Miniaturized Drug Delivery System for Biomedical Applications

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Abstract— A miniaturized 3D printed drug delivery device powered wirelessly is presented. The device is composed of an electrochemical micropump, a 3D printed reservoir with microneedles, and a wireless powering unit. The electrochemical pump features an expandable (up to 300%) Parylene C micro-bellows membrane fabricated by mold casting, using a two-photon polymerization 3D printing technique. The hollow microneedles are 100 μm in diameter and 300 μm long. The fabrication process offers customizable device properties, where the shape, size, and performance can be tailored to fit a wide range of in vivo drug delivery applications. Delivery of 3.8 ± 0.3 μL within 10 seconds of actuation is demonstrated, using inductive wireless powering at a distance of 10 mm between the primary and secondary coils.

Keywords—drug delivery, micropump, microneedles, 3D printed

I. INTRODUCTION

Conventional drug delivery methods tend to show severe drawbacks in the efficacy of treatment, due to the difficulties in administering the optimal drug dosage to the optimal tissue site with optimal frequency. Therefore, efforts have been concentrating on optimizing these critical parameters [1].

As an alternative to conventional techniques, implantable drug delivery systems have been a principal focus of development for the parenteral and oral drug administration, where extensive work has been done to optimize drug efficacy via localized delivery and dosage control providing new ways for accomplishing targeted therapeutic effects [1-2]. However, there remain opportunities for advancement by introducing novel microtechnologies in fabrication methods or engineering discoveries in concept realization, making such devices more versatile and effective [3]. In particular, microdevices based on electrolytic pumps have been greatly explored in the past [4-6]. These systems demonstrate the advantages of low power consumption, adequate driving force, and accurate flow control [7-8].

Bellow membranes are suitable as actuators for micro-electrolytic pumps, due to their fitting pressure ranges [9]. The predictable performance and expansion profile of micro-bellows translates to controlled dosage in drug delivery. Due to micro-bellows' malleability, they easily expand under internal pressure, making them ideal membranes in

electrolytic pumps [6-8]. Combined with Parylene C's biocompatibility, they act as a diaphragm isolating the drug reservoir from the pumping source preventing degradation and pH changes from water exposure [6]. Due to these pumps' minimal power requirements, wireless inductive powering units can be installed to achieve wireless actuation [10-11]. With an electromagnetic field from a transmitting coil, a current is induced in the receiving coil driving the electrolytic reaction in the pump. Past works have applied similar concepts, reporting drug delivery systems integrated with electrochemical micro pumps [6-8], [10-11].

Traditional fabrication and design methods used to limit the pump to be operated in very specific scenarios. With additive manufacturing methods such as two-photon polymerization, rigid applications can be avoided [12]. Following the same process, with minimal dimensional design edits, a set of versatile pumps can be fabricated and implanted at different sites, paving the way towards novel therapeutic options. Combined with the use of microneedles, these integrated systems have a promising potential for targeted drug delivery for the treatment of tumors and critical diseases like atherosclerosis. For such applications, the drug volume to be delivered ranges from 0.6 to 15 μL [13-14]. By employing a flexible design and fabrication method, significant progress can be made finding the optimal compromise between device size, drug dosage (volume and rate), and power consumption.

In this study, a miniaturized and wirelessly powered drug delivery system is presented. The system includes an inductive powering unit, interdigitated electrodes for electrolysis, a Parylene C micro-bellows membrane [9], and a 3D printed reservoir with microneedles. Utilizing the tools and components mentioned, the presented design displays some advantages in size, powering, integration ease, versatility, and flexibility. The remaining of this manuscript is arranged as follows; section II presents the prototype design principle and fabrication methods, while section III describes and analyzes experimental data and simulations, and section IV concludes with key results.

II. CONCEPT AND FABRICATION

The drug delivery system is composed of three main parts; a 3D printed reservoir with microneedles, an electrolysis micropump, and an inductive powering unit, as shown in

Fig. 1. Schematic diagram of the drug delivery system and operation concept.

Fig. 2. Interdigitated electrodes fabrication process. (a) Patterning electrodes. (b) Etching holes. (c) Photograph of the final sample.

Fig. 3. Fabrication process of micro-bellows membrane.

Fig. 1. The pumping mechanism is based on the inflation of a Parylene C micro-bellows membrane, due to gas bubbles generated from the water electrolysis reaction. Such an actuation mechanism is distinguished over other methods with a significant volume change even in a pressurized medium and low power consumption [6], [15]. First, the micro-bellows membrane was assembled on top of the interdigitated electrodes, and about 1.5 μL of 1 wt% NaCl solution in DI water was injected inside the membrane. Then, the 3D printed reservoir was assembled on top of the electrochemical pump and filled with the liquid drug through a refill port. The transmitter unit was composed of wireless transmission modules (XKT412 and XKT335, Shenzhen Core Ketai Electronics Co., Ltd., Shenzhen, China) and a transmitting coil (33 mm outer diameter, 5 mm inner diameter and 1 mm thickness). Powered with a DC voltage generator (5V, 0.1A), the transmitter unit provided an output voltage and current of ~ 10 mA and 5V, respectively, in the receiver's terminal (21 mm outer diameter, 10 mm inner diameter and 0.5 mm thickness) at 10 mm distance. When connecting the receiver terminal to the interdigitated electrodes, water electrolysis

initiates and oxygen/hydrogen bubbles are produced. Consequently, the bellows membrane is inflated pushing the drug through the microneedles.

A. Micropump fabrication

Interdigitated electrodes made of 5 finger pairs (100 μm / 100 μm elements width/spacing) with a total area of 1.25 mm^2 were fabricated on silicon substrate, as shown in Fig. 2. A liftoff process using AZ ECI 3027 (MicroChemicals GmbH, Ulm, Germany) photoresist was employed to pattern the Ti/Pt (30 nm / 300 nm) electrodes (Fig. 2a). Two holes (300 μm in diameter) were created through the silicon substrate by Deep Reactive Ion Etching following the process described in Fig. 2b using the photoresist AZ 9260 (MicroChemicals GmbH, Ulm, Germany). These holes served to inject the electrolyte solution (1 wt% NaCl solution in DI water) between the interdigitated electrodes and micro-bellows membrane.

The fabrication process of the Parylene C micro-bellows membrane summarized in Fig. 3 was previously reported [9]. The membrane's dimensions were 3 mm by 1.2 mm in length and width, respectively, with a height varying from 0.5 mm,

Fig. 4. 3D printed microchip fabrication process. (a) Design. (b) 3D printing. (c) Photograph of the 3D printed reservoir.

when the membrane is fully folded (deflated), to about 2 mm, when it is fully expended (inflated). This large deflection is facilitated by five outlying triangular corrugations (250 μm of corrugation depth and length).

B. 3D printed drug reservoir with microneedles

The reservoir (3.9 mm $\times$ 2.1 mm $\times$ 2 mm) features 4 microneedles of 100 μm in diameter and 300 μm in length. The structure was 3D printed using a two-photon polymerization 3D printer (Photonic Professional GT, Nanoscribe GmbH, Germany) on a 25 mm $\times$ 25 mm silicon substrate. A hole (1 mm in diameter) was etched in the center of the silicon substrate using a 50 Watts fiber laser (PLS6MW, Universal Laser Systems GmbH, Vienna, Austria) with a 1.06 μm wavelength, to facilitate the photoresist removal after 3D printing the reservoir structure. Before 3D printing, the silicon substrate was cleaned with acetone followed by isopropyl alcohol then it was rinsed with DI water and dried with a gentle stream of nitrogen gas. IP-S photoresist (IP-S, Nanoscribe GmbH, Germany) was then drop-cast. The 3D printer objective lens (25 $\times$ magnifications, NA 0.8) was immersed in the resin, and the designed reservoir structure was printed layer-by-layer (2 μm slicing distance) in a dip-in laser lithography configuration, (Fig. 4). Then, the structure (reservoir and microneedles) was developed by immersion in mr-DEV 600 (micro resist technology GmbH, Germany) to

Fig. 5. (a) Schematic of the micro-bellows membrane parameters. (b) Finite element modeling of the Parylene C micro-bellows membrane.

Fig. 6. (a) and (b) Photographs of Parylene C membrane expansion before and after wireless powering.

remove the unpolymersed excess of resin and washed with isopropyl alcohol. These two steps were repeated until the photoresist was completely removed. Then, the structure was dried with a gentle stream of nitrogen gas.

III. EXPERIMENTS AND RESULTS

A. FEM modeling of Parylene C micro-bellows membrane

Finite element modeling (FEM) analysis was applied to determine the optimal corrugation length and depth distances (Fig. 5a) of the triangular bellows shape that result in the maximum deflection of the membrane. In addition, the mechanical resistance and stress distribution of the Parylene C micro-bellows membrane was investigated (Fig. 5b). Using Solidworks software (Solidworks 2017, Dassault Systèmes SolidWorks Corporation, MA, USA), a 10 μm thick membrane design was simulated in a nonlinear static mode. The optimal corrugation length and depth parameters giving the largest deflection and lowest stress were 250 μm respectively.

B. Electrolysis pump assembly and test

The Parylene C membrane was assembled on top of the

Fig. 7. (a) Photograph of the delivery system components compared to a commercial 500 mg paracetamol tablet. (b) Photograph of the assembled delivery system. (c) Photographs of the dye delivery through micro needles using inductive wireless powering.

interdigitated electrodes using a Loctite 4011 instant adhesive (Loctite 4011, Henkel, Düsseldorf, Germany). The two holes on the backside of the silicon substrate allowed to inject the electrolyte solution (1 wt% NaCl solution in DI water) and purge the membrane from any trapped air bubbles, then the holes were sealed with Kapton tape. First, the electrochemical pump was tested by connecting a source meter (Keithley 2400 SourceMeter SMU Instruments, Tektronix, OR, USA). The applied voltage was set to 5 Volts, and the measured power consumption was 25 mW. The micro-bellows membrane expansion reached 1.85 mm within 40 seconds (initial height was 0.6 mm). Then, inductive wireless powering was used with a 10 mm distance between the transmitter and receiver coils. As shown in Fig. 6, The membrane reached 1.9 mm of total deflection starting from an initial height of 0.5 mm achieving about 300% expansion.

C. Actuator assembly and test

The 3D printed reservoir was connected to the electrolysis micro-pump using a Loctite 4011 instant glue (Fig. 7a-b). Then, the integrated system was validated by testing the full assembly. The reservoir was filled with red dye for ease of imaging to mimic the drug during the experiment as shown in Fig. 7c. The micro-bellows geometry and expansion determined the maximum volume to be delivered. In this case, for an expansion of 1.2 ± 0.1 mm, the amount delivered was 3.8 ± 0.3 μ L. Fig. 7 depicts the delivery of ~ 3.8 μ L red dye through the microneedles within 10 seconds of actuation.

IV. CONCLUSION

Fabrication process, assembly and testing of a miniaturized drug delivery system have been demonstrated. Emphasis was put on minimizing the device dimensions while providing flexibility in the fabrication process and wireless operation. This was achieved by combining a 3D printed reservoir and microneedles, a micro bellow membrane for large displacements and an electrolytic pump for low-power inductive pumping. The overall size of the device (3.9 mm $\times$ 2.1 mm $\times$ 2 mm) makes it suitable for biomedical applications especially localized drug injection inside the body. Successful delivery of about 3.8 μ L red dye through microneedles was achieved using wireless inductive powering at 10 mm distance between the transmitter and receiver. This delivery system showed a compromise between the device size, dose volume, power consumption, and design flexibility, comparing to previous works in [6-8] and [10-11].

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