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Magnetic micropump embedded in contact lens for on-demand drug delivery

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Abstract

In this paper, we report a thin magnetic micropump embedded in contact lens, which is capable of on-demand one-directional drug delivery. The proposed micropump can be actuated by the external magnetic field whenever needed without the need of battery. A micro check valve was integrated with the micropump for one-directional drug delivery from the micropump to the post-lens tear film. With actuation of the external magnetic field, the micro check valve is opened, and on-demand drug release can be realized. On the contrary, without an external magnetic field, the micro check valve is closed, and the undesired drug diffusion can be prevented. Through the control of the strength and the frequency of the magnetic field pulse, on-demand drug release and controlled dose can be realized.

Keywords: Magnetic micropump, Contact lens, Drug delivery

Introduction

In the recent decades, ophthalmic drug delivery has been extensively studied, but the drug delivery to the anterior chamber of eye is still a very challenging task [1–3]. The conventional methods for ophthalmic drug delivery are almost instilling eye drops into the eyes. Although these methods are relatively easy for drug delivery, they are accompanied by several disadvantages: low bioavailability to target ocular tissue, due to various pre-corneal loss factors, such as tearing and blinking, non-productive absorption through conjunctiva [4–6]. Thus, the eye drop therapy has a very short drug residence time in the tear film (1–3 min), and consequently a very-low bioavailability (1–3%). Hence, high dose and dosing frequency of eye drops is prescribed to compensate for the low bioavailability, but it causes the side effects and reduces patient compliance [7, 8]. To address these drawbacks, therapeutic contact lenses have been proposed for ocular drug delivery, due to their unique properties such as extended wear, high corneal bioavailability (more than 50%) and long drug residence time (over 30 min) in comparison to the eye drop therapy [9–14]. The current researches mainly focused on passive drug delivery through sustained diffusion, which still has long release duration and reduced patient compliance. Thus, there is a need to develop contact lens with controlled release duration or dose. The controlled drug release for eye disease therapy can be realized by external stimuli such as laser light, ultrasound, electric field or magnetic field [15]. Humayun et al. [16] have developed an electrically controlled device, but it needs battery, high cost and has to be fixed through surgery, and the complicated structure is hard to be integrated into contact lens. Pirmoradi et al. [17] proposed magnetically controlled devices which are battery-free and can be actuated within a safe magnetic field range. However, the leakage could continuously occur and may induce toxicity due to the opening of the device directly exposed to the treated retina. In our previous research, magnetic micropump with micro check valve have been proposed to successfully address the above problems [18], but in order to integrate these microdevices into contact lens for eye disease therapy with no need of surgery, the limitation on the device thickness still need to be overcome.

Here, we proposed a thin micropump to embed into contact lens for on-demand drug delivery. The proposed

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micropump is a battery-free system and actuated by the external magnetic field whenever needed (Fig. 1a). The proposed micropump was composed of top layer for membrane transfer, functional thin PDMS membrane as a part of check valve and actuator, magnetic nanoparticle-PDMS composite (MNPC) for actuation under magnetic field pulse, middle chamber for drug loading, and bottom cover including drug loading aperture. The top layer faces to the cornea and the drug can be released from the micropump to the post-lens tear film between lens and cornea. In addition, the micro check valve, which consists of elastic thin PDMS membrane and rigid thick Ostemer layer, was integrated with the micropump for one-directional drug delivery. The thin PDMS membrane and thick Ostemer layer has apertures with different sizes and locations, and the deflection of the thin PDMS membrane can be controlled by magnetic field acted on the MNPC which causes the drug release from the apertures [15]. Without an external magnetic field, no deflection will be induced and the micro check valve is closed, so the undesired drug diffusion can be prevented (Fig. 1b). On the contrary, with actuation of the external magnetic field, the MNPC moves under the applied magnetic field and enables the deflection of the PDMS membrane. Then, the internal pressure increases, and the micro check valve is pushed to be opened. As a result, the on-demand drug release is realized (Fig. 1c). Through the management of the strength and the frequency of the magnetic field pulse, the motion of MNPC and deflection of the PDMS membrane can be precisely controlled. Hence, the on-demand drug release and controlled dose can be easily realized (Fig. 1d). As shown in Fig. 1a, the proposed micropump has great potential to be inserted into soft or rigid contact lens and fixed with adhesive, or the simple structure of the micropump can be realized in

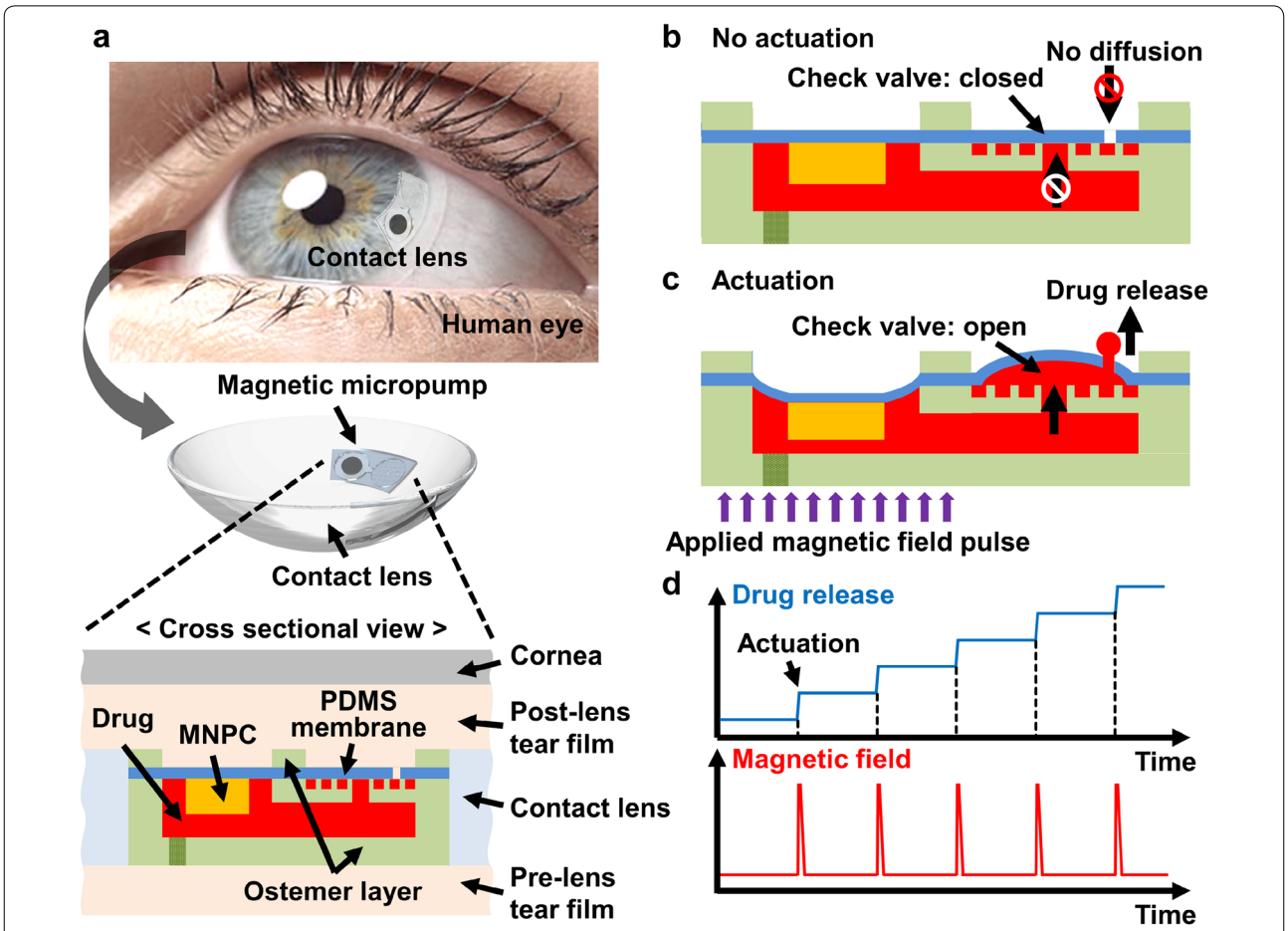

Fig. 1 **a** Schematic illustration of the proposed thin magnetic micropump integrated in contact lens. In the cross-sectional view, it shows the drug can be released from the micropump into the post-lens tear film through the aperture in the PDMS membrane. **b**–**c** The working principle of the proposed micropump: the status of the micropump under no actuation and actuation of magnetic field pulse, respectively. **d** The resulting on-demand drug release under an external controllable magnetic field pulse

rigid contact lens through photolithography-based master mold.

Materials and methods

Fabrication process for micropump embedded in contact lens

To construct the proposed micropump, we used Ostemer 322 (Mercene Labs, Sweden) as the main material to overcome the limitation of the material properties of PDMS. Ostemer 322 has several advantages, such as ability to fabricate stiff device by soft lithography (high Young's modulus of 1 GPa), two-step curing process for easy shaping, low absorbance of solution, solvent resistance and high transparency, and its biocompatibility has been also evaluated in Ostemer-based microfluidic device for organ-on-a-chip applications by Sticker et al. [19–22]. Figure 2 I shows the major fabrication process of the proposed micropump, including the PDMS master mold fabrication, the main body casting, and the total assembly. In the fabrication process of the PDMS master mold, at first, forming 25 μm-thick SU-8 pattern on silicon substrate through the standard photolithographic process to obtain a SU-8 master mold. The silicon substrate was silanized with (tridecafluoro-1,1,2,2,-tetrahydrooctyl)-1-trichlorosilane (Sigma Chemical Co., St. Louis, MO, USA) to reduce adhesion between the substrate and the newly coated PDMS (a). Then, pouring 10:1 PDMS pre-polymer to curing agent (Sylgard 184, Dow Corning Co., Midland, MI, USA) mixture onto the fabricated SU-8 master mold and curing at 95 °C for 1 h (b). Finally, peeling off the PDMS master mold from the wafer and dicing them into our desired size (c). After all the PDMS master molds including the upper and lower ones were prepared, aligning and pressing them together by using the alignment mark on them (d). To cast the main body of the micropump, injecting Ostemer 322 mixture with a ratio of 1.09:1 (A:B) into the assembled PDMS master mold, and then curing them by UV light (365 nm) for 2 min at 20 $mWcm^{-2}$ (e). After the UV curing, the Ostemer layer was soft, and it can be peeled off from the PDMS master mold and cut into the proper size easily (f).

For fabrication of the membrane assembly, a 25 μm-thick elastic membrane of 10:1 PDMS pre-polymer to curing agent mixture was spin-coated on the silanized silicon wafer at 500 rpm for 15 s, 1000 rpm for 15 s and 3000 rpm for 30 s in sequence and then baked at 95 °C for 1 h. The MNPC was prepared using the method previously reported [18, 23]. Briefly, EMG 1200 (Ferrotec, MA, USA) dry magnetic nanoparticles were dissolved in toluene, and the colloid dispersion of EMG 1200 nanoparticles was followed by stirring at room temperature and sonicating in a sonic bath for 30 min in order to obtain a homogeneously dispersed ferrofluid. Then, the PDMS pre-polymer was dissolved in toluene and stirred for 10 min to form a diluted polymer solution. Subsequently, the ferrofluid was mixed with the polymer solution at a mass ration of 1:1 (EMG 1200 nanoparticles to PDMS pre-polymer). The composite solution was sonicated in a sonic bath at room temperature and stirred for 30 min, and then stirred for 5 h under a fume hood to allow the toluene to completely evaporate. Finally, the cross-linker of PDMS was added and mixed fully for 15 min followed by degassing for 30 min. The resulting MNPC composite should be used as soon as possible after fully mixed since the magnetic nanoparticles tend to sediment and aggregate and this affects the homogeneity of the MNPC. The MNPC was spin-coated on a 25 μm-thick PDMS-coated silicon wafer and then baked at 150 °C for 1 h to obtain an MNPC layer with total thickness of 200 μm. Then, a cylindrical MNPC block with a diameter of 1.5 mm was punched by using a biopsy punch (Miltex, Inc., York, PA, USA). With O_2 plasma surface treatment, another 25 μm-thick PDMS membrane was bonded to a 100 μm-thick Ostemer layer which had two 3.5 mm holes punched by using biopsy punch, and then baked at 95 °C for 2 h to enhance the bonding strength and harden the Ostemer layer. Then, it was bonded to the pure PDMS side of the cylindrical MNPC block to fabricate the magnetically actuated membrane assembly (g). The micro check valve was composed of the top 25 μm-thick PDMS membrane and the bottom Ostemer layer. This mesh structure in the bottom Ostemer layer was designed to reduce the adhesion with the top PDMS layer. The apertures on the top PDMS membrane and bottom Ostemer layer were punched by using biopsy punches with a diameter of 350 μm and 500 μm, respectively. Before O_2 plasma surface treatment, the top and bottom layers were temporarily covered with PDMS blocks at the non-bonding region to realize partly O_2 plasma-treated surfaces. Then, the temporary PDMS blocks were removed and aligning and bonding of the top and bottom layers were carried out to make the micro check valve assembly (h). Finally, the bottom opening of the micropump was bonded to an Ostemer layer with Ø 500-μm hole for the drug injection, and the whole device was baked at 95 °C for 2 h.

Results and discussions

Figure 2 IIa shows the photography of the fabricated micropump (the width and length are 5 mm and 9 mm, respectively) and the micropump-integrated contact lens made of Ostemer 322. The microscope images of the top view of the membrane assembly region and the micro check valve region was shown in Fig. 2 II b, c, respectively. In the membrane assembly, the diameter of the MNPC block was 1.5 mm which was previously

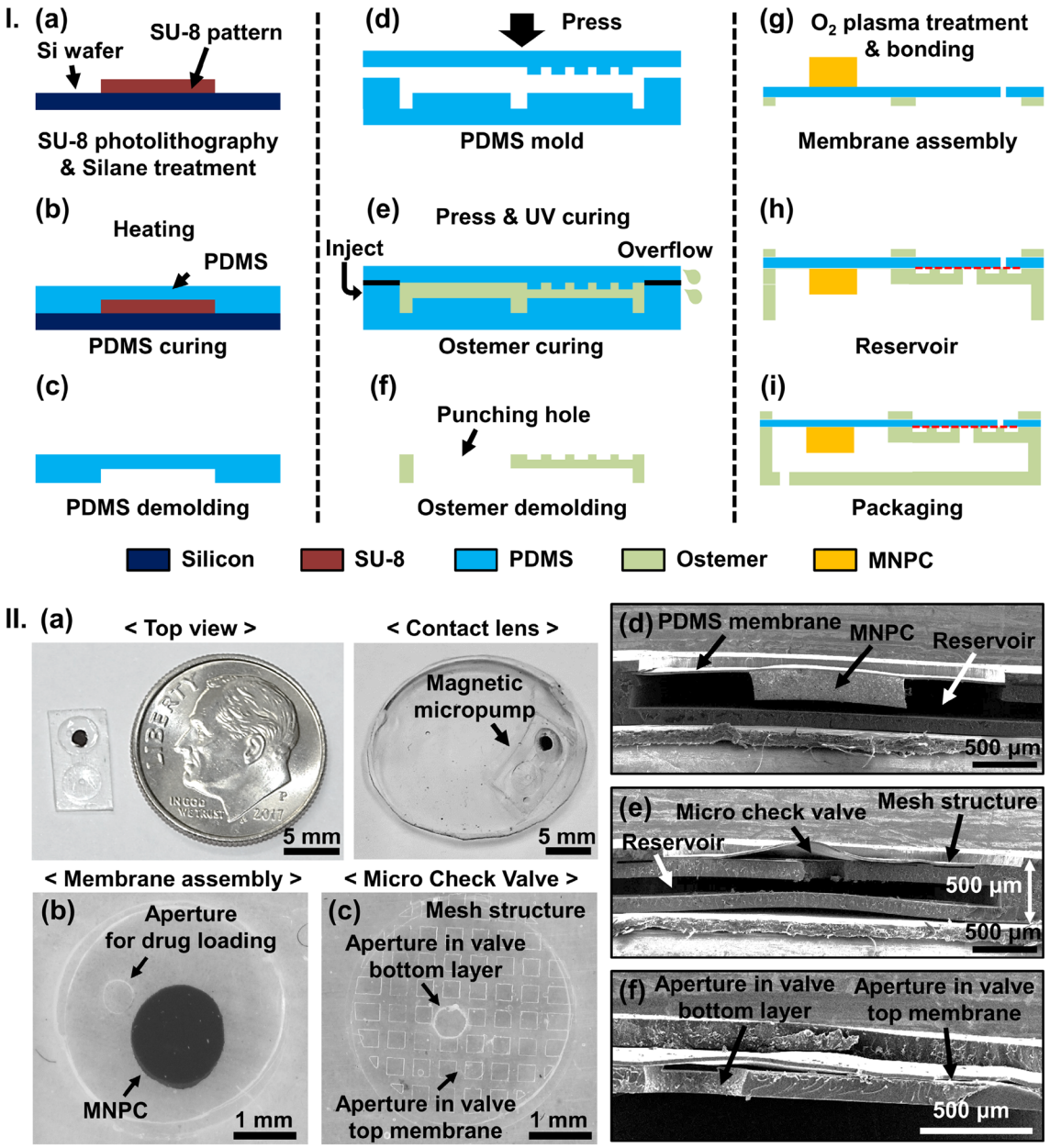

Fig. 2 **I** The fabrication process of the proposed magnetic micropump: **a**–**c** the PDMS master mold fabrication using the standard photolithographic method, **d**–**f** casting the main body of the micropump which is composed of Ostemer 322 using the PDMS master mold, and **g**—**i** the total assembly of the magnetic micropump through O_2 plasma treatment. The apertures on the PDMS membrane and Ostemer layer were punched by using biopsy punches. **II a** The photography of the fabricated micropump and the micropump-integrated contact lens. The microscope image of the top view of **b** the membrane assembly region and **c** the micro check valve region. The SEM images of the cross-sectional view of the fabricated magnetic micropump including **d** the membrane assembly region, **e** the micro check valve region, and **f** the apertures in the micro check valve

optimized by the numerical simulation [18]. The aperture in the bottom was used for loading drug, and then can be sealed with UV-curable adhesive. In the micro check valve, the depth of the mesh structure in the bottom Ostemer layer was 25 μm, and at the center, the aperture was Ø 500 μm, next to which the aperture in the top PDMS membrane was Ø 350 μm. The SEM images of the cross-sectional view of the fabricated magnetic micropump including (d) the membrane assembly region, (e) the micro check valve region, and (f) the apertures in

the micro check valve. The proposed micropump had a thickness of less than 500 μm, which is suitable for inserting into the contact lens

To visualize the process of drug release from the magnetic micropump, water-soluble red dye in PBS solution was injected into the micropump through the aperture in the bottom of the micropump (Fig. 2II b) using a gas-tight microsyringe (Hamilton Company, Reno, NV, USA). The micropump was fixed on the side wall of a two-chamber slide (SPL, Korea), and then the chamber was filled with PBS solution. A neodymium cubic magnet with an edge length of 1/2″ (B888-N52, K&J Magnetics, Inc., PA, USA) was used as the source for the magnetic field. The magnetic field of the permanent magnet was measured using a gaussmeter (GM08, Hirst Magnetic Instruments Ltd., UK). The magnet was mounted on a computer-controlled linear translation stage (DDSM100/M, Thorlabs, Newton, NJ, USA) connected to brushless DC motor controller (KBD101, Thorlabs, Newton, NJ, USA). In order to reveal the action of the micro check valve during the drug release, the motion of the valve and the microflow was monitored using a high-speed video camera (Photron Fastcam SA-3) with a filming frame rate of 500 fps. Figure 3a shows the sequential images of the release of the drug from the micropump, including the valve opening, the drug release, and the drug diffusion. Before the micro check valve was open, it showed no red ink appeared around the aperture on the top layer of the valve, which reveals that the micro check valve can effectively prevent the undesired drug release due to the diffusion. With a very short exposure (less than 1 s) of the magnetic field, the deflection of the membrane assembly was induced, and the micro check valve started to be opened. The drug was pushed into the zone between the top and bottom layer of the micro check valve, and the red region became larger. After 0.06 s, the valve was fully opened, and the drug started to come out from the micropump. The drug was successfully released from the proposed micropump in 0.76 s, and the check valve was closed simultaneously. Finally, the drug started to diffuse to the ambient solution.

For quantitative evaluation of drug release according to the strength of the magnetic field, the volume of the drug release was calculated by analysing the images. According to the experimental results shown in Fig. 3b, the amount of drug released was ~ 20 nl, ~ 70 nl, ~ 180 nl, and ~ 290 nl under the magnetic field of 152 mT, 217 mT, 319 mT and 469 mT, respectively, corresponding to ~ 0.4%, ~ 1.6%, ~ 4% and ~ 6.4% of the reservoir volume (~ 4.5 μl). It showed that the proposed micropump can precisely regulate the drug release at nanoliter scale. Moreover, a linear relationship was found between the volume of the drug release and the strength of the magnetic field. The magnetic field ranges from 152 to 469 mT, which is safe (less than 500 mT) to human health. A corresponding equation can be described as: $Y = 0.0008767 X = 0.1144$ ($R^2 = 0.98$), which can be used for the prediction of the amount of the drug release.

Conclusions

In this study, we proposed a thin magnetic micropump with thickness of less than 500 μm, which can be integrated into a contact lens for on-demand drug delivery. Moreover, the drug release of the proposed micropump according to the strength of the applied magnetic field was evaluated quantitatively, and it can be precisely

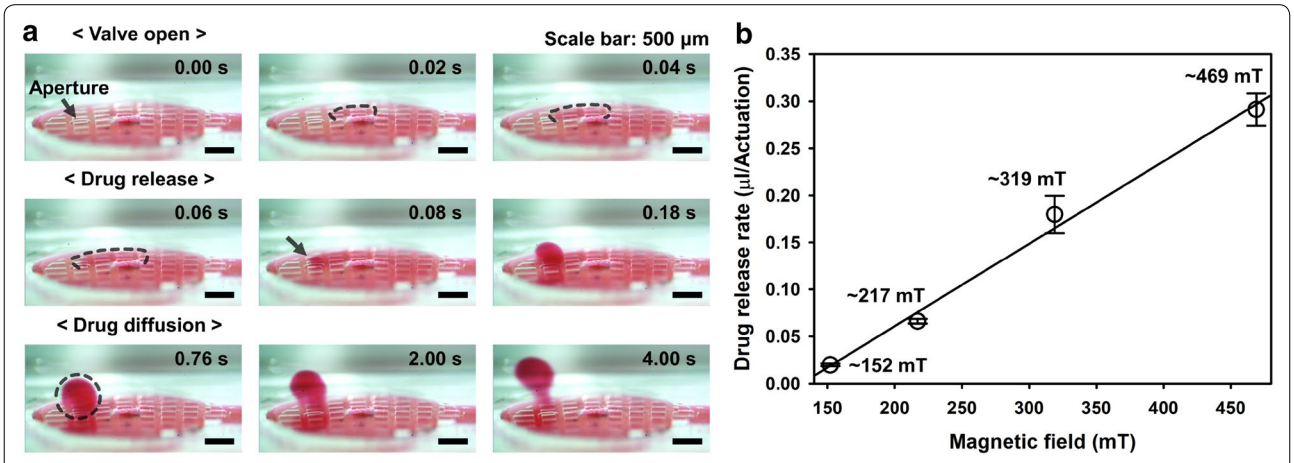

Fig. 3 **a** The sequential images show the drug release process of the proposed magnetic micropump with a short exposure (less than 1 s) of magnetic field (469 mT), including the valve opening, the drug release, and the drug diffusion. **b** The quantitative evaluation of the drug release according to the strength of the magnetic field from 152 to 469 mT. Error bars indicate the standard deviation (n = 10)

controlled by a safe magnetic field range from 152 to 469 mT. The proposed micropump has great potential to be embedded in not only contact lens but also periocular implant for eye disease therapy.

Abbreviations
PDMS: polydimethylsiloxane; MNPC: magnetic nanoparticle-PDMS composite; DMSO: dimethyl sulfoxide.

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Authors' contributions
CW carried out design and fabrication, measurement and analysis of the results, and drafted the manuscript. JYP performed analysis of results and drafted the manuscript. Both authors read and approved the final manuscript.

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Availability of data and materials
The datasets supporting the conclusions of this article are included within the article.

Competing interests
The authors declare that they have no competing interests. The datasets supporting the conclusions of this article are included within the article.

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