cells from ischemic IOP induced injury (Li et al., 2006). Cell survival in the controls was at 32% while Pedf peptide fragments ranged from 52 to 60.3%. Triamcinolone microspheres injected by the intravitreal route delivered levels of 25 µg/mL over a 4 month period (Cardillo et al., 2006). Particle size was in the range of 1 micron. In comparison free triamcinolone lasted for about 1 month. In this report injections were well tolerated in 10 patients in Brazil. A formulation study examined the duration of release of ganciclovir (GCV) from PLGA microspheres blended at different polymer ratios and containing resomer 502H (Janoria et al., 2006). Varying in vitro durations were achieved from 10 to 70 days. In rabbits, intravitreal GCV levels were monitored for 14 days. Continuous levels at 1 µg/mL were achieved compared to in vitro corresponding levels of 4.85 µg/day.

Another method of prolonging vitreal levels of drugs is with engineered
insolubility. Freeman and colleagues (Tammewar et al., 2006; Falkenstein et al., 2006) have been investigating more insoluble longer acting crystalline derivatives of drugs to improve dissolution time in the vitreous. In particular, they have developed lipophilic prodrugs (hexadecyloxypropyl derivatives) of cidofovir for therapy of CMV or cyclic peptide derivatives such as A36 (Angstrom Pharma) being investigated as an antagonist of the ocular urokinase receptor involved in VEGF upregulation. Delivery periods using these more insoluble forms have been extended out to 3–4 months.

As a result of experience gained from Vitrasert® implantation (Sanborn et al., 1992; Martin et al., 1997) and its next generation cousin, the Retisert™ (Driot et al., 2004; Mruthyunjaya et al., 2003), the intravitreal route is now considered more acceptable for implantation of solid drug delivery systems. Table 2.4 illustrates the current intravitreal devices which have either been commercialized or advanced into clinical trials. As shown, both reservoir and matrix devices have been developed. One unresolved concern with these systems is the need for anchoring the device to the sclera. Until definitive long-term studies are conducted, anxiety over the “sneaker in the dryer” effect of not tethering a system will exist. In non-anchored systems there is potential for adjacent tissue damage as patients alter their diurnal orientation. This is particularly relevant in patients with syneresis or where vitrectomy has been performed. Eventual published safety studies on systems which have not been tethered, such as the Posurdex® (Kuppermann et al., 2003) or Medidur™, will provide the needed guidance for development of future systems.

Three year data from the Phase III trials has been presented on the Retisert device for uveitis and diabetic macular edema (DME) indications and up to 1 year for the branch and central retinal vein occlusion trials (Jaffee et al., 2006; Pearson et al., 2006). For the uveitis trials the overall improvement in visual acuity (>3 lines = 22%) were not as good as reported in the 2 year results, suggesting replacement between 2 and 3 years. Recurrence rate increased from 11% at 2 years to 33% at 3 years. Almost all patients developed cataract with 43% having high enough IOP to require filtering procedures. For the DME trial the 0.59 mg device resulted in 58% of patients without edema compared to 30% in the standard of care group. Retinal thickness improvement was seen in 45% for the device vs 24% for the standard of care cohort. There was >3 lines improvement in 28% vs 15%.

### TABLE 2.4 Status of intravitreal drug delivery devices

<table>
<thead>
<tr>
<th>System</th>
<th>Company</th>
<th>System type</th>
<th>Drug</th>
<th>Drug duration</th>
<th>Indication</th>
<th>Status in 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitrasert®</td>
<td>B&amp;L</td>
<td>Non-eroding</td>
<td>Ganciclovir</td>
<td>5–8 months</td>
<td>CMV retinitis</td>
<td>Marketed/withdrawn</td>
</tr>
<tr>
<td>Retisert®</td>
<td>B&amp;L</td>
<td>Non-eroding</td>
<td>Fluocinolone Acetamide</td>
<td>2–3 years</td>
<td>Uveitis</td>
<td>Marketed</td>
</tr>
<tr>
<td>Medidur™</td>
<td>Alimera/pSivida</td>
<td>Non-eroding</td>
<td>Fluocinolone Acetamide</td>
<td>1.5–3 years</td>
<td>DME</td>
<td>Ph III</td>
</tr>
<tr>
<td></td>
<td>Allergan</td>
<td>reservoir matrix</td>
<td>Dexamethasone</td>
<td>1 month</td>
<td>DME</td>
<td>Ph III</td>
</tr>
<tr>
<td>Posurdex®</td>
<td>Surmodics</td>
<td>Erodible matrix</td>
<td>Triamcinolone Acetamide</td>
<td>Up to 2 years</td>
<td>DME</td>
<td>Ph I</td>
</tr>
<tr>
<td>I-Vation™</td>
<td>Neurotech</td>
<td>Non-eroding</td>
<td>CNTF</td>
<td>1–1.5 years</td>
<td>Retinitis pigmentosa</td>
<td>Ph II</td>
</tr>
<tr>
<td>NT-501 (ECT)</td>
<td></td>
<td>reservoir</td>
<td></td>
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</table>
for standard of care. Like the uveitis indication, most of the phakic patients required removal of cataracts. IOP increase occurred in 35%. In the small trial (19 eyes) examining both branch and central retinal vein occlusions, mean logMAR visual acuity (VA) improved from 20/126 to 20/80 with the device. For VA >2 lines improvement was seen in 11 eyes, unchanged in two eyes and worse in three eyes. At 1 year, seven eyes required filtration surgery for the IOP increase.

While the Posurdex is similar to the Retisert in being a sustained delivery dose form for steroid treatment of macular edema, it is distinguished in being both erodible and having shorter duration of action (Rego et al., 2004). As a result, dramatic improvement in the side effect profile is noted. Ultimately the final safety profile will depend on the retreatment schedule with the device. In the main trial, persistent macular edema patients refractory to other medical or laser therapies received Posurdex via surgical implantation (Kuppermann et al., 2006). Three arms of 105 patients per group (observation, 350µg and 700µg) were followed for 6 months. At the 6-month time point, 36% of the 700µg group and 27% of the 350µg group had at least a two-line improvement in best-corrected visual acuity, compared to 19% in the observation group. Nineteen percent of the 700µg patients had an improvement of three or more lines, which was statistically significant compared to the 8% in the observation group. IOP increases greater than 10mm were observed at any given point in 17% for the high dose group, 12% for the low dose and 3% in the observation patients. In a second study of 30 patients, which used the Posurdex injector device for placement, incidence of adverse events was lower than the incision group.

Although Phase III trials are ongoing, at the current time, only preclinical safety data from the flucinolone-containing Medidur has been reported (Glybina et al., 2006; See et al., 2006). Two rates (0.2µg/day and 0.5µg/day) have been developed. The implant was determined to be safe compared to controls for anterior parameters, reduction in ERG b-wave amplitudes, outer nuclear layer cell counts and change in intraocular pressure. With reference to drug release, rates were studied over a 1 year period. High dose devices initially released drug at 0.7µg/day which declined to 0.41µg/day over the next 100 days. Low dose devices released drug at 0.21–0.34µg/day. One eye developed cataract.

One of the more unique systems is the encapsulated cell technology from Neurotech being developed initially for treatment of retinitis pigmentosa. The Neurotech device uses sealed selectively permeable hollow fibers of polyethersulfone which encases an immortalized culture of the ARPE-19 cell line maintained on a polymer scaffold. A tethering loop of titanium or nitinol allows suturing the device in the pars plana (Kauper et al., 2005; Tao, 2006). Thus far, the devices, which release ciliary neurotrophic factor (CNTF) at rates from 11 to 58ng/day, have been reported to be safe in initial human safety trials (Kauper et al., 2005; Tao, 2006).

In the above intravitreal systems, all are required to be fully inserted into the vitreous space. However, intravitreal devices can also be designed to traverse the sclera, which then serves as an anchor for the device (Figure 2.5). Several types of transscleral pars plana anchored systems have been reported (Figure 2.6). Device A, made with non-eroding silicone, can either be prepared as a matrix or as a reservoir type with a refillable chamber (Weiner et al., 1995). Device B represents the I-Vation™ device which has advanced into Phase I trials. This system comprises a metal coil coated with drug/non-eroding polymer matrix that is essentially screwed into place following a small 30 gauge needle stick (Varner et al., 2004, 2003; Ratanapakorn et al., 2005; Tano et al., 2005). Finally, device C is an erodible matrix of PLGA polymers which has shown pre-clinical utility for
delivery of ganciclovir, and fluconazole (Ogura and Ikada, 1998; Sakurai et al., 2001; Yasukawa et al., 2001; Miyamoto et al., 1997).

Additional types and styles of intra-vitreal implants have been investigated for sustained delivery of triamcinolone (Ciulla et al., 2003), 2-methoxyestradiol (Robinson et al., 2002a,b), doxycycline (Chadid et al., 2001), dexamethasone (Morita et al., 1998), daunomycin (Rahimy et al., 1994), 5-fluorouracil (Rubsam et al., 1994), FK506 (Chen et al., 2002), and ciprofloxacin (Hainsworth et al., 1996). These studies further confirmed the ability of different implant designs to release drugs into the vitreous in a controlled fashion.

In pars plana implanted systems, the design and rate must facilitate getting sufficient levels of drug to distal tissue. Finite element modeling has been used to provide theoretical prediction of drug concentration from pars plana systems (Missel, 2002a,b, 2000; Weiner et al., 2006). In this type of modeling the factors which form the basis for the prediction are based on (a) tissue factors which include partition coefficient of drug in tissue, diffusion coefficient of drug in tissue, concentration boundary conditions surrounding the implant surface at the drug solubility limit, vascular clearance from the choroid, and anterior clearance from hyloid; and (b) fluid velocity factors which include hydraulic conductivity of tissue and pressure boundary conditions such as anterior IOP at the hyloid (14 mm).
and episcleral venous pressure (9 mm). These models show that while efficacious levels of drugs within macular tissue can be established at particular steady state release rates, much higher levels will be established and maintained proximal to the implant. From a toxicological point of view it is therefore not hard to understand the high rates of cataract and IOP increase from pars plana implanted steroids, particularly if the designed steady state rates are too high.

Release kinetics within the vitreous would be expected to vary depending on its physical state. Syneretic vitreous, vitrectomized eyes or those with tamponade replacements would likely impact drug release rate.

**H. Intrascleral Delivery**

The intrascleral route is not a common approach, as the tight physiologic space to inject materials makes it somewhat prohibitive. There has been some work to inject oligonucleotide (Edelhauser et al., 2002; Shuler et al., 2004) and integrin antagonist (Hanekamp et al., 2002), both demonstrating feasibility of achieving posterior drug levels from scleral tissue directly. An intrascleral injection device has been developed to facilitate accurate injection into the tissue with minimal trauma to or penetration of the underlying layers (Bowman et al., 2002a,b).

The intrascleral delivery of betamethasone has been reported using a non-eroding polymeric device (Okabe et al., 2003a,b). Zero order release of the drug over 4 weeks in rabbits was observed without substantial toxic response.

Using micro-electrical-mechanical systems (MEMS)-based technology a small chip type device has been engineered with multiple micron sized needles which penetrate into the intrascleral space (Jiang et al., 2006). Up to 100 µL of drug can be coated onto the needle tips which are beveled at a 45 degree angle. Studies examined dissolution of fluorescein from the needles compared to topical delivery of the same amount. Concentration in the anterior chamber was significantly higher after 3 hours but there was not an extension of higher levels to 24 hours.

**I. Subretinal Implants**

**BOX 2.1**

Drugs that have been injected directly into the subretinal space include tissue plasminogen activator (Olivier et al., 2004; Surguch and Gabel, 2006; Singh et al., 2006), P2Y2 receptor antagonist (Nour et al., 2003), triamcinolone (Equi and deJuan, 2003), and genes and viral vectors (Good et al., 2003; Behling et al., 2003; Kostic et al., 2003; Rolling et al., 2003). Despite such studies there are still many reports of damage caused by injections in this position (Kawaji et al., 2004; Maia et al., 2004; Holmes et al., 2002).

The practice of implanting solid materials in the subretinal space is a newer concept. The risk associated with potential retinal detachment has historically limited the desire to use this approach. However, greater impetus to try this approach has come from extensive work on implantation of microphotodiode array silicon chips to effect restoration of vision in conditions such as retinitis pigmentosa (RP) (Chow et al., 2004, 2001). Recent studies on the Optobionics chip has not demonstrated ERG responses in the RCS rat model (Kim et al., 2006a) but greater success has been achieved in C57B1/6 mice, a surrogate for RP (Walker et al., 2006). Human clinical data on contrast sensitivity and visual testing methods with this chip in RP patients has been assessed (Schuchard et al., 2006; Kiser et al., 2006). The Minimal Invasive Retinal Implant Project (also known as the Boston Retinal Implant) has provided significant data on material compatibility in the subretinal space (Friderichs-Gromoll et al., 2006; Ezelius and Gerding, 2006). Materials (Continued)
such as polyimide, aluminum oxide coated polyimide, amorphous carbon, parylene, poly(vinyl pyrrolidone) or polyethylene glycol have also been studied in the subretinal space in Yucatan miniature pigs (Montezuma et al., 2004). In this study no gross inflammatory reaction, fibrous proliferation or retinal pigment epithelial proliferation was evident. The amorphous carbon coated polyimide materials were free of the fibrous coating after implantation. Microchips which are designed to release drugs upon remote electrical stimulus have excellent future potential (Santini et al., 2005). Multiple chambers within the chip can be activated to provide pulse doses to the local tissue.

Aside from microphotodiode array chips, radiation implants with strontium-90 or palladium-103 have also been placed in the subretinal region for therapy of exudative age related macular degeneration (AMD) (Finger, 2001; Rossi et al., 2004). The potential to control release of drugs from subretinal implants using both eroding and non-eroding materials is an ongoing effort. Triamcinolone has been studied either when injected as a suspension (Tu et al., 2004) or in a poly-e caprolactone filament (Beeley et al., 2004, 2005a). At least 1 month of delivery from the filament was observed in rabbits without significant inflammatory response. Surgically the technique involves conjunctival peritomy, sclerotomy with a 20 g MVR blade 1 mm posterior to the limbus in the superotemporal quadrant (superonasally in eyes that underwent vitrectomy) and then insertion of the lament with intraocular microforceps (Beeley et al., 2005b). Delivery of the filament has also been done using a novel injection device which is designed to minimize trauma (Komaromy et al., 2004). Sustained delivery of rapamycin has also been evaluated from 2–3mm long nitinol implants placed in the subretinal and sub-RPE spaces (Stewart et al., 2005). This was done in both vitrectomized and non-vitrectomized animals. The study showed some damage to photoreceptors overlying the implant but normal retinal anatomy elsewhere. Drug release was followed for 1 month. Similar studies have been extended to examine additional biomaterials for the release. Filaments made from poly(methyl methacrylate) or a chronic gut core coated with poly(butyl methacrylate) and poly(ethylene-co-vinyl acetate) mixture with drugs have been appraised for their subretinal release of triamcinolone or sirolimus (Beely et al., 2006). Triamcinolone implants were well tolerated but the sirolimus implants produced some drug related signs of toxicity.

IV. CONCLUSIONS

It is clear from the foregoing discussions that a profusion of efforts have been and continue to be devoted to improving delivery of drugs to the eye. It is therefore inconsistent that only a few systems have actually been commercialized or advanced into human clinical trials. One need only consider the mantra of this chapter – duration, targeting and compliance – to begin to understand why the challenge is still monumental. Unfortunately, many if not most studies are deficient in not addressing all three attributes simultaneously. In studies focused on long-term release of drugs, the issue of distribution from the administration site to achieve sufficient efficacious levels at target tissue is often missed. Alternatively, systems sometimes are engineered to work perfectly in achieving a long-term efficacious level at a tissue site, but require the patients or physician to perform procedures which cannot be complied with.

It is also possible that some potentially useful drugs did not surface on the basis of perceived drug inactivity. If a drug is effective upon standard administration, a
natural conclusion is that it should also be effective if delivered from a sustained or controlled release system. However, the converse is not always true, i.e. if the drug is ineffective, therefore the drug delivery system should not work either. This is not necessarily the case, since an inactivity resulting from a rapid turnover of the drug may be solved by having continuous levels of the drug in the target tissue which may be accomplished with a delivery system.

The physical constraints in the eye are a further element restricting successful development of delivery systems. Lower potency drugs necessitate construction of systems that become prohibitively large. Tiny devices with low potency drugs either never reach efficacious rates and/or don’t achieve sufficient duration of action. Ideally, the drug should have a wide therapeutic index without compromising the ability to fabricate a workable device.

A primary consideration in the development of a new delivery system is the approval through the various global regulatory agencies. For example, the removability of a delivery system from the eye is likely to be a main discussion point with regulators concentrated on the safety perspective. Clinical studies must present rescue strategies to deal with unexpected adverse events, and easy device removal should be considered in design control and risk assessment evaluations during development. For erodible systems, agencies are looking for effective in vitro–in vivo correlations of dissolution testing to help predict durations. While the original 1975 USP guidance on dissolution was concerned with oral capsule and tablet forms, today the agencies are more concerned with performance relative to the dissolution characteristics established at the site of implantation, in this case ocular tissues.

An important aspect concerns the time for development by the various companies. A device that is designed to release drug over a long period of time will require longer preclinical animal toxicology studies before Phase I studies can be conducted, and longer Phase II and III studies will also be required to determine safety in humans. A shorter-term biodegradable device may provide easier administration and fewer adverse effects while eliminating the need for device removal at the end of the treatment period. However, a long-term non-degrading device (e.g. 1–2 years) may provide superior control of drug release, superior retrievability in case of serious adverse effects, and fewer invasive procedures for chronic therapy, than the biodegradable device. Both perspectives need to be weighed in the strategy for developing a new system.

V. REFERENCES


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