A WIRELESSLY CONTROLLED FULLY IMPLANTABLE MICROSYSTEM FOR NANO-LITER RESOLUTION INNER EAR DRUG DELIVERY

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ABSTRACT

Site-directed and programmable drug delivery systems are important to leverage recent developments in protective and restorative biotherapies. Therapy development in the mouse model system requires advanced nano-liter precision implantable microsystems. Here, an implantable and scalable drug delivery system is presented consisting of a miniaturized, wirelessly controlled phase-change peristaltic micropump and a refillable microreservoir. 3D-printing technology has been used to fabricate the micropump around a microcatheter tubing on the backside of a printed circuit board. *In vitro* characterization results demonstrate nano-liter resolution control over the desired flow rates of 10-100 nL/min in the presence of backpressure 40× larger than experienced in the physiologic system. *In vivo* implantation results show consistency with previously published syringe pump results.

INTRODUCTION

Over 450 million people all around the world suffer from auditory dysfunction, according to World Health Organization [1]. Recent advances in protective and restorative biotherapies have created new opportunities to address auditory and vestibular disorders with site-directed, programmable drug delivery systems. Successful therapy development leveraging the transgenic, knock-in, and knock-out variants of human disease in the mouse model system requires advanced microsystems specifically designed to function with nano-liter precision and with system volumes suitable for implantation.

However, delivering into the inner ear is extremely challenging due to small size, relative inaccessibility, sensitivity to mechanical and chemical stress [2], and the small volume of the cochlear fluid (perilymph), which is approximately 620 nL for mice [3]. Inner ear drug delivery systems need to meet several requirements to address these challenges to be able to provide safe and efficient delivery. Such a system requires precise ultra-low flow rates with a controllable profile while being sufficiently small with a planar form factor to facilitate subcutaneous implantation in animals, and mastoid cavity implantation in humans [4], [5]. Moreover, it must be sufficiently robust to enable long-term, time-sequenced, precise flow rate control with remote activation/deactivation capability.

These requirements limit the application of current microsystem-based drug delivery devices. The state of the art micropump for intracochlear drug delivery provides controlled, automated pumping, but the size is prohibitive for implantation in the mice [4]. The only commercially available micropumps for implanting in mice either provide power-free delivery at fixed flow rates (Alzet®, Durect Co., Cupertino, CA, USA), or controllable and programmable delivery, at a relatively large size (iPRECIO®, Primetech Corporation, Tokyo, Japan). Recently, a miniaturized planar peristaltic micropump for this domain was reported that employed gallium as the phase-change material [6]. However, it was fabricated using micromachining processes and had to overcome traditional microfluidic interconnection challenges [7]. Additionally, unless custom circuits are integrated directly with the microelectromechanical system (MEMS) based micropump, incorporation of control electronics adds significant bulk. Scaling

of MEMS-based systems requires modification of the fabrication processes and masks, creating challenges in scalability to human clinical translation.

In this paper, we present a miniaturized, wirelessly controlled and fully implantable phase-change peristaltic micropump to provide programmable and accurate drug delivery for inner ear applications. Employing 3D-printing technology, the micropump is built on the backside of a printed circuit board (PCB) around a microcatheter tubing (OD= 250 μ m, ID= 125 μ m) to integrate the mechanical and control electronic components while providing a leak-free biocompatible flow path without complex microfluidic interconnects. A refillable and collapsible 50 μ L microreservoir is integrated with the micropump while maintaining a form factor optimized for subcutaneous implantation in mice (Figure 1). We present the micropump architecture, control electronics details, and heat transfer analysis for phase-change peristalsis, along with *in vitro* and *in vivo* results, with an emphasis on the functionality of the micropump at ultra-low flow rates.

MICROPUMP ARCHITECTURE

Using a sub-millimeter microcatheter tubing as the fluid-carrying component limits the options for pumping approaches, particularly those that require in-line rectifying valves which add unacceptable bulk for this size-constrained application. Here we employ peristalsis with the microcatheter tubing sequentially compressed in three locations to induce directional flow. Different actuation methods have been used for peristaltic micropumps in the literature such as piezoelectric, pneumatic, thermopneumatic [8], and phase-change [6].

In this study, a phase-change actuation method has been used due to its low driving voltage, small size, and high actuation force enabling effective pumping against backpressure. The actuation material is encapsulated in the body of the micropump surrounded by stiff structures except for one side that is exposed to the deformable microcatheter tubing. Peristalsis takes place by sequential melting / solidification of the phase-change material driving cyclic expansion / shrinking and compression of the tubing to directionally push the pumped fluid from inlet to outlet.

Figure 1: The overall drug delivery system for inner ear application includes a micropump and an integrated refillable microreservoir, designed for subcutaneous implantation. The system can be programmed and wirelessly controlled via an Android device.

Different phase-change materials have been used in the literature such as gallium [6], and paraffin wax [9]. Paraffin wax was used for this micropump for its stable phase-change behavior, high actuation pressure, and flexible melting point based on the molecular weight.

The micropump was built directly on the backside of PCB employing 3D-printing technology. Three chambers were fabricated in a linear pattern adjacent to the microcatheter tubing separated by 1.2 mm. Paraffin wax was precisely deposited in the chambers. Three pairs of resistive heaters and thermistors were placed in the chambers for precise control of the temperature. A peristaltic sequence was applied to the micropump, with timing control ensuring two closed chambers at each moment in time.

MICROPUMP CONTROL ELECTRONICS

On the front side of the PCB, the control electronics were fabricated for actuation and control. The micropump electronics use off-the-shelf components and have been designed for ultra-low-power operation. The system is powered by a lithium polymer battery and includes a single cell lithium ion battery charger (BQ25100, Texas Instruments), which was chosen for its low battery leakage current (75 nA) and small footprint. The TPS62743 (Texas Instruments) is a step down buck converter that provides sufficient current output (maximum 300mA) while pumping, high conversion efficiency, and low quiescent current (360nA) when the system is in shutdown mode. Each pump chamber consists of a 40-ohm resistive element for heating, and a thermistor (NCP03WF104F05RL, Murata). Each resistive element uses a discrete NMOS for microprocessor control of the chamber. A 1.8V system power rail minimizes power consumption of the wireless microcontroller.

The wireless microcontroller (MCU) includes a Bluetooth Low Energy transceiver (BLE 4.2), a 32-bit ARM Cortex-M3 processor with a clock speed of up to 48 MHz, and an ultra-low-power sensor controller (CC2640, Texas Instruments). This system provides an ultra-low shutdown current of 100nA, which is important since the system will spend the majority of time in deep sleep mode when the pump is not actively delivering drugs. The system real-time clock utilizes a 32kHz oscillator (SiT1532, SiTime) based on silicon

Figure 2: Block diagram of the pump control electronics. Res. and Ther. stand for resistive heater and thermistor, respectively. Inset: An image of the fabricated electronics on top side of the PCB. The electronics assembly is used for actuation, closed-loop feedback to control the temperature in each chamber, and wireless control.

MEMS technology, which has the smallest footprint and lowest power for a commercially available oscillator. A wire antenna with a length of 10 mm keeps the overall device footprint as small as possible. The control electronics are configured and operated using a custom Android application via Bluetooth Low Energy. Figure 2 shows the block diagram of the electronics along with an image of the front side of PCB.

MICROPUMP HEAT TRANSFER ANALYSIS

A phase-change peristaltic micropump with three adjacent actuation chambers requires proper transfer of heat in and out of the medium, affecting actuation frequency and flow rate. COMSOL® simulations were carried out to optimize the heat transfer function of the micropump. The 3D geometry details were designed in SolidWorks® and imported into COMSOL. The material properties were obtained from the COMSOL library or datasheet of the components. Free convection in water was considered for the surface boundary condition, to simulate the *in situ* application of the device. Heat generation was applied to the middle surface of the resistors in the chambers by applying a sequential user-defined function, while the temperature was controlled according to the temperature of the resistor using a user-defined function for closed-loop control.

To achieve the maximum target flow rate of 100 nL/min, high actuation frequencies were required necessitating a 10 °C differential between the wax melting point and the environmental temperature. Simulation results revealed a reduction of the thickness of the Copper in the PCB from 36 μm (1 oz.) to 18 μm (0.5 oz.) enabled the actuation frequency to increase by 14% due to reduced thermal mass and heat transfer away from the chamber. The addition of a copper pad in the bottom of each chamber improved the homogeneity of the temperature distribution in the chambers by 33%.

Using the model with optimized material and geometry, the results of a steady state simulation while chambers 1 and 3 are on, and chamber 2 is off, shows that the chambers are well-insulated. In particular, while two side chambers are set at the melting point the middle chamber stays ~9 °C colder than the melting point as shown in Figure 3A. To estimate the temperature rise of both the micropump exterior surface and the pumped fluid, transient analysis was performed. The surface temperature of the micropump remained 2 °C below the ambient temperature.

Figure 3: 3D heat transfer analyses were performed on the micropump. A) The design provides effective thermal insulation of the chambers. B) The temperature distribution in the length of the tubing in the last 5 seconds of the simulation of the pump working at 0.33 Hz and 1.5 Hz for 30 seconds. The results show that the drug temperature never exceeds more than 9 °C higher than the ambient temperature and it cools down to ambient temperature before leaving the actuation region of the micropump. The temperatures are normalized to the ambient temperature in all figures.

Figure 4: A new low-cost fabrication methodology is presented leveraging 3D printing of micropump features on the backside of a PCB. A) The electronic components for actuation, temperature control, and wireless communication are assembled on the front side of the PCB. B) The micro-heaters and thermistors are assembled on the backside of the PCB, forming a template for three linear chambers and a microcatheter tubing. C) A commercially available catheter microtubing (250 μ m OD, 125 μ m ID) is placed within a printed template. A precise volume of Nonadecane with a melting point of 31.8 °C is placed in each chamber in contact with the microtubing and integrated micro-heater and thermistor. D) The chambers are covered with a rigid resin. A microreservoir is integrated to the micropump and the entire system is encapsulated with PDMS and parylene-C for biocompatibility.

The pumped fluid temperature increased to 9 °C above the ambient within the micropump, but returned to ambient temperature before leaving the pump platform.

MICROSYSTEM FABRICATION PROCESS

A new fabrication process (Figure 4) was developed using 3D-printing technology, enabling direct write printing of the mechanical structure of the micropump on the backside of a PCB, while on the other side control electronics were populated employing standard PCB assembly technology. Three pairs of thermistors and resistors were fabricated on the backside of the board, forming a template for three linear chambers and a microcatheter tubing. The structure of the micropump was 3D-printed using an inkjet printer (Roland VersaUV LEF-12, Tokyo, Japan) and the microcatheter tubing was fixed and sealed in the designated site using cyanoacrylate resin. A precise volume (240 nL) of Nonadecane (Sigma-Aldrich, USA) was placed in the chambers and the chambers were covered with the resin.

The micropump was bonded to a 3D-printed biocompatible substrate (MED610, Stratasys, MN, USA). A refillable biocompatible PDMS-based microreservoir was fabricated using

Figure 5: The completed drug delivery microsystem. The system achieves first in class miniaturization for this application for subcutaneous implantation. It is readily scalable by selection of microtubing size, 3D-printed chambers, and actuation frequencies.

PDMS molding method into a 3D-printed (MakerBot, NY, USA) acrylonitrile-butadiene-styrene (ABS) mold. After curing at 60°C for 4 hours, the PDMS replica was peeled-off and bonded to the substrate using uncured PDMS adhesive layer. The structure was then cured at 40 °C for 12 hours. For biocompatibility, the entire system was encapsulated with a ~2 μ m-thick parylene-C (Specialty Coating Systems, Indianapolis, Indiana) using a custom-built parylene deposition tool (Figure 5).

IN VITRO CHARACTERIZATION

The micropump was first characterized *in vitro*; flow rate measurements were taken at different actuation frequencies and back pressures. The actuation set temperature of the chambers was calibrated based on actuation frequency. The micropump was placed in a petri-dish full of water to simulate the *in situ* conditions. The microcatheter was filled with dyed deionized water, and flow rates were measured considering the fluid front displacement using a ruler at the outlet.

Flow rates were measured for actuation frequencies from 0.0167 to 0.2 Hz at eight different frequencies to cover the entire range of reported drug delivery infusion flow rates of 10-100 nL/min [10]–[13]. Flow rates were measured at two back pressures of 0 and 20 kPa (40 $\times$ larger than the physiological back pressure).

The results (Figure 6) show that the micropump can provide almost linear results ($R^2 = 0.98$) through the 10-100 nL/min range. Moreover, results show that applying 20 kPa back pressure does not significantly affect the flow rates.

IN VIVO EXPERIMENT

To evaluate the *in vivo* functionality of the micropump, it was tested using an inner ear drug delivery paradigm in the mouse model system, and the results were compared to our previous publication [12]. Salicylate has been shown to cause inhibition of outer hair cells electromotility which can result in a reversible elevation of distortion product otoacoustic emissions (DPOAE) thresholds. Therefore, it was delivered to the round window membrane (RWM) with an assessment of auditory function using DPOAE method. Three micropumps were tested in eight mice with the microcatheter tubing implanted at the RWM niche. The micropumps were held in a water bath to simulate heat transfer associated with implantation. The details of the surgery were presented in our previous work [12]. In the previous publication the salicylate was delivered to RWM using a syringe pump at a flow rate of 50 nL/min for 20 minutes (1000 nL total), and then the pump was deactivated for 40 minutes.

Figure 6: *In vitro* test results illustrate precise control over the drug delivery flow rate in the desired range (10-100 nL/min) in the presence of 20 kPa backpressure, which is approximately forty-fold higher than mouse intracochlear back pressures.

Figure 7: Micropump delivery real-time shifts in DPOAE thresholds as a function of infusion time were consistent with our previously published results [12] which used a syringe pump for delivery of salicylate at the same flow rate. Error bars are standard error of the mean (SEM).

The DPOAE threshold was measured for the entire 60 minutes of the experiment to find the DPOAE shifts during 20 minutes infusion and 40 minutes recovery. The same procedure was repeated for the micropumps.

Figure 7 shows the average in the DPOAE shifts of the 3 micropumps tested in 8 mice, compared to the syringe pump during infusion and recovery. Results show a promising consistency between the two experiments, demonstrating the accuracy and reliability of the micropump.

CONCLUSION AND FUTURE WORKS

In this paper progress on a microsystem for ultra-low flow rate drug delivery for inner ear applications was presented. 3D-printing technology has been employed to fabricate the micropump around a microcatheter tubing on the backside of a PCB, to integrate with the electronics assembled on the front side. The *in vitro* characterization results show precise control over the required ultra-low flow rate of 10-100 nL/min in presence of up to 20 kPa back pressure. In addition, the *in vivo* results show a promising match with a previous experiment using syringe pump. Moreover, the micropump was integrated with a 50 μ L microreservoir, keeping the planar form factor for subcutaneous implantation. This microsystem architecture leveraging 3D printing technology and direct peristaltic actuation of the catheter tubing is readily scalable for future human translation.

Future work will focus on the optimization and characterization of the microreservoir and subcutaneous implantation of the microsystem. In addition, a thermal flow meter for feedback control of the flow rate of the micropump will be developed.

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