Pharmaceutical Research, Vol. 27, No. 4, April 2010 (© 2010)
DOI: 10.1007/s11095-009-0042-9

Expert Review

New Techniques for Drug Delivery to the Posterior Eye Segment

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Received November 11, 2009; accepted December 15, 2009; published online February 13, 2010

ABSTRACT. Ocular drug delivery has become an increasingly important field of research especially when treating posterior segment diseases of the eye, such as age-related macular degeneration, diabetic retinopathy, posterior uveitis and retinitis. These diseases are the leading causes of vision loss in developed countries which require repeated long-term administration of therapeutic agents. New drugs for the medication of the posterior ocular segment have emerged, but most drugs are delivered by repeated intravitreal injections associated with ocular complications. Advances in ocular drug delivery system research are expected to provide new tools for the treatment of the posterior segment diseases, providing improved drug penetration, prolonged action, higher efficacy, improved safety and less invasive administration, resulting in higher patient compliance. This review provides an insight into the recent progress and trends in ocular drug delivery systems for treating posterior eye segment diseases, with an emphasis on transscleral iontophoresis.

KEY WORDS: drug delivery; Iontophoresis; ocular; posterior segment.

INTRODUCTION

In recent years, diseases of the posterior eye segment have become an important therapeutic target with unmet medical needs. Diseases such as age-related macular degeneration, retinal vascular diseases, posterior uveitis, and glaucoma causing damage to the retina and optic nerve are the most prevalent causes of visual impairment and blindness for millions of patients in the industrialized countries. Even though, the ocular drug market is still dominated by anterior segment drug therapies, typically eye drop formulations, remarkable progress has been made in the field of ocular drug delivery systems and therapies for posterior ocular diseases (1,2). The delivery of therapeutic doses of drugs to the tissues in the posterior segments of the eye, while minimizing systemic and local side effects, is the major goal in the treatment of these ocular diseases. The unique anatomy and physiology of the eye and its protective barriers offer many challenges to the development of effective ophthalmic drug delivery systems. However, the rapid progress of the biomaterial sciences and our increasing understanding of ocular drug absorption and disposition mechanisms have opened new possibilities of ocular treatment (3). Systems range from simple solutions to novel delivery systems, such as biodegradable polymeric systems, liposomes, nanoparticles, iontophoresis and gene delivery systems. Table I summarizes the main ocular delivery systems divided into topical and intraocular systems, and notes the systems which may deliver drugs to the posterior segment of the eye.

This review focuses on recent progress and trends in ocular drug delivery systems for treating posterior eye segment diseases, with an emphasis on transscleral iontophoresis.

CONVENTIONAL DOSAGE FORMS AND RESTRICTIONS

Topical Administration

The most common drug delivery method for treating ocular disorders is topical administration, due to its convenience and safety. Eye drops were already used at the time of Cleopatra for the treatment of ocular conditions. For example, Belladonna was used as a mydriatic in ancient Egypt (1). The majority of topical ophthalmic preparations available today are in the form of aqueous solutions, a simple dosage form for large-scale manufacture. Viscosity agents, such as polyvinyl alcohol, hydroxypropyl cellulose and Hyaluronic acid, are commonly added for improving drug bioavailability by affecting the viscosity of formulation and increasing contact time in the precorneal space(4).

Drug suspensions are an important dosage form for many recently developed hydrophobic drugs with limited solubility in water. The drug is homogenously suspended in an aqueous solution at an average particle size of less than 10 μm. The particles are readily dispersed due to many inactive ingredients in the formulation, such as dispersing and wetting agents, suspending agents and buffers.

Ophthalmic ointments and gels are another topical administration, mainly for night-time use and when prolonged therapeutic actions are required. Ointment bases and mucoadhesive polymers are able to extend the contact time of the drug

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Table I. Main Types of Ocular Delivery Systems

Topical delivery systems	Intraocular delivery systems
Solutions, suspensions, emulsions	Injections[a]
Gels, *in-situ* forming gels	Inserts[a]
Ointments	Implants (degradable/non-degradable)[a]
Mucoadhesive polymers	Micro/nanoparticulates[a]
Conjunctival inserts	Liposomes[a]
Contact lenses	
Micro/nanoparticulates	
Liposomes	
Iontophoresis[a]	

[a] Possible drug delivery to posterior segment of the eye

with the biological tissues, and thereby improve drug bioavailability and reduce administration frequency (4).

The major deficiencies of the topical conventional dosage form include poor ocular drug bioavailability, high administration frequency, pulse-drug entry, systemic exposure due to absorption in the conjunctiva and nasolacrimal drainage system, and poor entrance to the posterior segments of the eye due to the lens-iris diaphragm (5). The ophthalmic ointments and gels have improved drug bioavailability, but the patients suffer from inaccurate dosing, matted eyelids and blurred vision due to the refractive index difference between the tears and the non-aqueous nature of the ointment base (6,7).

The anterior segment of the eye has various protective mechanisms for maintaining visual functions. After instillation of an ophthalmic drug, most of it is rapidly eliminated from the precorneal area due to drainage via the nasolacrimal duct and dilution by the tear turnover (approximately 1 µl/min) (8,9). In addition, there is a finite limit to the size of the dose that can be applied and tolerated by the cul-de-sac (usually 7–10 µl) and the contact time of the drug with the absorptive surfaces of the eye. It has been determined that as much as 90% of the 50 µl dose administered as eye drops is cleared within 2 min, and only 1–5% of the administered dose permeates the eye (10,11). The cornea itself is a highly selective barrier with five different layers which exclude compounds from the eye. The main corneal barriers are the lipophilic epithelium layers (50 µm) with its tight junctions and high turnover of one cell layer per day, and the hydrophilic stroma (450 µm) which represent a rate-limiting barrier for absorption of lipophilic drugs (12,13). The drug finally absorbed may exit the eye through the canal of Schlemm or via absorption through the ciliary body into the episcleral space. Conjunctival uptake of topically applied drugs is typically in an order of magnitude greater than the corneal uptake, due to the relative leakiness of the membrane, the rich blood flow and the large surface area (14). However, most drugs are rapidly removed by systemic uptake through the vessels embedded in the conjunctival tissue, before diffusion to the intraocular tissues. Also, enzymatic metabolism may account for further loss, which can occur in the precorneal space or in the cornea (9).

Clearly, the physiological barriers to topical absorption are formidable. Therefore, high administration frequency and high drug doses are required, resulting in fluctuations in ocular drug concentrations and local and/or systemic side effects. Either way, the amount of drug absorbed into the posterior segment of the eye will only be a minute fraction of the amount attained in the anterior segment (15).

Injectable Systems

Periocular or intraocular injections of drugs are routinely applied in the clinical setting, generating elevated intraocular concentrations with minimal systemic effects. In order to minimize the number of injections, the therapeutic drug concentration should ideally be maintained for prolonged periods. This is quite a challenge, since the drug injected is eliminated via the anterior route, through the outflow of the aqueous humor, or posteriorly through the retina to the systemic circulation. Multiple injections usually have low patient compliance due to the inconvenience and pain, and are associated with complications such as cataract, retinal detachment, vitreous hemorrhage and endophthalmitis (16,17).

Systemic Administration

Systemically administered drugs have poor access to the eye because of the blood-ocular barrier, which physiologically separates the eye from the rest of the body by epithelial and endothelial components, whose tight junctions limit transport from blood vessels to the eye. This barrier is comprised of two systems: (a) the blood-aqueous barrier composed of the uveal capillary endothelia and ciliary epithelia, which prevents drugs from entering the anterior chamber, and (b) the blood-retinal barrier, which prevents drugs from entering into the extravascular space of the retina and into the vitreous body (18). Drugs with adequate permeability (*i.e.* lipophilicity or active transport) in the retinal capillaries and in the retinal pigment epithelium (RPE) can cross the blood-retina barrier to reach the retina and vitreous. Access to the choroid is easier owing to the extensive blood flow and leaky vessels in this tissue. However, only a small fraction of the blood flow circulates through the posterior ocular segment, and therefore high doses are needed and systemic adverse effects are common. Such an approach is not feasible for potent drugs with narrow therapeutic indices (1).

PENETRATION ROUTES TO THE POSTERIOR SEGMENT

The delivery of drugs to the posterior eye segment is difficult mostly due to the long diffusion distance, the lens-iris barrier and the acellular nature of the vitreous body.

The first choice when treating posterior segment diseases is injecting directly into the posterior segment, bypassing the corneo-scleral barriers. But, as discussed before, low patient compliance and possible complications are involved. Systemic administration is another major route for drugs to reach the chorio-retinal tissue through the blood circulation. However, poor drug concentrations and high systemic side effects are involved, as described above.

The alternative route for posterior segment treatment is delivering the drug via the sclera using a drug delivery system placed into the periocular space. Several possible sites are available, including subconjunctival, sub-Tenon, peribulbar, posterior juxtrasclera and retrobulbar spaces(2). The phar-

macokinetics of drug diffusion through the sclera are influenced by the scleral surface area (in humans, 16–17 cm^2) and scleral thickness. Thus, the ideal location for transscleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus, where the sclera is thinnest (16).

As discussed by Ranta *et al.* (2), the drug may permeate from the periocular space into the vitreous via 1) anterior chamber, 2) systemic circulation or 3) direct penetration pathway, as seen in Fig. 1. In the anterior chamber route, the drug diffuses into the aqueous humor either directly across the sclera and ciliary body or indirectly via the tear fluid and cornea, followed by diffusion into the posterior chamber. In the systemic circulation route, the drug is absorbed into the general circulation via conjunctival, episcleral or choroidal vessels and later returned into the eye with blood flow. However, experimental data confirmed the rational thought that these routes are secondary to the predominant route of direct penetration of the drug to the vitreous through the underlying tissues, depending on the application site on the sclera (19–21). If placed around the anterior part of the eye, the drug may diffuse through the ciliary body to the posterior chamber and vitreous, and if placed around the posterior part of the eye, the drug has to penetrate across the choroid, RPE, neural retina and then reach the vitreous (2). The direct penetration pathway involves several membrane barriers, which contribute to the factors affecting transscleral drug delivery to posterior ocular tissue, including diffusion across these tissues, active transport in RPE, distribution and clearance via circulation. These factors and more were taken into consideration when pharmacokinetic models were built for better understanding of the transscleral drug delivery to the posterior segment, as well reviewed by Ranta *et al* (2).

ADVANCED DELIVERY SYSTEMS FOR POSTERIOR SEGMENT DISORDERS

Various attempts have been made to improve drug bioavailability by increasing both drug retention in the precorneal area and drug penetration through the cornea and sclera. In addition, patient compliance and comfort considerations in drug administration are very important factors that may impact the drug's therapeutic efficacy (22). These attempts can be divided into two main categories: bioavailability improvement and controlled release drug delivery. The first category includes gels, emulsions, viscosity enhancers, penetration enhancers, pro-drugs, liposomes and iontophoresis. The second category includes various types of polymeric inserts, implants and nanoparticles (5). Table II summarizes the advantages, disadvantages and duration of action of advanced delivery systems with potential clinical application for posterior segment diseases of the eye.

In this section, we will describe the main advances in ocular drug delivery systems aimed at the treatment of posterior segment disorders, emphasizing iontophoretic delivery.

Injectable Pro-drugs

The bioavailability of an active drug can be enhanced by using a pro-drug derivative. A pro-drug is defined as an inactive species obtained by chemical modification of the active drug which, when delivered, will release the active drug essentially in a single step (*i.e.*, enzymatic conversion). Usually, ophthalmic pro-drugs are lipophilic esters or diesters with better permeability than the parent compound. Indeed, increased lipophilicity facilitates the pro-drug uptake by and the diffusion across the lipophilic membranes which act as a

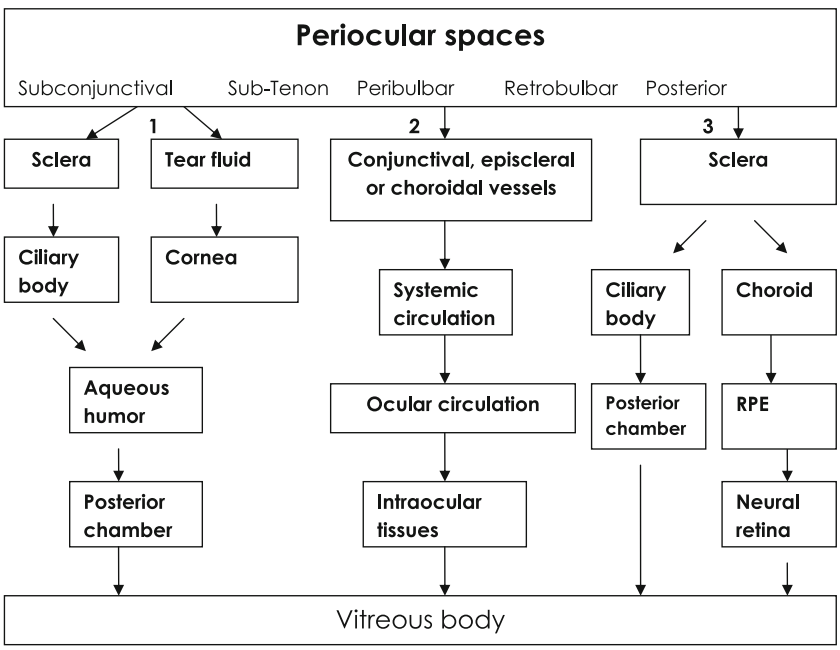

Fig. 1. Drug penetration routes from the periocular spaces to the vitreous and posterior ocular tissues using transscleral drug delivery. This scheme describes three suggested penetration routes: 1. anterior chamber route, 2. systemic circulation route, and 3. direct penetration route.

Table II. Advantages, Disadvantages and Duration of Action of Advanced Delivery Systems with Potential Clinical Application for Posterior Segment Diseases of the Eye

Methods	Advantages	Disadvantages	Duration of action
Non-biodegradable implants	- Controlled release of drug over a long period of time - Increased half-life of drugs - Drug stabilization - Improved patient compliance	- Requires surgical implantation associated with ocular complications - Requires surgery to harvest the device once is depleted of the drug	Years
Biodegradable implants	- Controlled release of drug over a moderate period of time - Increased half-life of drugs - Drug stabilization - Improved patient compliance - Removal not required - Various shapes	- Surgical implantation or injection associated with ocular complications - Final uncontrolled 'burst' in the drug-release profile	Weeks to months
Intraocular liposomes, micro- and nanoparticulates	- Increased half-life of drugs possible - Decreased peak concentration resulting in decreased toxicity - Localized delivery of drugs (*e.g.* targeting RPE cells) - Improved patient compliance	- Requires injection with associated risks - Vitreous clouding	Days to weeks
Transscleral iontophoresis	- Non-invasive technique - Easy to use - Short application process - May be combined with other drug delivery systems - Ability to modulate dosage - Broad applicability for delivering different drugs or genes to posterior segment of the eye - Good acceptance by patients	- Does not increase drug half-life - Mild pain	Hours to days

barrier to the hydrophilic drugs. Mandel *et al*. were the first to formally introduce the concept of pro-drugs in the late 1970s with the testing of dipinefrin (a pro-drug of epinephrine) for improvement of corneal penetration of epinephrine. Since then, several other ocular drugs have been studied for pro-drug derivatization (23). In order to avoid the nonspecific absorption of drugs into nontargeted tissues and to avoid systemic toxicity, intravitreal administration of pro-drugs may be justified. Also, subconjunctival injection may be used to deliver pro-drugs targeted to specific transporters expressed on the basolateral side of the RPE. Following subconjunctival administration, the pro-drug first diffuses into the sclera and then into the choroidal circulation, where it interacts with transporters expressed on the RPE. These transporters will carry the pro-drug into the retinal tissue, where it is cleaved into the parent drug. If the drug is incorporated into a polymeric vehicle which controls the release of the pro-drug, a sustained delivery of drug to retina and vitreous layers may be possible (24).

Polymeric Implants

The goal of the intraocular implant design is to provide prolonged activity with controlled drug release from the polymeric implant material, as an alternative to multiple injections. These polymeric devices containing a drug are implanted in the vitreous cavity or into the sclera. Drug release occurs either by diffusion across a permeable membrane or by degradation of the polymer block (25,26). Although this is an invasive technique, the implants have the benefit of (1) by-passing the blood-ocular barriers to deliver constant therapeutic levels of drug directly to the site of action, (2) avoidance of the side effects associated with frequent systemic and intravitreal injections, and (3) smaller quantity of drug needed during the treatment.

The ocular implants are classified as non-biodegradable and biodegradable devices, depending on the polymer used. Non-biodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but require surgical implant removal with its associated risks (1). The polymers commonly used for non-biodegradable implants are polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA) and silicone, whereas for biodegradable implants, a variety of polymers can be used (PLA, PGA, PLGA, polycaprolactones, polyanhydrides and polyorthoesters). The erosion rate and spontaneous degradation of these polymers can be modulated to allow for the desired intraocular kinetics of drug release to take place. Moreover, biodegradable polymers can be used to form solid or injectable viscous/semi-solid implants in various shapes, which do not require their removal (27).

Vitrasert® (27) and Retisert® (25) (Bausch & Lomb, USA) are clinically used non-biodegradable implants. Vitrasert® is the first implantable ganciclovir delivery device, approved by the FDA in 1996 for the treatment of cytomegalovirus (CMV) retinitis. However, occasional endophthalmitis and an increased rate of retinal detachments have been associated with this implant (27).

The Retisert® (25) implant releases fluocinolone acetonide for the treatment of chronic non-infectious uveitis of the posterior segment (approved by the FDA in 2005). PVA and silicone laminate govern the release of the corticosteroid over 3 years. Although the device is effective in controlling the uveitis, it also has side effects such as cataract formation and increased intraocular pressure.

Iluvien® (Alimera Sciences, USA) is a fluocinolone acetonide non-biodegradable implant that can be inserted intravitreally as an injection, instead of via surgery, due to its small size (Medidur® technology). This tube-shaped device is in Phase III multi-center clinical trial to evaluate the safety and efficacy of the implant for diabetic macular edema. The device is very small (3.5 mm long and 0.37 mm in diameter), designed to provide a low daily dose of 0.2–0.45 μg fluocinolone acetonide for 24 to 36 months after injection (28).

Ocular delivery systems with biodegradable polymers are under ongoing investigation. Although biodegradable systems present significant advantage since the inert polymers are eventually absorbed or excreted by the body, the main obstacle is to get the optimal formulation for achieving the desired drug release profile. Many researchers have demonstrated in animal models the effective sustained ocular delivery of anti-metabolites, steroids and other substances, by using this type of device (26,29,30). However, few have reached the clinical stage.

Posurdex® (Allergan, USA) (31) is a biodegradable implant of dexamethasone in clinical Phase III studies. Posurdex® is designed for the treatment of macular edema due to retinal vein occlusion, diabetic macular edema and uveitis by sustained release of dexamethasone over a month after intravitreal placement. A Phase II clinical trial showed that patients who had received a 700 μg dose in the implant had the greatest improvement in vision.

Liposomes

Liposomes are vesicles composed of one or more phospholipid bilayers separated by aqueous compartments. There are liposomes of different sizes and morphology, divided into small (20–80 nm in diameter) to large (80–1000 nm), unilamellar vesicles, multilamellar vesicles (100–4000 nm), and multivesicular liposomes (1–100 μm) (32). Generally, liposomal membranes are formed with an arranged mixture of phospholipids and other additives involving cholesterol, sphingosine, glycolipids, or other amphiphilic substances. Liposomes can encapsulate hydrophilic drugs in the aqueous cavity or introduce hydrophobic drugs into the membrane as a component. Even hydrophilic drugs, if modified to amphiphilic pro-drugs by conjugation with other molecules, can be introduced into the membrane (33). They act as "reservoir-type" carriers and possess qualities which can make them ideal for certain posterior segment uses (26).

As summarized by Bochot *et al.* (32), intravitreally administered liposomal systems could both significantly increase drug half-life and minimize the intraocular side effects of drugs used (*i.e.*, ganciclovir and 5-fluorouridine). Intravitreal injection of liposomes containing a lipid pro-drug of ganciclovir inhibited CMV retinitis in rabbits (34). However, the fate of liposomes themselves after intravitreal administration is still unknown. It should be mentioned that the pharmacokinetic behavior of intravitreal liposomes might be affected not only by the composition and size of the liposomes but also by the condition of the eye (33).

Some problems with the use of liposomes need to be overcome before clinical application, including difficulties in preparation and storage, transient impaired vitreous, induced cataract and inflammation, and unknown long-term effects. In addition, drug release is complicated because it may result not only from the diffusion of drug from intact liposomes but also from a burst from disrupted liposomes. Liposomes may be disrupted by interaction of the membrane components with other proteins, lipids, or cellular components (32).

Nevertheless, liposomes are attracting many researchers as the biotechnology develops. Theoretically, liposomes can be designed to intervene in intercellular biological responses between receptors and ligands in physiological or pathological conditions and also to receive external signals by laser beam or an electric or magnetic field. Therefore, liposomes may become available for a drug-targeting system by modifying the liposomal surface to allow preferential binding, for example, to the endothelium of proliferative neovascular vessels (1).

Liposome technology has been used to develop light-induced systems for the retinal diseases. Verteporfin (Visudyne®, Novartis Pharmaceuticals, USA) (35) is the only ocular liposomal drug currently in clinical use. It works as photodynamic therapy to treat choroidal neovascularization and age-related macular degeneration. After intravenous infusion of Visudyne®, a non-thermal red laser is applied to the retina to activate verteporfin that causes local damage to neovascular endothelium, thus resulting in occlusion of the targeted vessels. Photodynamic therapy itself induces an increased local production of VEGF and potential reappearance of the choroidal neovessels. Hence, the effect of Visudyne® is insufficient in some cases and the patients need repeated treatments.

Rostaporfin (Photrex®, Miravant Medical Technologies, USA) (36) is another liposomal photosensitizing agent that aims to treat age-related macular degeneration. FDA approval is currently pending. The frequency of the required treatments is significantly lower than that of Visudyne®.

Nano/microparticles

Nanoparticles are polymeric colloidal particles ranging in size from 1 to 1000 nm. They consist of macromolecular materials in which the drug is dissolved, entrapped, encapsulated, and/or to which the drug is adsorbed or attached (37). They can be classified into two groups: nanospheres and nanocapsules. *Nanospheres* are small solid monolithic spheres consisting of dense solid polymeric network, developing over a large specific area. Drugs can be either incorporated into the matrix of the nanospheres or adsorbed onto the surface of the colloidal carrier. *Nanocapsules* are small capsules formed of a central cavity (usually an oily droplet containing the dissolved drug) surrounded by a polymeric membrane (Fig. 2) (14).

Nanoparticles are one of the most studied colloidal systems over the past two decades, with the object of improving targeting of drugs to organs and increasing drug bioavailability across biological membranes, including the corneal epithelium. The colloidal character of the carrier improves corneal drug penetration by augmenting their ocular residence time, reducing the nasolacrimal clearance

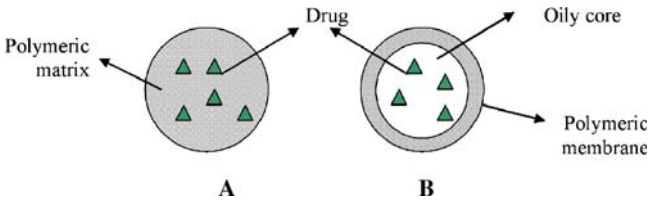

Fig. 2. Schematic representation of nanoparticle systems for drug delivery to ocular tissues: nanospheres (**A**) and nanocapsules (**B**)(58).

and increasing interaction with the corneal surface. Compared with other potential systems of controlled drug delivery, such as implants or inserts, colloidal carriers present the advantage of easy administration in a liquid form (38–40). Moreover, nanoparticles have the advantage of higher drug-loading capacity and higher stability in biological fluids and during storage as compared to other colloidal carriers similar in size, such as liposomes (22).

Ocular administration of nanoparticles has been widely investigated as a topical suspended system or a local injectable system for treating various eye disorders, such as glaucoma (41–45), ocular infections (46–48), ocular inflammations (49–51) and immune-mediated ocular disorders (52–54). Drug-loading capacity, drug release rate and biocompatibility of the polymer are of utmost importance for a successful treatment. The drug-loaded nanoparticle system is suspended in aqueous or non-aqueous medium and instilled topically in the cul-de-sac of the eye, from whence the drug is slowly released into the lacrimal pool by dissolution, diffusion or mechanical disintegration of the polymer matrix. However, when the posterior segment of the eye is targeted for drug delivery, local injections can provide a slow-releasing depot of drug in the vitreous cavity with a reduced frequency of injections and increased patient compliance (55–57).

The success of a nanoparticulate system for ocular delivery is heavily influenced by the polymer selection. So far, various natural and synthetic biocompatible polymers have been used for the preparation of nanoparticles to ocular drug delivery, allowing different degradation rates, such as poly(methyl) methacrylate, poly(alkyl)cyanoacrylate, polycaprolactone, albumin, gelatin, polylactic acid, chitosan and Eudragit (58). However, very few scientists have investigated the posterior segment penetration and distribution of these particles and their drug release profile. Bourges *et al.* (57) showed that an intravitreal injection of PLA nanoparticles resulted in trans-retinal movement, with a preferential localization in the retinal pigment epithelium (RPE). The presence of the nanoparticles within the RPE cells for 4 months after a single injection shows that a continuous and specific delivery of drugs can be achieved. Tamoxifen, a non-steroidal estrogen receptor modulator, was incorporated into polyethylene glycol (PEG)-coated cyanoacrylate nanoparticles and first evaluated for the treatment of experimental autoimmune uveoretinitis (EAU) in rats (54). This study demonstrated that tamoxifen-loaded nanoparticles injected into the vitreous inhibited the onset of the EAU as compared to injected free tamoxifen. It was suggested that this could be related to the progressive release of the drug from the particle and the prevention of its *in vivo* metabolism. This study also investigated the biodistribution of tamoxifen nanoparticles after intravitreal injection using fluorescence particles. Large numbers of nanoparticles penetrated the intraocular tissues from the vitreous, causing a modest inflammatory reaction. Nanoparticles remained in the ocular tissue for 3 to 9 days, whereas after injection to inflamed eyes, an earlier and more impressive accumulation of nanoparticles occurs.

Drugs may also be encapsulated within microcapsules or dispersed in microspheres (1–1000 μm), composed of biodegradable or biocompatible polymers, such as polylactide and PLGA, both approved by the FDA. Microparticulates act like a reservoir after intravitreal injection but may have a shorter life in vitrectomized eyes, while nanoparticulates appear to diffuse rapidly and to internalize in ocular tissues (57,59). However, microspheres larger than 2 μm tend to sink as a result of gravity, resulting in fewer clouding of the ocular media (33).

To date, some microsphere formulations have reached the pre-clinical stage, but have not yet undergone clinical trials. Microspheres loaded with doxorubicin have been shown to reduce the rate of experimental proliferative vitreoretinopathy formation in rabbits (60), as well as 5-FU- and Ara-C-loaded microspheres (26,61,62). Microspheres of PKC412, an inhibitor of protein kinase C, and receptors for vascular endothelial growth factor (VEGF) were used to treat choroidal neovascularization. After a periocular injection, PKC412 penetrated the sclera and significantly suppressed choroidal neovascularization (63). In addition, biodegradable PLGA microspheres have been shown to release an anti-VEGF aptamer (Macugen®, Pfizer, USA) in a sustained manner over a period of 20 days *in vitro*. Co-encapsulation of the aptamer with the disaccharide trehalose maintained the stability of the aptamer and bioactivity of the aptamer, was preserved after release, as indicated by inhibition of endothelial cell proliferation. Also, *in vivo* evaluation on rabbits showed aptamer delivery from the microspheres through the sclera, as determined spectrophotometrically (64,65). Recently, a second drug delivery system for pegaptanib sodium was described: intravitreal PLGA microspheres released aptamer over several weeks after injection (66).

The major developmental issues for nano- and microparticles include formulation stability, control of particle size, control of drug release rate and large-scale manufacture of sterile preparations (67). The activity of the biomolecule must be maintained during the entire encapsulation, manufacturing procedure, sterilization and after release.

Non-viral Delivery Systems for Gene Therapy

Gene-based drugs include gene therapy and other approaches that rely on the specific nucleotide sequences. The nucleotide sequence of DNA, RNA, or their modifications is used to induce gene expression (gene therapy), suppress translation of the target mRNA (siRNA, antisense oligonucleotides, ribozymes), or bind to a specific protein target (aptamers). These approaches are applicable for the treatment of ocular diseases, with the advantage of easier delivery than conventional drugs. Also, genes can express their protein products for prolonged periods, and further control can be obtained by cell-specific or inducible promoters (68,69). The delivery systems of gene-based medicines are classified into viral and non-viral vectors. Although viral vectors are more efficient in the delivery of genes, the non-viral systems have some advantages, such as the lack of immune response, the ease of formulation, and unlimited gene size (1).

Pre-clinically investigated systems for ocular gene delivery include microparticles (64,66), nanoparticles (55,70–72), liposomes (73) and iontophoresis (16). The use of particulate system delivery protects the oligonucleotide/gene from the degradation after injection and prolongs its vitreal residence time and activity within the posterior ocular tissues. Cationic lipids and polymers are frequently used owing to binding and condensing of DNA and RNA to small particulates in the range of 100 nm. Despite their small size, the nanoparticulate systems have limited diffusion in the tissues, possibly due to the barriers placed by the vitreous and retina (74,75). This may be due to the steric hindrance and electrostatic interactions with ocular polyanions, such as hyaluronic acid and chondroitin sulfate.

Currently, there are two ocular gene-based drugs in clinical use. The first one was Vitravene®, fomivirsen sodium, an intravitreal phosphorothioate oligonucleotide for the treatment of CMV infection in AIDS patients (69). The second one, pegaptanib sodium (Macugen®), is an anti-VEGF aptamer for the treatment of wet-type age-related macular degeneration (76). The aptamer is conjugated to polyethylene glycol (PEG) to increase its half-life and stability in the vitreous. The same drug is currently in Phase II trials for the treatment of diabetic macular edema. In addition, two siRNA molecules (bevasiranib and Sirna-027) that modify the activity of VEGF and its receptor (VEGFR-1) are in clinical trial (http://www.gene.com/gene/index.jsp, http://www.sirna.com), both given as intravitreal injections.

Iontophoresis

Basic Concepts

The recent interest in drug delivery to the back of the eye has stimulated new interest in ocular iontophoresis, broadly defined as a non-invasive technique for the enhancement of ionic drug penetration through tissue, using a low electric current. The donor electrode containing the drug carrying the same charge as the electrode is placed on the eye, and the return electrode is placed on another body surface (Fig. 3). The drug serves as a conductor of the current through the ocular tissues. Generally, iontophoresis enhances drug delivery by three mechanisms: electrophoresis, electroosmosis and electroporation. *Electrophoresis* is the enhanced movement of ionic species by the applied electric field. *Electroosmosis* is the transport of both neutral and charged species by an electric field-induced convective solvent flow. *Electroporation* is the alteration of the tissue barrier that increases the intrinsic permeability of the membrane (77–80).

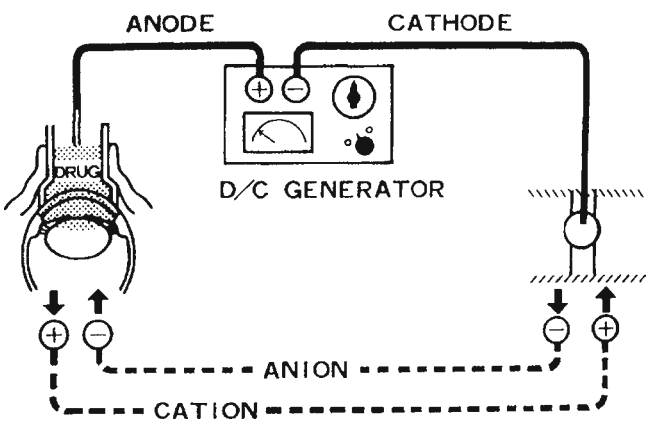

Fig. 3. Diagram of ocular iontophoresis delivering a positively charged drug(90).

The ease of application, the reduction of systemic side effects and the increased drug penetration directly into the target region, resulted in extensive clinical use of iontophoresis mainly in the transdermal field delivering local anesthetics, antibiotics, pilocarpine, *etc.* (81–88).

Ocular iontophoresis was first investigated in 1908 by the German investigator Wirtz, who passed an electric current through electrolyte-saturated cotton sponges placed over the globe for the treatment of corneal ulcers, keratitis and episcleritis (89). Despite its widespread use and study during the first 60 years of the twentieth century, iontophoresis was never fully adopted as standard procedure. The lack of carefully controlled trials and the paucity of toxicity data were among the reasons that precluded its acceptance as an alternative for drug delivery. However, the last decade has witnessed the development and optimization of the technology of ocular iontophoresis for fast and safe delivery of high drug concentrations to a specific ocular site (90). Iontophoresis was extensively investigated for delivering ophthalmic drugs, including antibacterial (91–95), antiviral (96,97), and antifungal (98) drugs, steroids (99–103), antimetabolites (104–107) and even genes (108–111). Ocular iontophoresis seems to be an answer to the low bioavailability of drugs after topical administration and to the potential serious complications following intraocular injections used for the treatment of many eye disorders.

The Ocular Iontophoretic Device

There are two approaches for retaining the drug in the iontophoretic device: the eye-cup solution and the drug-saturated hydrogels. The more common approach is to fill an eye-cup with the drug solution, while a metal electrode extended from the current supply is submerged into the solution. The eye-cup with an internal diameter of 5–10 mm is placed over the eye using slight suction, and the drug solution is continuously infused into the cup during the iontophoretic treatment (Fig. 3). Different eye-cup shapes and sizes exist, including an annular-shaped silicone probe for transscleral iontophoresis. In the last few years, several publications on drug-loaded hydrogels for ocular iontophoresis have revealed a novel approach for iontophoretic applicators. Hydrogels, three-dimensional networks of hydrophilic polymers, have attracted increasing attention in recent years in view of their swelling behavior, biocompatability and stability (112). Incorporation of drugs into hydrogels permits modulation of their release kinetics, which is an important issue for the development of novel pharmaceutical formulations and for the delivery of drugs to a specific site of action (113,114). Also, in the transdermal iontophoreic delivery field, the hydrogels plays an important role in delivering various drugs (112,115–117). Drug-containing hydrogels, rather than drug solutions, facilitate drug handling, minimize tissue hydration, and allow drug release rate control by changing the characteristics of the hydrogel (118). Recent publications on drug-loaded hydrogels for ocular iontophoresis reported effectiveness in transferring high drug amounts into various eye tissues (95,102,103,106,119–128).

OcuPhor (Iomed, Inc., Salt Lake City, Utah, USA) is a custom-manufactured hydrogel composed of polyacetal sponge for transscleral iontophoresis (119–122). The drug applicator is a small silicone shell that contains a patented silver-silver chloride ink conductive element; a hydrogel pad to absorb the drug formulation; and a small, flexible wire to connect the conductive element to the dose controller. At the time of administration, the dry hydrogel matrix is hydrated with the drug solution and placed against the sclera in the lower cul-de-sac of the rabbit eye. The return electrode can be positioned anywhere on the body to complete the electrical circuit. A very similar applicator called Visulex (Aciont, Inc., Salt Lake City, Utah, USA) was developed for ophthalmic applications and reported by Hastings and Li (123). Frucht-Pery and Eljarrat-Binstock *et al*. used a small polyacrylic-porous hydrogel saturated with different drug solutions (gentamicin, dexamethasone, methylprednisolone and methotrexate) for transcorneal and transscleral iontophoresis. The hydrogel is inserted into a well at the tip of the electrode of a portable iontophoretic device and placed onto the eye (Fig. 4) (95,102,103,106,125,129).

Animal Studies

Ocular iontophoresis is classified into transcorneal and transscleral iontophoresis, according to treatment location; the latter is related to drug transfer to the posterior segment, which is the subject of this review. *Transcorneal iontophoresis* has been widely investigated over many years with some good results in delivering high and sustained drug concentrations to the anterior segment, with the potential of treating anterior segment diseases. Corneal penetration, therapeutic efficacy and pharmacokinetic profiles of mainly antibiotics such as gentamicin, tobramycin, ciprofloxacin and vancomycin were investigated (93,95,125,130–134). However, this approach was partly abandoned since potent new drugs were developed for topical administration in cases of anterior segment diseases.

Transscleral iontophoresis overcomes the lens-iris barrier and delivers drugs directly into the vitreous and retina through the choroid or indirectly through systemic circulation or anterior chamber, as previously discussed. The iontophoretic device is placed on the conjunctiva, over the pars-plana area to avoid current damage to the retina. Tables III summarizes the variety of drugs investigated that can be iontophoretically delivered to the posterior eye segment, using different iontophoretic devices.

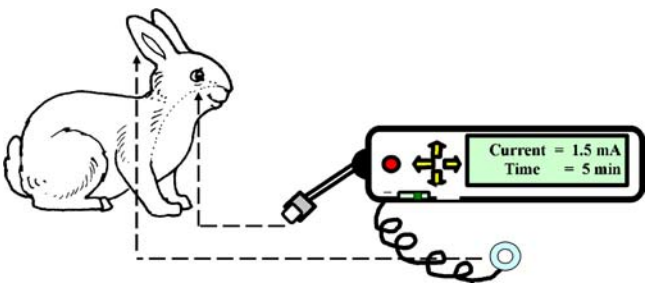

Fig. 4. Schematic structure of the iontophoretic device applied for ocular delivery of drugs using hydrogels as drug carriers. The device is composed of a cylindrical well for the insertion of a disposable hydrogel, two electrodes and a control panel for time and current control. The hydrogel-electrode is placed onto the eye surface, and the ground electrode is attached to the ear of the animal (124).

Table III. Drugs Investigated for Transscleral Iontophoresis

Drug delivered	*Investigation group, year*	*Reference*
Antibiotics		
Gentamicin	*Burstain et al.* 1985	(150)
	Braza et al. 1986	(91)
	Barza et al., 1987	(135,143)
	Grossman et al., 1990	(130)
	Eljarrat-Binstock et al. 2004	(129)
Amikacin	*Vollmer et al. 2002*	(122)
Cephazolin	*Barza et al. 1986*	(91)
Tocarcillin	*Barza et al. 1986*	(91)
Ciprofloxacin	*Yoshizumu et al.* 1991	(94)
Vancomycin	*Choi et al.* 1988	(131)
Antiviral Drugs		
Ganciclovir	*Lam et al.*, 1994	(97)
	Chapon et el., 1999	(136)
Foscarnet	*Sarraf et al.*, 1993	(138)
	Yoshizumi et al. 1996	(151)
Antimetabolic Drugs		
5-fluorouracil	*Kondo et al.*, 1989	(105)
Carboplatin	*Hayden et al.* 2004	(104)
	Eljarrat-Binstock et al., 2007	(107)
Methotrexate	*Eljarrat-Binatock et al.*, 2007	(106)
Antifungal		
Ketoconazole	*Grossman et al.,* 1989	(98)
Steroids		
Dexamethasone	*Lam et al.*, 1989	(101)
	Eljarrat-Binatock et al., 2005	(102)
	[*Tuitupou et al.,* 2007]	(152)
Methylprednisolone	*Behar-Cohaen et al.* 2002	(99)
	Halhal et al., 2003, 2004[a]	(147,149)
	Eljarrat-Binatock et al., 2008	(103)
Triamcinolone acetonide	[*Higuchi et al.,* 2006, 2007]	(126,127)
Immunosuppressant		
Mycophenolic acid	[*Papangkorn et al.*, 2007]	(128)
Genes/Oligonucleotides		
NOSII antisense	*Voigt et al.,* 2002	(111)
Oligonucleotide	*Ashara et al.*, 2001	(108)
Plasmids (pPDE-PDE)	*Souied et al.*, 2008	(140)
Generic Drug		
Diclofenac	*Voigt et al.* 2002	(139)
Aspirin	*Fischer et al.,* 2002	(119)
	Kralinger et al., 2003	(137)
Others		
Iodide	*Horwath-Winter et al.*, 2005[a]	(153)
Nanoparticles	*Eljarrat-Binstock et al.*, 2008	(124)

[a] Studied on patients with anterior segment disorders [Meeting abstract only]

A number of antibiotics, including gentamicin, cephazolin, ticarcilin, amikacin and vancomycin, have been successfully delivered into the vitreous of rabbit eyes. Barza *et al.* further investigated the efficacy of transscleral iontophoresis of gentamicin for the treatment of pseudomonas endophthalmitis in rabbits. They found that two sessions of iontophoresis in addition to an intravitreal injection of gentamicin resulted in significantly lower number of bacterial colonies in the vitreous than injection alone (135).

Transscleral iontophoresis of steroids (dexamethasone and methyl prednisolone) can be an alternative treatment for many ocular inflammations. Lam *et al.* (101) demonstrated high dexamethasone penetration to the vitreous; however, a very high current density was used (about 400 mA/cm^2). Eljarrat-Binstock *et al.* (102) achieved therapeutic dexamethasone levels in different eye segments using a lower current density (5.1 mA/cm^2) for only 4 min. The efficacy of dexamethasone iontophoresis was studied on rat and rabbit models for endotoxin-induced uveitis (EIU) by Behar-Cohen (100) and Hastings (123), respectively. Behar-Cohen used a 6 mm diameter eye-cup covering the cornea and sclera of the rat, while Hastings used a saturated hydrogel applicator placed in the superior cul-de-sac. The applied electrical current was 0.4 mA (1.2 mA/cm2) for 4 min by Behar-Cohen, and 4 mA for 20 min by Hastings. Both studies showed that the iontophoretic treatment inhibited anterior and posterior signs of intraocular inflammation as effectively as systemic administration of dexamethasone, with a significant improvement over the control groups. Also, methylprednisolone, a well-known effective steroid, was extensively investigated for penetration and distribution properties in posterior ocular tissues after application of different iontophoretic current intensities and durations (99,103). The results, seen especially in posterior ocular tissues, demonstrated the high potential clinical value of iontophoretic delivery of methylprednisolone.

The current density and the treatment duration have a direct and important influence on the achieved tissue drug levels. This was demonstrated using transscleral iontophoresis of amikacin (122), gentamicin (91), methotrexate (106), and methyl-prednisolone (99). Moreover, the contact area of the drug with the application site is of utmost importance due to its influence on the current intensity applied and ocular toxicity.

Detailed pharmacokinetic studies were performed on transscleral iontophoresis of various drugs (97,99,104,106,130,136–139). Each drug resulted in different patterns of distribution in the vitreous: for example, carboplatin distribution in the vitreous after iontophoretic delivery demonstrated heightened levels in a controlled manner from 1 to 6 h after treatment (104), whereas foscarnet iontophoresis demonstrated a very low elimination rate in which therapeutic levels in the vitreous were maintained for up to 60 h (138). Methyl-prednisolone and methotrexate obtained a peak concentration in the vitreous 2 h after treatment (99,106), and gentamicin showed a peak concentration 16 h after the transscleral iontophoresis (130). Thus, each drug has to be evaluated separately for its penetration capacity and pharmacokinetic distribution profile, due to different physicochemical properties of the drug molecules.

A novel combined approach was suggested by Eljarrat-Binstock *et al.* for delivering charged nanoparticles by hydrogel iontophoresis. This approach has the benefit of (1) ocular drug penetration, regardless of drug's ionic strength and diffusion properties in ocular tissues, (2) controlled release of the drug and prolonged therapeutic activity, (3) targeting to a specific desired tissue. These advantages can be achieved by changing the particle size, particle charge and chemical properties of the nanoparticles or by using different ligands attached to the particle. As described by the authors, iontophoretic delivery of small nanoparticles using 1.5 mA for 5 min revealed strong fluorescent evidence, indicating nanoparticle penetration into ocular tissues, with preference to the positively charged particle. Particle distribution profile revealed a rapid electrical

Table IV. Conventional and Advanced Treatments for Posterior Segment Diseases of the Eye

Diseases	USA population affected (2007 estimate)	Conventional treatment	Disadvantages	Advanced technologies	Developmental stage	Ref.
Age-related macular degeneration	1.7 million (aged over 50 years)[a]	Laser surgery, photodynamic therapy	Possible irreversible damage to the macula	Light-induced liposomal system Verteporfin (Visudyne)	FDA approved 2000	(35)
		Intraocular injections of anti-VEGF antibodies (Lucentis, Avastin-"off-label")	Possible complications of frequent intraocular injections, such as infection	Intraocular injections of nucleic acid aptamer (Macugen)	FDA approved 2004	(76)
Diabetic retinopathy	4.1 million	Laser surgery, vitrectomy or injections of triamcinolone acetonide	Creation of chorioretinal scars, complications of vitreous and intraocular injections	Iontophoresis of triamcinolone acetonide	Preclinical studies	(126,127)
Diabetic macular edema	500,000	Laser photocoagulation therapy	Creation of scars	Dexamethasone implant (Posurdex)	Phase III	(31)
			Possible irreversible damage to the macula	Fluocinolone injectable implant (Iluvien)	Phase III	(28)
Uveitis	346,000	Topical, injected or systemic prednisolone	Frequent instillation, injection-associated complications or systemic adverse effects	Iontophoresis of dexamethasone and methylprednisolone	Preclinical/clinical studies	(99,102,103,147,149)
				Fluocinolone implant (Retisert)	FDA approved 2005	(25)
Retinal degenerative disease or retinitis pigmentosa	5.3 million	Systemic Vitamin A	Systemic hypervitaminosis A	Gene therapy using iontophoresis of β-PDE cDNA	Preclinical studies	(140)

[a] Only cases of late-related macular degeneration are included

repulsion into the outer ocular tissues (conjunctiva, sclera and cornea) within the first 30 min of treatment, followed by particle migration into the inner tissues (retina and choroid) up to 12 h from treatment (124).

Transscleral iontophoresis may be used also for delivering oligonucleotides and genes to posterior eye segments, without losing their physical integrity or biological function. Ashara *et al.* detected short-labeled oligonucleotides and a green protein-expressing plasmid in the anterior chamber, vitreous and posterior retina at 5, 10 and 20 min after transscleral iontophoresis, respectively (108). Also, Voigt *et al.* demonstrated the ability of the transcorneoscleral iontophoresis to enhance intraocular penetration of anti-nitric oxide synthase II oligonucleotides (anti-NOSII-ODN) in a rat model of endotoxine-induced uveitis. The anti-NOSII-ODNs were detected in the iris/ciliary body and retina/choroid layers from one to six h after the transscleral iontophoresis, resulting in down regulation of NOSII mRNA in ciliary body (111). Recently, Souied *et al.* investigated the iontophoretic delivery of plasmid containing normal β-PDE (c-GMP phosphodiesterase) cDNA to the retinal photoreceptors as a potential strategy to treat retinitis pigmentosa. Three consecutive iontophoretic applications of pPDE-PDE were conducted using 200–400 μA for 5–10 min covering the cornea and sclera surface of a mutant mice model of autosomal recessive retinitis pigmentosa. Morphological examination and ERG measurements of the iontophoretic treated retinas showed substantial rescue of the photoreceptor cells from degeneration. Furthermore, the detection of cGMP-PDE subunits on a Western blot from treated retinas constituted scientific proof of the effective delivery of the β-PDE to the photoreceptor cells (140).

Toxicity

In spite of the advantage of introducing high doses of drug into the eye by iontophoresis, preventing the systemic side effects and sparing the use of intraocular injections, one should be aware of the tissue damage that high current intensity may induce. Such damage is dependent upon the site of application, the current density and the iontophoretic duration (77). Corneal opacities and burns were reported following application of iontophoresis with high current densities (141); however, a current density of up to 20 mA/cm^2 for 5 min was reported to be harmless to the cornea (142). Following transscleral iontophoresis of 5.0 mA/cm^2 for 10 min, no retinal detachment, abnormal histological findings or other intraocular complications were reported, except for slight conjunctival injection that disappeared after 8 h (137,139). Although, there are reports on safe transscleral iontophoretic procedure when using current densities lower than 50 mA/cm^2 (99), others report observing lesions, scleral burns and corneal vascularization when using 8.5 mA/cm^2 for 10 min (140) and burning sensation when applying 7.4 mA/cm^2 on humans (120). Obviously, when using high current densities of 100–700 mA/cm^2 chorio-retinal lesions, retinal and choroidal burns, hemorrhagic necrosis, edema and infiltrations were observed (91,143–145).

Clinical Studies

Several investigators conducted clinical studies using transscleral iontophoresis of the anti-inflammatory corticosteroid, methylprednisolone hemisuccinate (SoluMedrol). Chauvaud (146) *et al.* presented initial findings of Phase II clinical trial for transscleral iontophoresis of the above drug using the coulomb-controlled annular applicator. The transscleral iontophoresis was safe, well-tolerated and easily applied for the treatment of severe ocular inflammation, thereby reducing the need for systemic corticotherapy and its side effects. The same iontophoretic system and drug were used to assess the efficacy of the treatment on three subjects with acute corneal graft rejection. The patients were treated with SoluMedrol (methylprednisolone) iontophoresis (1.5 mA, 3 min) once a day as supplement to topical dexamethasone drops. The treatment was tolerable, no side effects were observed, and visual acuity improved rapidly after the second treatment (147). Behar-Cohen and Halhal *et al.* presented similar results in a study with 17 to 18 patients with acute corneal graft rejection. Iontophoretic treatment of methylprednisolone using 1.5 mA (3 mA/cm^2) for 4 min was performed once daily for three consecutive days, with no need for analgesia. Eighty-eight percent of the treated eyes demonstrated complete reversal of the rejection processes, with no significant side effects (148,149).

Saline-iontophoresis on healthy volunteers for evaluating ocular tolerance using the transscleral OcuPhor^{TM} hydrogel drug delivery applicator was reported by Parkinson *et al.* (120). Different current intensities were used (0, 0.1, 0.5, 1.0, 2.0, 3.0 or 4.0 mA) for 20 or 40 min of transscleral iontophoresis. Maximal current density applied was 7.4 mA/cm^2. The applicator and iontophoresis procedure were well-tolerated. When 4 mA current was applied, half of the subjects reported a burning sensation, which resolved after 22 h.

FUTURE DIRECTIONS AND CHALLENGES

In terms of drug delivery, the eye is a complex organ presenting a number of unique challenges. As new pharmacotherapies continue to be developed for posterior segment diseases, novel techniques for sustained intraocular delivery of drugs will be required, with preference for non-invasive methods. Ophthalmology is currently rife with many exciting opportunities for improving drug delivery for potential clinical application in cases of posterior ocular diseases, such as age-related macular degeneration, macular edema, uveitis and proliferative vitreoretinopathy (Table IV). The main goals of future development in this field are to increase bioavailability and efficacy of drugs, prolong their action, minimize side effects of current drug-delivery techniques, target the posterior segment, achieve patient compliance and also find new effective drugs/peptides to be delivered using old/new delivery systems. Apparently, no single device/technology will be sufficient to meet the range of needs, and a combination of approaches with multidisciplinary integration is required to optimize delivery to the eye.

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