Coated Microneedles for Drug Delivery to the Eye

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PURPOSE. To test the hypothesis that coated microneedles can deliver drugs into the eye via intrascleral and intracorneal routes in a minimally invasive manner.

METHODS. Solid metal microneedles measuring 500 to 750 μm in length were coated with model drugs, protein, and DNA; inserted into nonpreserved human cadaveric sclera; and imaged. Microneedles coated with sodium fluorescein were then inserted into rabbit cornea in vivo. After needle removal, fluorescein concentration in the anterior segment of the rabbit eye was measured for 24 hours. Similar experiments were performed using pilocarpine-coated microneedles, and the rabbit pupil size was monitored afterward.

RESULTS. In vitro insertion tests showed that microneedles were mechanically strong enough to penetrate into human cadaveric sclera and that the drug coating rapidly dissolved off the needles within the scleral tissue within 30 seconds after insertion. In vivo delivery from fluorescein-coated microneedles showed that fluorescein concentrations in the anterior chamber were 60 times greater than those achieved by topical application without microneedles. Similarly, microneedle delivery of pilocarpine caused rapid and extensive rabbit pupil constriction. There were no measurable inflammatory responses caused by microneedle insertion.

CONCLUSIONS. This study demonstrated for the first time that coated microneedles can deliver drugs into the eye via intrascleral and intracorneal routes. This minimally invasive approach may avoid the complications associated with intraocular injection and systemic administration. (*Invest Ophthalmol Vis Sci.* 2007;48:4038–4043) DOI:10.1167/iovs.07-0066

Drug delivery to the eye is challenging, and delivery of macromolecules to the back of the eye is especially difficult, because delivery across the cornea after topical administration has very low bioavailability, systemic delivery is often accompanied by side effects, and intraocular injections introduce safety concerns.[1–3] Therefore, improved ocular drug delivery methods are needed that locally deliver useful quantities of drugs to the eye for treatment of anterior- and posterior-segment diseases without risk of vision-threatening complications. To address this need, we hypothesize that coated microneedles can deliver drugs into the eye via intrascleral and intracorneal routes in a minimally invasive manner.

Microneedles are individual needles or arrays of micrometer-sized needles that are manufactured by adapting the tools of the microelectronics industry. Originally developed for drug delivery to the skin, microneedles have been shown to be large enough to pierce the skin and deliver a broad range of compounds, but small enough to avoid pain or significant tissue damage.[4–7]

In one scenario, the shafts of solid microneedles have been coated by drugs and then allowed to dissolve off rapidly within the skin after insertion.[8] Using this and other approaches, animal studies have shown that microneedles can deliver useful amounts of a variety of different compounds, including peptides, such as insulin, desmopressin, and human growth hormone; genetic material, such as oligonucleotides and plasmid DNA; and vaccines against diseases, such as hepatitis B and anthrax.[4,5]

In this study, we propose that microneedles can be used as a minimally invasive method to deliver drugs into the anterior and posterior segments of the eye via either intrascleral or intracorneal routes. Because microneedles penetrate just to a depth of hundreds of micrometers into the sclera or cornea, but do not cross the ocular tunic, we expect that this approach should minimize the risk of complications. In this first study to investigate microneedles for ocular drug delivery, we sought to design, fabricate, and test coated microneedles that penetrate the sclera and the cornea to deliver drugs into the eye with high bioavailability and safety.

MATERIALS AND METHODS

Microneedle Fabrication and Coating

As described previously,[8] microneedles were cut out of stainless steel sheets (SS304, 75 μm thick; McMaster Carr, Atlanta, GA) by using an infrared laser (Resonetics Maestro, Nashua, NH) and then dip-coated at room temperature using an aqueous coating solution containing 10% (wt/vol) poly-vinyl-pyrrolidone (1300 kDa; Sigma-Aldrich, St. Louis, MO) and 0.05% (wt/vol) sulforhodamine (Invitrogen-Molecular Probes, Eugene, OR), 1.0% FITC-labeled bovine serum albumin (Invitrogen-Molecular Probes) or 0.05% YOYO-3-labeled (Invitrogen-Molecular Probes) luciferase plasmid DNA (gWiz; Aldevron, Fargo, ND) for in vitro experiments, and 0.5% (wt/vol) sodium fluorescein (Sigma-Aldrich) and 10% (wt/vol) pilocarpine hydrochloride (Sigma-Aldrich) for in vivo experiments. The dose coating the microneedles was measured by dissolving the coating into deionized water and measuring the compound concentration by using fluorescence spectrometry (Photon Technology International, Lawrenceville, NJ) for fluorescent molecules or UV spectrometry (Molecular Devices, Sunnyvale, CA) for pilocarpine.

Microneedle Insertion and Delivery In Vitro

Human sclera was obtained from the Georgia Eye Bank (Atlanta, GA) with approval of the Georgia Tech IRB and stored under refrigeration without chemical fixation. Pieces of scleral tissue were cut to 0.7 × 0.7

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cm using surgical scissors and rinsed with deionized water. Adherent retina, choroid, and episclera were removed with a cotton swab. The scleral tissue was then placed on top of a hemispherical surface (0.6-cm radius), which simulated the curvature of the ocular surface.

To examine whether microneedles are strong enough to penetrate into the sclera, single, noncoated microneedles were manually pierced approximately halfway into human cadaveric sclera and then removed. The insertion site was stained with blue tissue dye (Tissue Marking Dye, Shandon, Pittsburgh, PA) for visual examination by stereomicroscopy (SZX12; Olympus, Lake Success, NY).

Microneedles were also coated with fluorescein-labeled molecules and manually inserted into the sclera. After insertion, needles were left within the tissue for 20 seconds to allow the coating to dissolve. After needle removal, the scleral tissue was placed in a sample block containing optimal cutting temperature (OCT) freezing agent (Sakura Finetechnical, Tokyo, Japan), snap-frozen in liquid nitrogen, and sectioned into 10-μm-thick pieces with a cryostat microtome (Richard Allan Scientific, Kalamazoo, MI) for histologic examination by fluorescence microscopy (IX-70; Olympus).

Microneedle Delivery of Fluorescein and Pilocarpine In Vivo

A New Zealand White rabbit (2.2 kg) was used in the study. All experiments were conducted in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the Institutional Animal Care and Use Committee of Emory University. After anesthesia, with intramuscular injection of 5 mg/kg xylazine (Butler, Columbus, OH) and 35 mg/kg ketamine (Bedford Laboratories, Bedford, OH), a microneedle coated with 280 ± 14 ng of fluorescein was manually inserted in the upper region of the cornea to a depth approximately halfway into the cornea, left in place for 2 minutes, and then removed. The fluorescein concentration in the anterior segment of the eye was measured periodically with a fluorometer (Ocumetrics, Mountain View, CA). Using the confocal properties of the fluorometer, we generated a fluorescein concentration profile along the visual axis from the corneal surface to the lens at each measurement.

As a negative control, fluorescein concentration in the untreated eye was also monitored. As a positive control, a 50-μL drop of fluorescein solution (Sigma-Aldrich) was applied topically to the rabbit's eye. The topical drop had a concentration of 60 μg/mL, and therefore a dose of 3 μg fluorescein. To generate three replicates of each experimental condition, the animal was returned to its cage and given a recovery period of >24 hours before the next experiment was performed on the untreated eye.

To assess delivery of a bioactive drug, five microneedles, each coated with 1.1 ± 0.5 μg pilocarpine, were individually inserted halfway into the cornea with the rabbit under anesthesia and then removed after 20 seconds. The needles were spaced approximately 4 mm apart in a radial pattern around the center of the cornea. Pupil diameter was measured over time to assess pilocarpine-induced constriction.[9,10] Experiments were performed in a bright room with consistent light intensity.

As a negative control, pupil size of the untreated eye was measured at the same time points. As positive controls, a 50-μL drop of 0.01% (wt/vol) pilocarpine (Sigma-Aldrich) solution (5 μg pilocarpine) was topically applied to the eye, and a 50-μL drop of 1% (wt/vol) ophthalmic pilocarpine (Falcon Pharmaceuticals, Fort Worth, TX) solution (500 μg pilocarpine) was topically applied to the eye.

Safety Examinations

To assess possible damage to the eye, single, uncoated microneedles were inserted into the cornea of an anesthetized rabbit. After insertion, the eye was periodically examined by a clinical ophthalmologist who used a slit lamp to identify (1) whether a hole remained in the cornea at the site of insertion and (2) whether there was any inflammatory response, as indicated by the occurrence of anterior chamber cells or

flare.[11] Before each examination, a drop of fluorescein solution (0.5% wt/vol; Falcon Pharmaceuticals) was applied topically to stain sites of corneal damage.

Results and Discussion

Characterization of Coated Microneedles

Single, solid microneedles were made by laser-cutting the needle structures from stainless-steel sheets (Fig. 1). Guided by the average human scleral thickness of 600 μm[12] and possible tissue deformation during the needle insertion, the microneedles used for in vitro scleral insertion tests were 750 μm in length, 200 × 50 μm in width along the shaft, and 55° in tip angle. For the in vivo rabbit experiments, the microneedles were modified to 500 μm in length, 100 × 50 μm in width along the shaft, and 45° in tip angle, to avoid penetration through the thinner rabbit corneal tissue.

We envisioned delivering drugs into sclera and cornea by covering microneedles with a stable drug coating that can rapidly dissolve off the microneedle on insertion into tissue. Toward this end, dip coating was used to coat microneedles with sodium fluorescein (Fig. 2A), bovine serum albumin (Fig. 2B), and plasmid DNA (Fig. 2C). This shows the versatility of coated microneedles that can be used for applications involving many different types of molecules. Arrays of multiple microneedles were also coated (Fig. 2D).

In Vitro Microneedle Insertion

To determine whether microneedles are strong and sharp enough to insert into sclera and cornea, noncoated microneedles were manually inserted into human cadaveric sclera. Topical staining with a blue dye identified the site of microneedle insertion into the tissue, having a width of ~100 μm and a depth of ~300 μm (Fig. 3A), which indicates that the microneedle penetrated into the middle of the sclera and did not pierce across it, which is important for safety. Microneedles were similarly shown to insert into rabbit cornea in vitro (data not shown).

As a model for drug delivery, the sclera was pierced with sulforhodamine-coated microneedles for 20 seconds and then removed. The representative histologic image shown in Figure 3B indicates that the sulforhodamine coating was deposited to a large extent within the microneedle hole, which shows that

FIGURE 1. Brightfield microscopy image of a single solid stainless-steel microneedle used for intrascleral and intracorneal drug delivery shown next to a U.S. penny for size comparison. *Inset*: magnified view of the needle, which is 500 μm in length and 45° in tip angle.
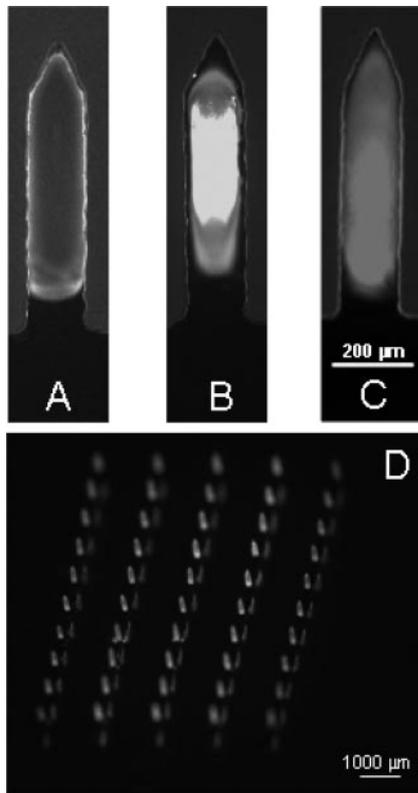
FIGURE 2. Microneedles coated with model drugs, including (**A**) sodium fluorescein, (**B**) fluorescein-labeled bovine albumin, or (**C**) fluorescein-labeled plasmid DNA, using a dip-coating method. (**D**) A 50-needle array of microneedles coated with sodium fluorescein, which exhibited good needle-to-needle uniformity and no contamination of the base substrate with excess coating material.

the coating was rapidly dissolved off the needle shaft within the sclera. In a parallel experiment, bovine serum albumin-coated microneedles were inserted into human cadaveric sclera and shown to deposit the albumin within the tissue (Fig. 3C). Similar results were found for insertion and delivery of model drug coatings into rabbit cornea in vitro (data not shown).

After each insertion and delivery experiment, microneedles were examined microscopically for mechanical defects. Neither needle breakage nor bending was observed, which suggested that microneedles were sufficiently strong and sharp to penetrate into rigid scleral and corneal tissues. Evidence of residual coating, however, was typically seen on the bottom half of microneedle shafts, probably because of incomplete microneedle insertion into the tissue. Compared with our previous experience with microneedle insertion into skin,[13] insertion into scleral tissue required greater force, which is consistent with anatomic and physiological differences between these tissues that give the sclera greater mechanical strength.[14]

In Vivo Fluorescein Delivery

To determine whether coated microneedles can deliver a model drug into the eye in vivo, single microneedles coated with 0.28 µg of sodium fluorescein were inserted into the cornea of an anesthetized rabbit. To facilitate fluorometric analysis and imaging, we chose to deliver fluorescein into the optically transparent cornea, rather than the sclera. After a single fluorescein-coated microneedle insertion, fluorescein concentration in the anterior segment was monitored for 24 hours.

The measured fluorescein concentration over time was plotted as a function of distance along the visual axis from the cornea to the lens in the rabbit eye using a confocal fluorometric apparatus (Fig. 4A). Before microneedle insertion, minimal background fluorescence was detected in the aqueous humor. Just 1 minute after microneedle insertion, a sharp increase of intraocular fluorescein concentration was observed. Fluorescein concentration further increased, peaked at 3 hours, and then gradually decreased to background levels within 24 hours. These fluorescein concentration profiles suggest that after the fluorescein coating dissolved off the microneedle (within seconds), a depot was formed within the cornea, which steadily released fluorescein into the anterior segment for hours.

For comparison, we applied a conventional topical fluorescein eye drop and similarly measured fluorescein concentration in the rabbit eye over time. However, there were only very
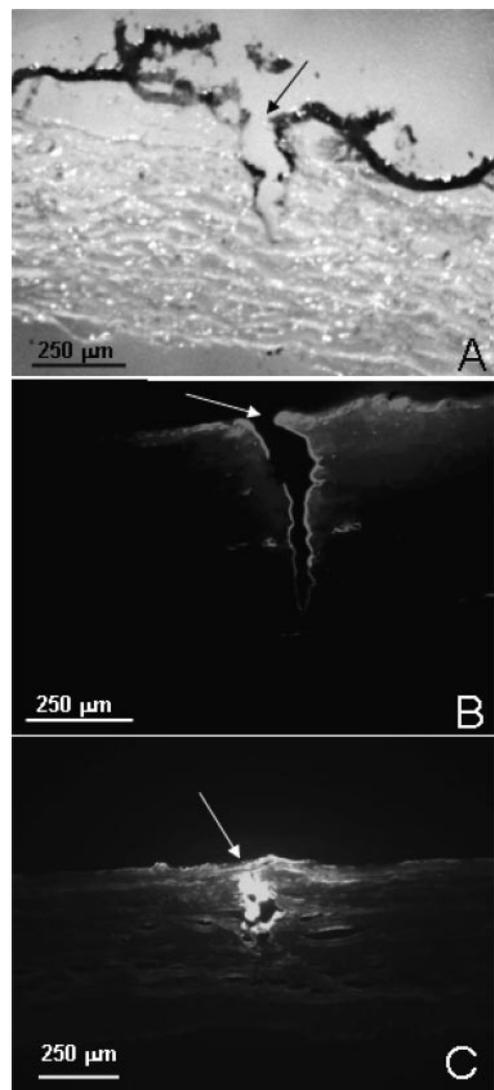

FIGURE 3. Histologic sections of human cadaveric sclera pierced with a single microneedle (750 µm in length and 55° in tip angle). (**A**) An uncoated microneedle was inserted into the sclera and removed. The sclera was then stained with a blue tissue-marking dye to identify the site of penetration. Microneedles coated with (**B**) sulforhodamine and (**C**) fluorescein-labeled bovine serum albumin were inserted to deposit their model drug coatings within the sclera. *Arrow*: site of microneedle insertion through the scleral surface.
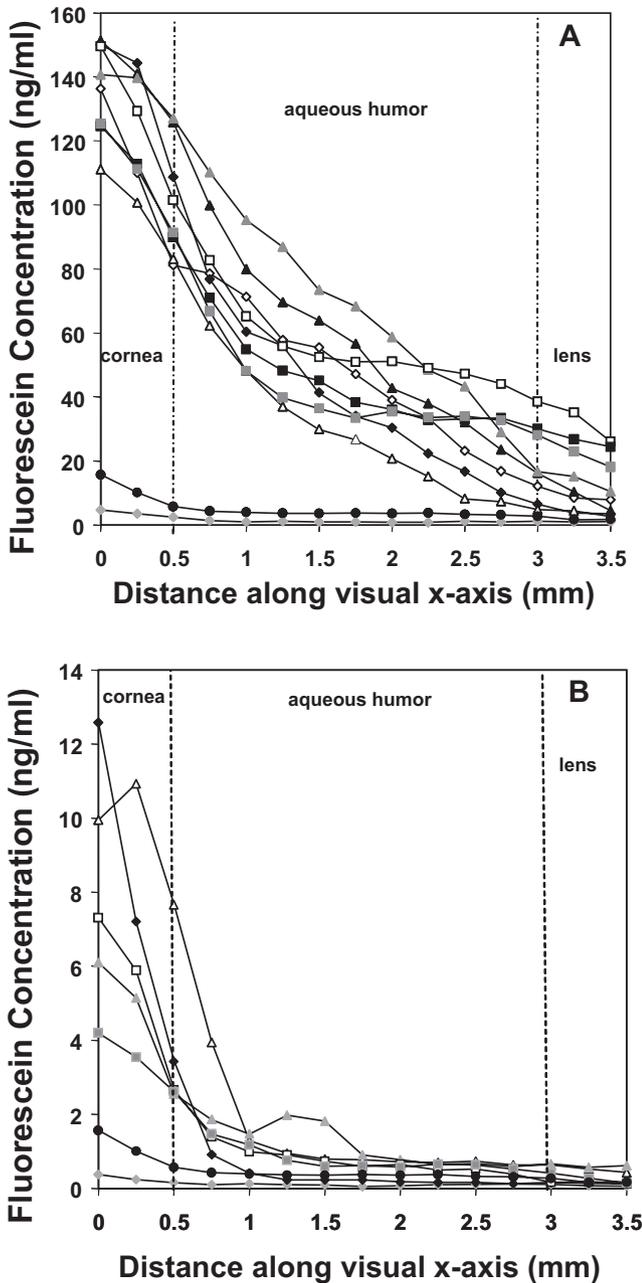
FIGURE 4. Representative fluorescein concentration profiles in the rabbit eye in vivo as a function of time and position in the anterior segment after (**A**) fluorescein-coated microneedle delivery and (**B**) topical administration of an equivalent dose of fluorescein. Measurement times were before treatment (*gray diamond*) and 1 minute (*open diamond*), 30 minutes (*black diamond*), 1 hour (*open triangle*), and 2 (*black triangle*), 3 (*gray triangle*), 4 (*open square*), 5 (*black square*), 6 (*gray square*), and 24 (*black circle*) hours after treatment. Topical administration was performed with a dose of 3.0 μg, which is 11-fold greater than the 0.28-μg dose delivered by the microneedle. Assuming a proportional relationship between the topical dose delivered and the fluorescein concentration, the *y*-axis values in (**B**) have been divided by 11 to give the fluorescein concentration profile expected for topical administration of 0.28 μg, which provides a more appropriate comparison with microneedle delivery at the same dose.

low levels of fluorescein delivery to the aqueous humor after topical delivery of an equivalent dose of fluorescein (Fig. 4B).

Using representative data like those shown in Figure 4, we combined concentration profiles from multiple experiments,

to determine the average fluorescein concentration in aqueous humor over time (Fig. 5). The improved efficiency of microneedle delivery is evident, showing that microneedles delivered much more fluorescein into the eye over a longer period. For example, at 3 hours after application, intraocular fluorescein concentration produced by a single coated microneedle was 60 times higher than that from topical delivery of an equivalent dose. Moreover, statistical analysis shows that the average fluorescein concentration depended significantly on time after microneedle delivery (ANOVA, $P < 0.01$), but did not after topical application (ANOVA, $P = 0.12$).

In Vivo Pilocarpine Delivery

To further assess microneedles for ocular drug delivery, we coated five microneedles with pilocarpine, a drug known to cause pupil constriction and used in treatment of glaucoma,[9,10] and inserted them into rabbit cornea in vivo. Pupil size was measured over time (Figs. 6, 7). In the negative control animal that received no treatment, pupil size remained unchanged. Microneedle delivery of pilocarpine caused pupil constriction from 8- to 5.5-mm diameter within 15 minutes. Topical delivery of an almost identical dose of pilocarpine caused pupil constriction to just 7 mm with slower kinetics. As a positive control, topical delivery of a pilocarpine dose more than 90 times greater than the microneedle dose caused pupil constriction to 4 mm with similar kinetics. ANOVA analysis showed that changes in pupil diameter over time were all different from each other among the four experimental conditions ($P < 0.0001$). Altogether, these data show that microneedles are capable of delivering a bioactive drug to the eye with improved efficacy relative to topical administration of the same dose.

Safety Examination

As an initial assessment of the safety of microneedle insertion, single, noncoated microneedles were inserted into rabbit cornea in vivo. Slit lamp examination of three treated eyes coupled
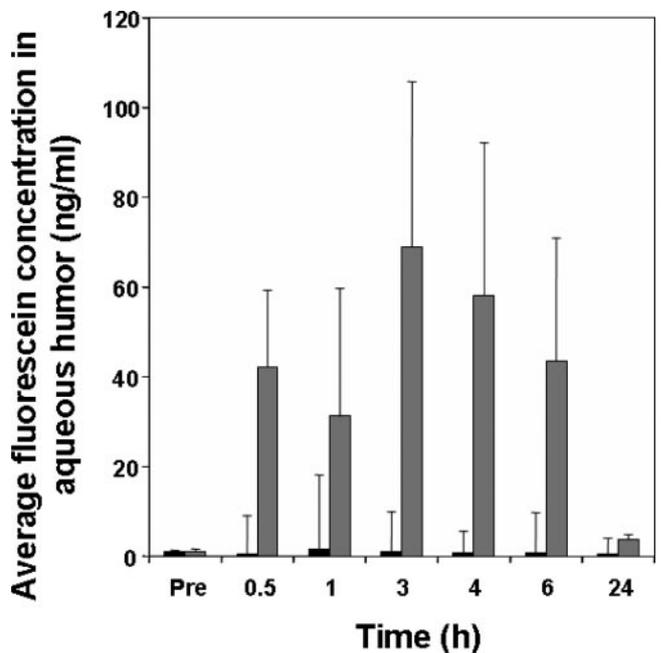

FIGURE 5. Average fluorescein concentration in the anterior chamber of the rabbit eye delivered by microneedle insertion (*gray bars*) and topical administration of an equivalent dose (*black bars*) as a function of time after treatment. Data represent the average of four measurements. Error bars, SD.
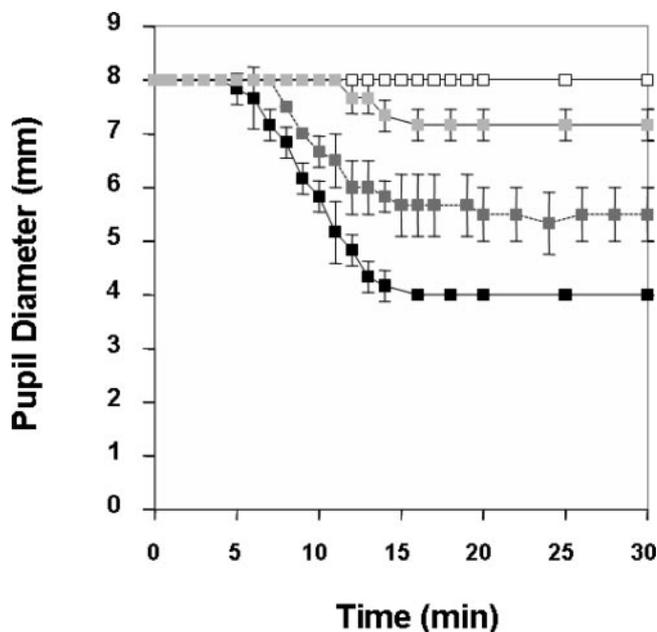
FIGURE 6. Changes in rabbit pupil diameter over time in an untreated eye (*open square*) and in eyes treated with a topical application of 5 μg pilocarpine (*light gray square*), microneedles coated with 5.5 μg pilocarpine (*dark gray square*), and a topical application of 500 μg pilocarpine (*black square*). Data represent the average of at least three measurements. Error bar, SD.

with topical application of sodium fluorescein to stain sites of corneal damage identified a small abrasion at the site of microneedle insertion, which disappeared after 3 hours, indicating resealing of the hole, perhaps by epithelial cell migration and restitution.[15] At all times, there was never evidence of an inflammatory response, as shown by lack of anterior chamber cells and flare. Overall, no adverse effects were seen in any experiments in this study. Although this analysis suggests that microneedle insertion into the eye may be well tolerated, additional studies are needed to assess safety more fully.

Microneedle Delivery Efficiency

To determine the total dose of fluorescein delivered into the eye after microneedle treatment, we used a one-compartment pharmacokinetic analysis of the in vivo fluorescein delivery data (see Appendix I, online at http://www.iovs.org/cgi/content/full/48/9/4038/DC1). Using equation 5 in Appendix I to analyze experimental data shown in summary form in Figure 5, the total fluorescein delivered into aqueous humor was calculated as 196 $\pm$ 15 ng, which represents 69% bioavailability of fluorescein coated on the microneedle. Performing similar pharmacokinetic analyses of our data for topically applied fluorescein yields a bioavailability of just 1%.

We also carried out an in vitro experiment to directly measure the fluorescein delivered into rabbit cadaver cornea from fluorescein-coated microneedles, and closed the mass balance by also measuring the fluorescein remaining on the needle after insertion (see Appendix I, online). This analysis determined that 74% $\pm$ 27% of fluorescein coated onto the microneedle was delivered into the cornea in vitro, which is similar to the in vivo pharmacokinetic analysis.

Altogether, we conclude that most fluorescein was released from the microneedle to form a depot in corneal tissue, which provided subsequent drug release with ~70% bioavailability, representing a 70-fold increase relative to topical application. The rest of the fluorescein either remained adherent to the

microneedle or may have been washed away by the tear fluid. Alternative explanations are discussed online in Appendix II (http://www.iovs.org/cgi/content/full/48/9/4038/DC1).

To roughly assess pilocarpine bioavailability, the data show that topical delivery of 5.0 μg of pilocarpine caused pupil constriction of 1 mm and topical delivery of 500 μg of pilocarpine cause pupil constriction of 4 mm. Microneedle delivery caused pupil constriction of 2.5 mm, which, by assuming a linear dose-response relationship and performing linear interpolation of the two topical delivery doses, corresponds to topical delivery of ~250 μg of pilocarpine. Because microneedles delivered just 5.5 μg of pilocarpine, this represents a 45-fold increase in pilocarpine bioavailability relative to topical administration.

Implications for Ocular Drug Delivery

Many inflammatory and proliferative diseases in the posterior segment of the eye, such as macular degeneration and diabetic retinopathy, require long-term pharmacological treatment.[16] However, it is difficult to deliver effective drug doses to the back of the eye using conventional delivery methods such as topical application, which has poor efficacy.[17] Systemic administration often causes significant side effects. Direct injection into the eye is often effective, but requires professional training and safety is a major concern.[3]

Because of their small size, microneedles can be designed to insert into, but not across, the ocular tunic with minimized physiological damage, which should be an asset in ocular drug delivery. In this study, we demonstrated that microneedles are capable of delivering drugs into the eye via cornea or sclera in a minimally invasive way. Using a simple, aqueous, room temperature coating process with FDA-approved excipients, microneedles can be coated with compounds ranging from small
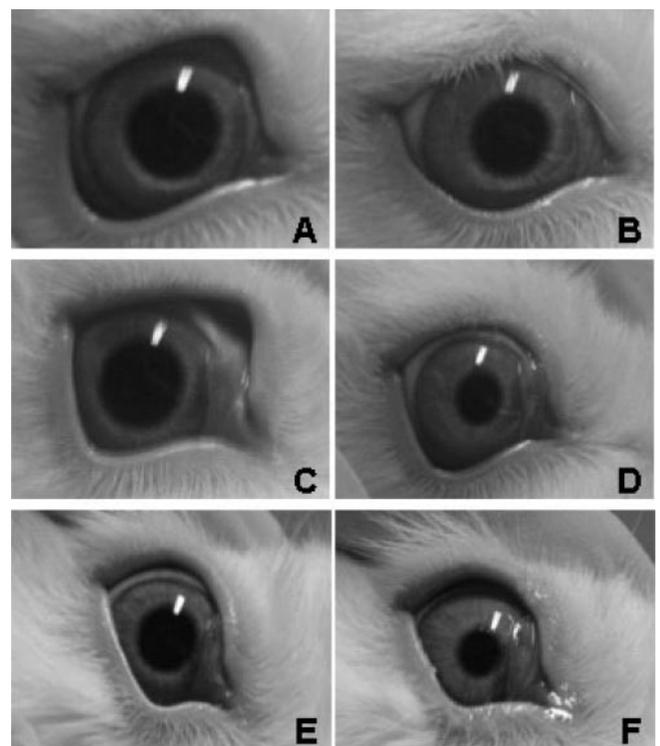

FIGURE 7. Representative images of rabbit eyes before (**A**, **C**, **E**) and 20 minutes after (**B**, **D**, **F**) topical application of 5 μg pilocarpine (**A**, **B**), microneedles coated with 5.5 μg pilocarpine (**C**, **D**), and topical application of 500 μg pilocarpine (**E**, **F**). These images are of representative rabbit eyes for which the data are presented in Figure 6.

molecules (fluorescein) to proteins (bovine serum albumin) to plasmid DNA. In vitro and in vivo studies showed that ocular tissues could be partially penetrated by microneedles and followed by deposition of drug formulations within the tissue to provide treatment for hours. Microneedles improved bioavailability by 1 to 2 orders of magnitude compared to topical application and should cause less tissue damage and risk of complications compared with intraocular injection.

CONCLUSION

This study demonstrated that coated microneedles can deliver model drugs into the eye via intrascleral and intracorneal routes in a minimally invasive manner. In vitro studies using human cadaveric sclera showed that microneedles can be designed to insert into, and not across, the sclera and to rapidly deposit coated drug formulations in the sclera, including small molecules, proteins, and DNA as model drugs. In vivo studies showed that fluorescein can be rapidly delivered into the rabbit cornea for sustained delivery for many hours from a depot formed in the cornea with approximately 70% bioavailability. Additional in vivo studies showed effective pilocarpine delivery that caused rapid and extensive pupil constriction with increased bioavailability in rabbit cornea. Slit lamp examination of microneedle-treated eyes revealed no adverse effects. This study shows for the first time that microneedles can be used for ocular drug delivery and may be applicable to minimally invasive treatment of diseases of the anterior and posterior segments of the eye.

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