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An ocular iontophoretic device using PEDOT electrode for local drug delivery

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ABSTRACT

An ocular iontophoretic device using a biocompatible planar PEDOT electrode is reported. *In vivo* experiments on rabbit eyes demonstrated that the device can realize ocular iontophoresis effectively, simply, and conveniently. Compared with conventional eye cups, this device can be placed under the eyelid and deliver ions through a small area on the eyeball, reducing tissue damage during ion penetration. Devices were fabricated in different sizes for different cases. The efficiency was a function of the current, work time and solvent water content. The highest iontophoretic efficiency observed in the *in vivo* experiments was 396 ng/mL, while the efficiency observed in the controlled experiments was only 2.69 ng/mL. The temperature distribution was simulated and measured, and thermal injuries were not observed under an applied current of 1.5 mA.

1. Introduction

Iontophoresis is an ion delivery method in which a small electric current is applied to enhance ion penetration into a tissue [1–3]. Over the past few years, it has received increasing attention among researchers as a new non-invasive technique for ionized drug delivery. In particular, ocular iontophoresis has great significance in the treatment and diagnosis of eye diseases. Compared with drug delivery in other parts of the body, however, ocular iontophoresis is faced with more challenges due to the barriers in and fragility of the eyes.

Majority of the reported iontophoretic devices [4–7] had to be pressed onto the eye manually and delivered the drug through a large area on the eyeball. In some cases, the delivered ions could damage the sensitive cornea or sclera. For example, Mn^{2+}, as a tracer to detect eye diseases, could harm the corneas during penetration. Additionally, the electric field in the reservoir was produced by a probe-type electrode, which was less homogeneous than a planar electrode. Recently ocular drug delivery devices and systems based on Micro-Electro-Mechanical Systems (MEMS) technology [8–11] were also investigated, but most of them were invasive and iontophoresis was difficult.

In our previous work, a simple PDMS-based device with a planar PEDOT electrode was proposed and the preliminary results was reported in Ref. [12]. In this paper, the more technical details and latest results, including the simulation of the concentration and the thermal effect analysis, are presented. The device can be placed under the eyelid and deliver the ions through a small area. Devices were fabricated in different sizes for different cases. The electrical characteristics of the device were tested and *in vivo* experiments were conducted on rabbit eyes, which showed that the device can enhance the penetration of the ionized drug into the eyeball. The thermal effects were also analyzed to assess the possible damage that occurred during the iontophoresis process. The simulated temperatures in response to different currents and times coincided with the tested values in *in vivo* experiments.

2. Principle and simulation

The principle of the device is schematically shown in Fig. 1. As the micro-fabrication technology was utilized, the device based on PDMS in a cup shape with a planar PEDOT electrode can be realized in a small size with the external diameter of 4–6 mm and 2–4 mm inner diameter of the reservoir. The ionized or charged drugs should be dropped to the eye under the eyelid, and can be supplied by

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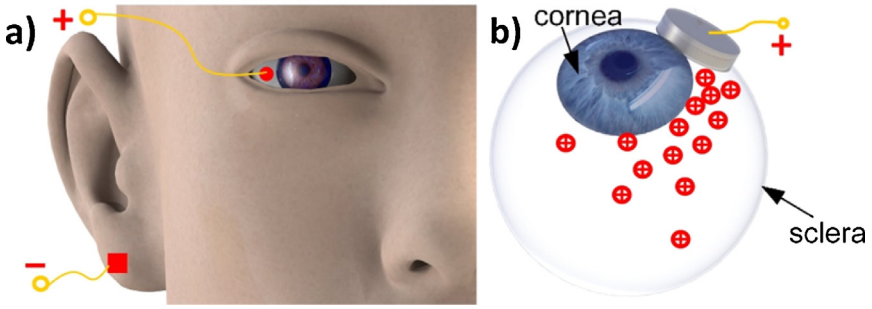

Fig. 1. Schematic view of the ocular iontophoretic device. The device can be placed on a small area of the eyeball and the ions can be driven into the vitreous cavity by an electric field, penetrating the corneal epidermis.

more drops added around the device in the eye. The reservoir of the device is also filled with the solution and the device was seated on the sclera of the eye as anode or cathode, while the other electrode is connected on the ear. Applied current in several milliampere, ions or charged molecule in the liquid can be driven into the vitreous cavity by the electric field through iontophoresis, penetrating the corneal epidermis. In our cases, the device is used as the anode while the electrode on the ear is used as the cathode. The positive ions can be driven under 1–2 mA with the safe voltage of 2–5 V. The ion distribution and the temperature during iontophoresis were simulated.

2.1. Ion concentration simulation

To study the diffusion of the ions in response to an electric field, the concentration distribution was simulated by the COMSOL software, as shown in Fig. 2. In the model, considering the symmetry of the structure, the eyeball was constructed as a 2-D circular shape with a 12 mm radius in order to simplify the calculation. A 0.2 mol/L Mn^{2+} solution was used as a source of ions with a constant concentration, at the outside surface with 4 mm in length, referring to the size of the device. The concentration distribution was measured after 300 s of free diffusion without an electric field, as shown in Fig. 2(a), and the average concentration of the eyeball was calculated with the result of 5.6 ng/mL. Contrastively, Fig. 2(b) shows the results in response to an applied current of 1 mA for 300 s and the average concentration is 194 ng/mL, which indicates that the diffusion distance is obviously increased under the electric field. For further simulated, Fig. 3(c) shows the free diffusion results for 600 s, while Fig. 2(d) shows the results in response to an applied current of 1 mA for 600 s. The average concentration of the eyeball in the model is 11.2 ng/mL without an electric field and 389 ng/mL under 1 mA current.

Also, the concentrations at 1 mm, 2 mm, and 3 mm diffusion depth varied as a function of time in response to the 1 mA current and are shown in Fig. 2(f); these concentrations were also far greater than those, in Fig. 2(e). The distribution results of the simulation also indicated that free diffusion time was required for a uniform ion distribution after 600 s of iontophoresis.

2.2. Thermal effects simulation

The temperature increases due to the heating effect of current, leading to heat injury during iontophoresis. The thermal effects of our device were simulated under various current intensities to analyze the temperature and ensure that the tissue would not suffer heat injury, which can help us design the ranges for the current intensity and time duration in the *in vivo* experiments.

The contact resistance between the device and eyeball generated heat and increased the local temperature when a current was applied. A device with an inner diameter of 4 mm and a thickness of 1 mm was used in the simulation model, and the thickness of the PEDOT electrode layer was 50 μm. Using a Joule heat model and applying current on a cross-section of the wire, a stationary temperature distribution and a general heating process were obtained. Using 1 and 1.5 mA currents for 600 s, the local highest temperatures around the PEDOT electrode are 36.96 °C and 39.86 °C, respectively, as shown in Fig. 3(a) and (b). Using a 2 mA current for 600 s, the temperature is 43.68 °C, as shown in Fig. 3(c). Additionally, the temperature in response to a 2.5 mA current only for 180 s is 42.10 °C (Fig. 3(d)).

3. Experimental procedure

3.1. Device fabrication

PEDOT: PSS solution was prepared as described below. The experiment started with 1 mL of Clevios PH1000, in which the volumetric ratio of PEDOT (poly(3,4-ethylenedioxythiophene)) to PSS (poly(sodium-*p*-styrenesulfonate)) was 1:1.25. Five vol% DMSO (dimethylsulfoxide) was added to enhance the conductivity and 0.5 vol% GOPS ((3-glycidyloxypropyl)trimethoxysilane) added to improve stability. 2 mL of IPA was also added to adjust the surface tension and improve the coating properties, without significantly changing the conductivity.

The schematic in Fig. 4 illustrated the simplified device fabrication process. The PDMS wafer was first cut into a circular chip. Approximately 0.5 mL of the PEDOT:PSS solution was dripped and spread on the PDMS chip, and the chip was heated on a hot plate for 30 min at 150 °C to form a dried film on the surface of the chip (Fig. 4(a)). Next, a thin copper wire was fixed on the opposite surface of the chip and connected to the dried PEDOT film by electrargol (Epotek H20E), as shown in Fig. 4(b). Then, a piece of annular PDMS with the same external diameter as the chip was bonded to the PEDOT film by half-polymerized PDMS (Base: Curing = 8:1, in mass; heated for 25 min in 60 °C) or medical silica gel, as shown in Fig. 4(c). The bottom and the side face of the device was wrapped with half-polymerized PDMS or medical silica gel for biocompatible isolation (Fig. 4(d)), and the whole device was heated for 60 min at 60 °C in an oven.

The devices were fabricated in different sizes for different cases, three of which are shown in Fig. 5(a). In the subsequent *in vivo* experiments, the device with an inner diameter of 4 mm and thickness of 1 mm was tested as an example. The device can be placed under the eyelid of the rabbit during the experiments, as shown in Fig. 5(b) and (c).

3.2. Testing the properties of the device

To study the electrical characteristics of the devices, they were tested in 0.9% normal saline using a semiconductor parameter analyzer (HP 4156B). The device using in the following experiments

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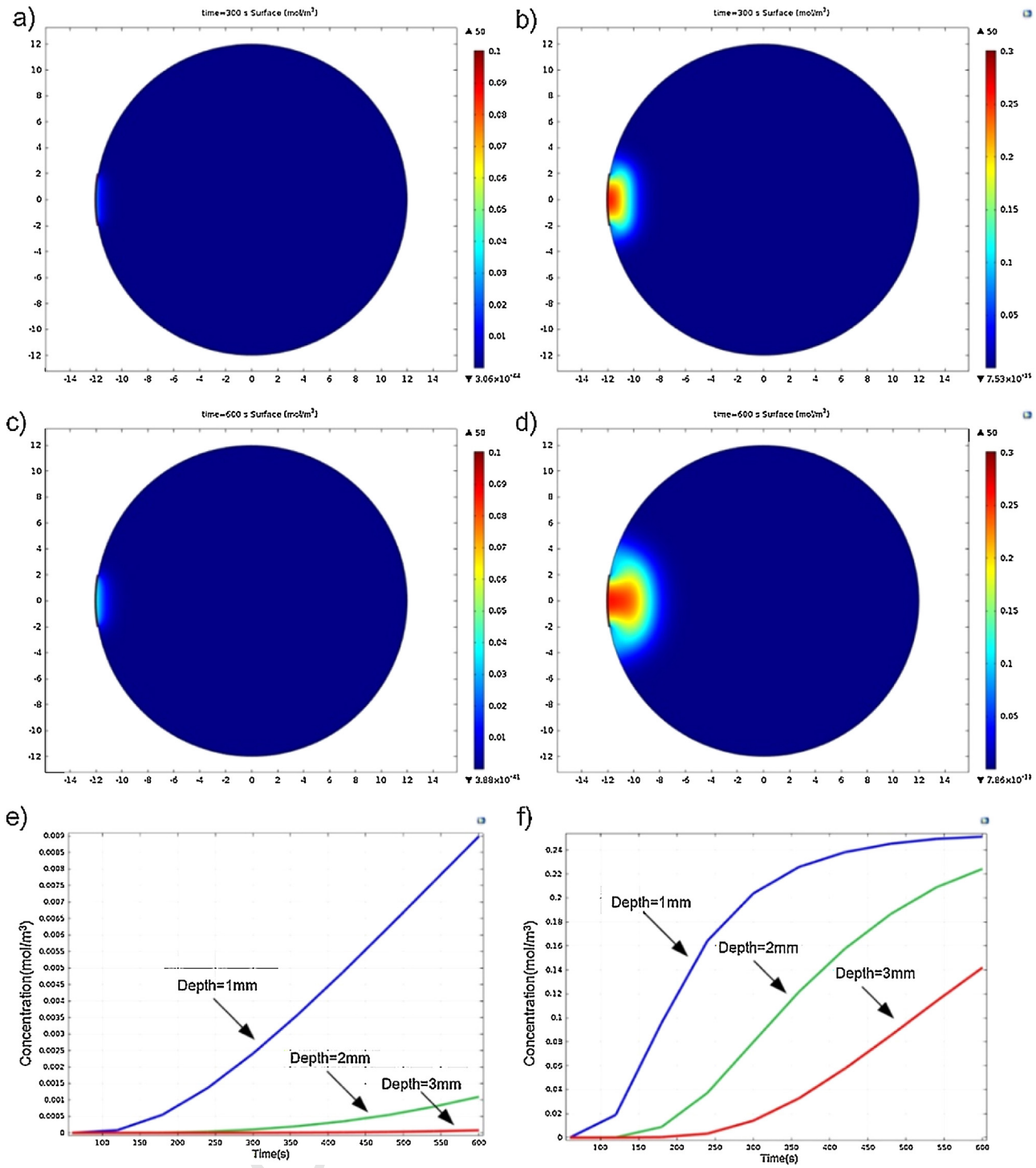

Fig. 2. The concentration simulation of the iontophoresis: (a) concentration distribution for 300 s using free diffusion without current applied, (b) concentration distribution for 300 s using 1 mA current, (c) concentration distribution for 600 s using free diffusion without current applied, (d) concentration distribution for 600 s using 1 mA current, (e) varying concentrations as a function of time using free diffusion without voltage, and (f) varying concentrations varied as a function of time using 1 mA current.

was tested for five times to ensure the stability I–V characteristics. Using Voltammetry, the current intensities were recorded using voltages ranging from −1 V to 1 V.

Cyclic voltammetry and the AC impedance method were introduced to analyze the electrochemical properties of the electrode. The electrochemical properties were tested using a CHI 660 electrochemistry work station (CH Instruments Co., USA) connected to a computer and a three-electrode system in PBS solution (0.01 M, pH 7.4), where the PEDOT electrode was used as the working electrode, a platinum wire as a counter electrode and an Ag/AgCl electrode as the reference electrode. Cyclic voltammetry was performed in the range from −0.5 V to 0.5 V at a scan rate of 0.05 V/s, and the AC impedance method was performed using frequencies ranging from 10^2 Hz to 10^5 Hz.

3.3. In vivo *experiments*

Fig. 5(d) shows the design of the *in vivo* experiments. Healthy New Zealand white rabbits weighing approximately 2 kg were used in the experiments. Five minutes before the iontophoresis began,

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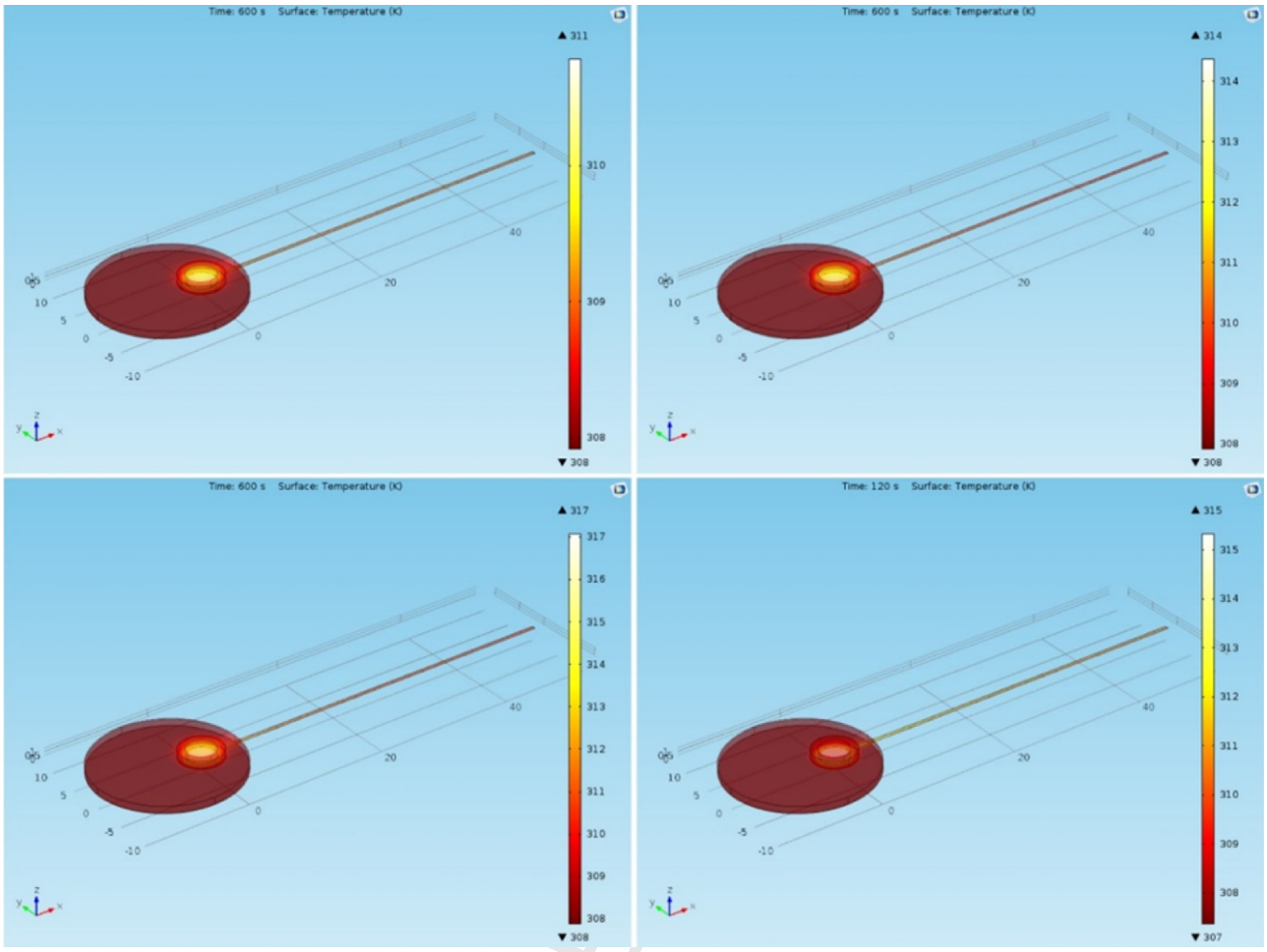

Fig. 3. Thermal effect simulation results: (a) $I = 1$ mA, $t = 600$ s and $T = 36.96\,^{\circ}$C; (b) $I = 1.5$ mA, $t = 600$ s and $T = 39.86\,^{\circ}$C; (c) $I = 2$ mA, $t = 600$ s, and $T = 43.68\,^{\circ}$C; (d) $I = 2.5$ mA, $t = 180$ s, and $T = 42.10\,^{\circ}$C.

the rabbit received general anesthesia. 150 μL of 0.2 mol/L $MnCl_2$ solution was dropped into the eye of the rabbit, and the reservoir of the device was also filled with the solution. The device was seated on the sclera of the right eye as the anode, while the cathode was on the left ear. The hair was removed from the rabbit's left ear and a piece of medical cotton infiltrated with normal saline was seated between the cathode clamp and the bare rabbit ear to reduce the contact resistance. Then, a direct current was applied to the device for iontophoresis. However, current was not applied to the left eye, which served as the control group. To study the individual influences of the current intensity and time a fixed time of 600 s and 0.5 mA, 1 mA and 1.5 mA currents were used in one experiment, while a fixed current of 1 mA and times of 60 s, 300 s and 600 s were tested in another experiment.

To identify more effective methods, medical hyaluronate gels with $MnCl_2$ were introduced to replace the $MnCl_2$ solution. In this case, the gels only needed to be placed into the device reservoir, but not into the eye, which simplifies the operation. Evy gel, containing 0.88 mol/L MnCl2, and Vioscoat gel containing 0.95 mol/L MnCl2,

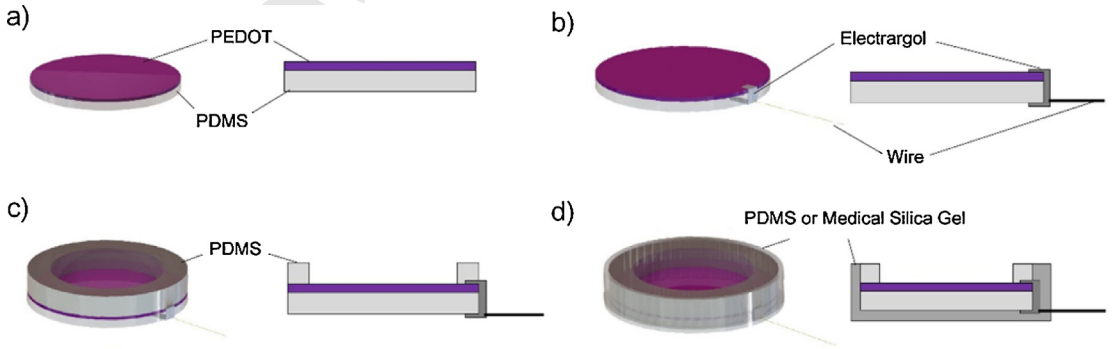

Fig. 4. The schematic of the fabrication process includes the 3D sketch (left) and sectional view (right) in each figure: (a) constructing the PEDOT film on a piece of PDMS; (b) connecting a wire to the dried PEDOT film by electrargol; (c) bonding with a piece of annular PDMS; and (d) wrapping the bottom and the side face of the device with half-polymerized PDMS or medical silica gel for insulation.

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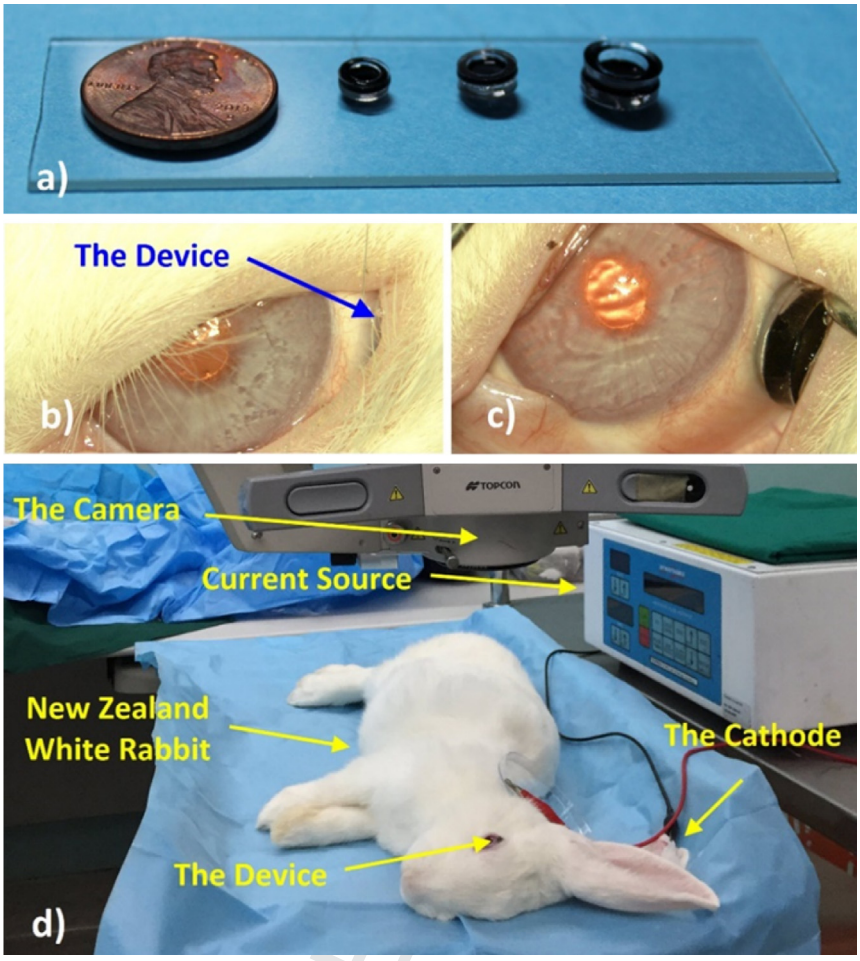

Fig. 5. Photos of the experiments: (a) the fabricated devices in different sizes; (b) and (c) the device under the eyelid; (d) the experimental setup.

were used and iontophoresis was tested for 600 s using a current of 1 mA.

After iontophoresis and a 30-min incubation to allow the ions to diffuse in the vitreous cavity, the vitreous humor was extracted and Mass Spectrometry was performed to detect the concentration of Mn^{2+}.

4. Results and discussion

4.1. Device properties

As shown in Fig. 6, the I–V curves of the device tested in 0.9% normal saline show a nonlinear voltage-current relationship and the low DC resistance of the device using a voltage of 1 V. The current was less than 1 mA when the voltage was under 1 V. The device was tested five times shown as I1–I5, which show that the device can keep a stable I–V characteristics during the *in vivo* experiments.

The cyclic voltammetry results for the PEDOT electrode and a comparison with a platinum (Pt) electrode are shown in Fig. 7(a). The charge delivery capacities were calculated, using the formula

$$Q_{CDC} = \frac{1}{v}\int_{E_c}^{E_a} |i| dE \left(\frac{mC}{cm^2}\right),$$

where E is the electrode potential (*vs.* Ag/AgCl), i is the measured current density, E_a and E_c are the anodic and cathodic potential limits, respectively, and v is the corresponding scan rate [13]. It shows that the PEDOT electrode has a higher charge capacity (5.5 mC/cm^2) than the Pt electrode (2.1 mC/cm^2), and the latter is a widely used bio-electrode.The electrochemical impedance spectroscopy (EIS) of the PEDOT electrode obtained by the AC impedance method, including the amplitude and the phase, shows that the PEDOT electrode has low impedance and exhibits both capacitive and resistive characteristics using a 1 KHz frequency (Fig .7(b)). The electrochemical properties of the electrode indicate that the device can still work well for iontophoresis using a double-pulse current (usually with a frequency of 1 KHz), which means reduced electric

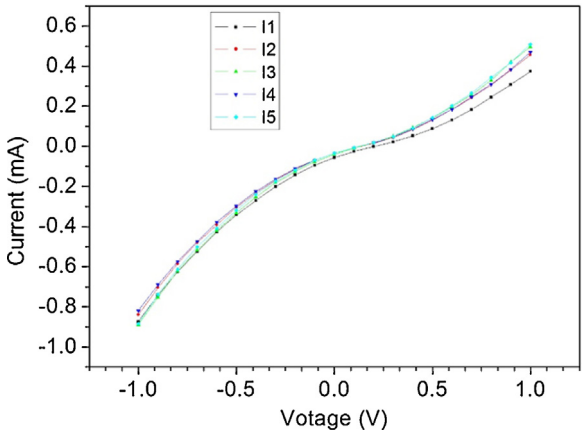

Fig. 6. Electrical characteristics testing results: the voltage current curves of the device was tested in normal saline for five times, shown as I1–I5.

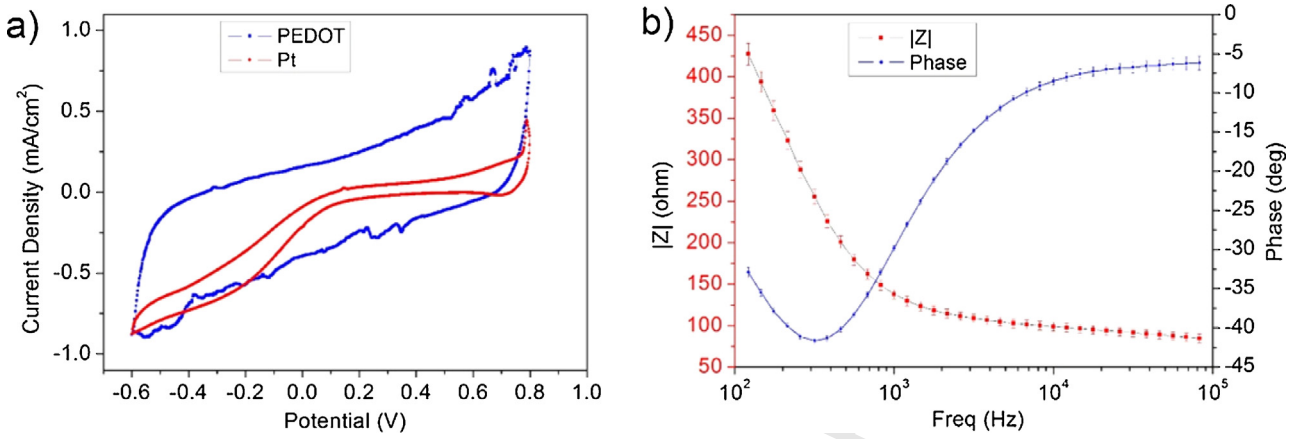

Fig. 7. The electrochemical properties of the device. (a) The cyclic voltammetry testing result and (b) the impedance of the device.

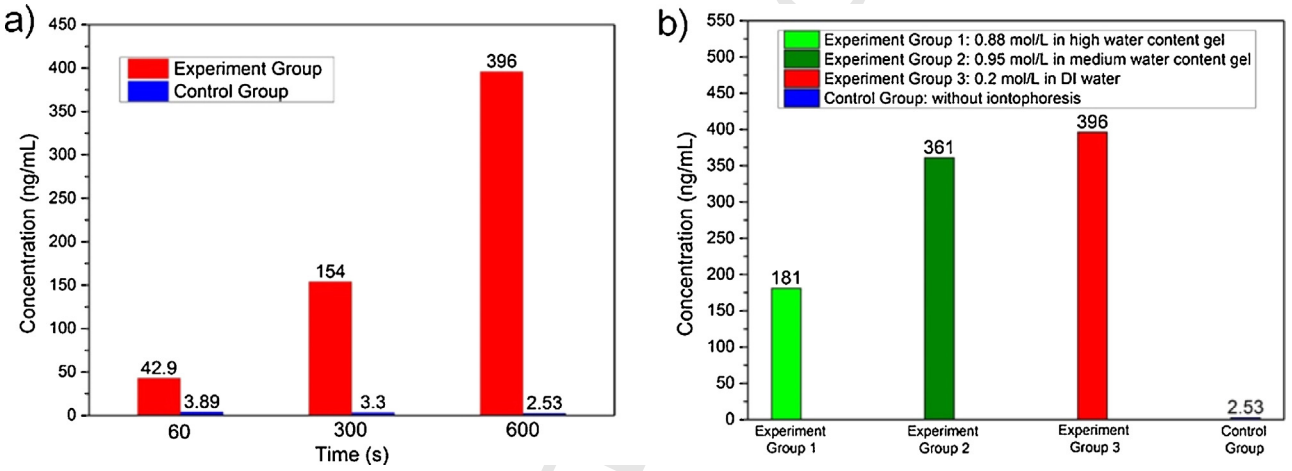

Fig. 8. Iontophoresis efficiency (a) for different working time using 0.2 mol/L Mn^{2+} in DI water, and (b) in different solvents for 600 s.

current damage compared with the constant current. The PEDOT and PDMS used in the device are both known to be stable, biocompatible materials. Combined with the electrical and electrochemical characteristics, these results suggest that the device can work well in the *in vivo* experiments. The electrical and electrochemical properties of the device can also be controlled by the thickness of the PEDOT:PSS film for different demands.

4.2. In vivo *iontophoresis*

The Mn^{2+} concentrations in response to different currents or times are shown in Table 1 and Fig. 8(a). It shows that the devices have an obvious effect on ocular iontophoresis. The highest efficiency was 396 ng/mL using a 1 mA current for 10 min, while the efficiency in the controlled experiment without iontophoresis was only 2.69 ng/mL. Fig. 8(a) shows that the efficiency for different working time using 0.2 mol/L Mn^{2+}. Fig. 8(b) shows that the efficiency decreased as the water content of the solvent was reduced, with the same working time for 600 s. In this case, the ionization proportion decreased, even though the Mn^{2+} concentration increased, as shown in Table 1. It also showed that the efficiency increased as the working time increased.

The concentration in the simulation was 389 ng/mL and the highest one in the experiments was 396 ng/mL when using 1 mA for 600 s. Also, the concentration in the simulation is 189 ng/mL and the highest one in the experiments was 154 ng/mL when using 1 mA for 300 s. Although there still was a difference between the simulation and the experiments, the efficiency of the device was in the same order of magnitude as the results obtained in the simulation. The little difference between the simulation and the experiments caused by the ideal approximation and the estimation of the simulation model. The eyeball in three-dimensional sphere shape was simplified to a two-dimensional model. Also, the complex structure

Table 1
The Mn^{2+} concentration in the vitreous cavity in different conditions.

Number	Current(mA)	Time (s)	Mn^{2+} in the experiment eye (ng/mL)	Mn^{2+} in the controlled eye (ng/mL)	Drug solvent and concentration	Comments
Rabbit 1	0.5	600	169.40	2.14	0.2 mol/L in DI water	
Rabbit 2	1.0	600	396.32	2.69	0.2 mol/L in DI water	
Rabbit 3	1.0	600	361.89	1.7	0.88 mol/L in Evy gel	Higher water content gel
Rabbit 4	1.0	600	181.7	3.31	0.95 mol/L in Vioscoat gel	Medium water content gel
Rabbit 5	1.5	600	48.18	1.69	0.2 mol/L in DI water	
Rabbit 6	2.5	180	109.61	2.5	0.2 mol/L in DI water	Sclera damage

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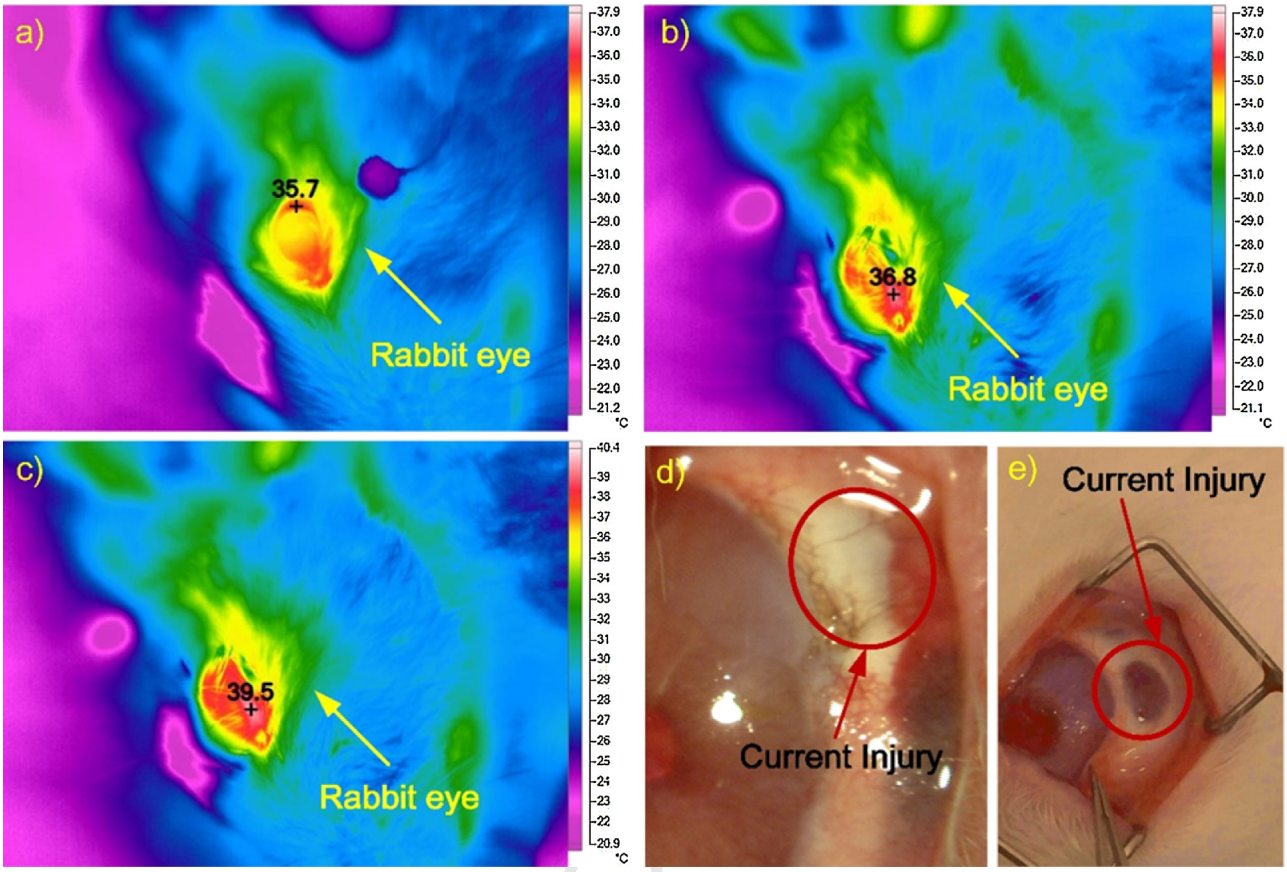

Fig. 9. Thermal effect during the iontophoresis: (a) the temperature distribution without current; (b) the temperature distribution using 1 mA for 600 s; (c) the temperature distribution using 1.5 mA for 600 s; (d) the current injury using 2 mA for 600 s; and (e) the current injury using 2.5 mA for 180 s.

inside the eyeball, which can affect the movement of the ions, was ignored.

Because of its small size, the MEMS device for ocular iontophoresis can be placed under the eyelid and deliver ions through a small settled portion on the eyeball, reducing tissue damage during ion penetration compared with conventional eye cups. The planar electrode can provide a uniform electric field in the device. Additionally, the PEDOT film can be much thinner, allowing the device to be transparent to easily monitor the condition of the sclera during the iontophoresis.

4.3. In vivo *thermal effect testing*

To study the heat injury during iontophoresis, the temperature during the iontophoresis was assessed using a thermal imager (Fluke TiX640/660). Fig. 9 shows the temperature distribution, including the point with the highest temperature, and current injury under different conditions. Without an applied current, the temperature near the canthus was the highest at 35.7 °C (Fig. 9(a)). Using 1 and 1.5 mA currents for 10 min, the highest local temperature was under the device, with temperatures of 36.8 °C (Fig. 9(b)) and 39.5 °C (Fig. 9(c)), respectively. The results show that heat injury did not occur with currents less than 1.5 mA for 600 s.

Two and 2.5 mA current densities were applied to study the thermal injury. Injury occurred when a 2 mA current was used for 600 s, as shown in Fig. 9(d), in which the highest local temperature was 40.8 °C. Using 2.5 mA current, thermal injury occurred after only 180 s (Fig. 9(e)) with 41.6 °C highest local temperature, which shows that currents more than 2 mA are not safe.

The highest local temperature was 36.96 °C under 1 mA and 39.86 °C under 1.5 mA in the simulation, while the highest temperature was 36.8 °C under 1 mA and 39.5 °C under 2 mA measured during the experiments. Also, using 2 mA for 600 s, the highest temperature in the simulation and experiments were 43.10 °C and 41.6 °C individually. Using 2.5 mA for 180 s, the highest local temperature in the simulation and experiments were 42.68 °C and 40.8 °C individually. Thus the results of the simulation and experiments were nearly coincident. The little difference between the simulation and the experiments caused by the ideal approximation of the simulation model. For example, the thermal transmission between the air and the device was not considered in the simulation but occurred in the experiments. T

5. Conclusions

An ocular iontophoretic device using biocompatible planar PEDOT electrodes was fabricated in different sizes for different cases. According to the electrical and electrochemical characteristics, the device can work well, and the *in vivo* experiments on rabbit eyes indicate that the device can realize ocular iontophoresis effectively, simply and conveniently. The highest iontophoretic efficiency observed in the *in vivo* experiments was 396 ng/mL, while the efficiency in the controlled experiment without iontophoresis was only 2.69 ng/mL. There was no heat injury during iontophoresis with the device using a current of 1.5 mA, as the local temperature was less than 40 °C.

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Biographies

Yushi Zhang was born in 1988. He received his Bachelor's degree in Science and dual-degree in Economics from Peking University in 2011. Currently, he is a Ph.D. student in the Institute of Microelectronics at Peking University under the supervision of Prof. Zhihong Li. His research is primarily focused on BioMEMS, particularly invasive devices used on the human eye.

Yao Chen received his M.Sc. degree in medicine from WenZhou Medical University in 2010. He is currently a Ph.D. student in Peking University under the supervision of Prof. Zhizhong Ma. His research activities have been focused on new ocular drug delivery systems, primarily ocular iontophoresis techniques.

Yangjia Qi received her B.Sc. degree in Microelectronics from Peking University. She was a former research assistant of Prof. Zhihong Li in the MEMS Research Center, Department of Microelectronics in Peking University. She is currently pursuing her M.Sc. degree at the University of California, San Diego, with a major in Medical Devices and Systems.

Dong Huang received his Bachelor's degree in Microelectronics from the University of Electronics and Technology of China in 2014. Currently, he is a Ph.D. student in the Institute of Microelectronics at Peking University under the supervision of Prof. Zhihong Li. His research is primarily focused on developing advanced microfluidics and BioMEMS methods, specifically for cell transfection.

Mu Yang received his M.Sc. degree at Peking University in China. His research is focused on the properties of PEDOT and microelectrode fabrication.

Xiaoxue Yu is a graduate student in the Institute of Microelectronics, Peking University, Beijing, China. Her research is focused on BioMEMS, specifically implantable devices for neural stimulation and recording.

Yuntao Hu graduated from the Second Military Medical University in Shanghai, China. He received his doctoral degree from the Peking University Health Science Center in China and was a postdoctoral research fellow in the Doheny Eye Institute, Keck School of Medicine, University of Southern California, USA. He serves as a director and associate professor in the Department of Ophthalmology, Beijing Tsinghua Changgung Hospital, Tsinghua University, China. His specialties include retinal surgeries, traumatic eye treatments, and studies of the optic nerve. His studies include micropuncture of retinal veins, transplantation of sheets of RPE and optic nerve tracing.

Zhihong Li received his B.S. degree from the Department of Computer Science and Technology, Peking University, China, in 1992. He received his Ph.D. degree at the Institute of Microelectronics, Peking University in 1997, majoring in VLSI technology and reliability. He then joined the MEMS group at this institute. He was a visiting scholar at Cornell University and the University of California, Davis from 2000 to 2004, respectively. Currently, he is a Professor at the MEMS Research Center, Institute of Microelectronics, Peking University. His research interests include the design and fabrication of Microelectromechanical Systems (MEMS), particularly BioMEMS and RF MEMS. Dr. Li has published more than 200 scientific articles in prestigious peer-reviewed journals.

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