NEUROMEDICATOR – A DISPOSABLE DRUG DELIVERY SYSTEM WITH SILICON MICROPROBES FOR NEURAL RESEARCH

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ABSTRACT

We report on a novel disposable drug delivery system for neural research which allows to infuse 16 discrete liquid portions of 0.25 µL directly into neural cell tissue. The system comprises an 11×14.5×3 mm³ fluidic chip with a pluggable electrical micro connector and two 8-mm-long micromachined silicon fluidic microprobes with a cross-sectional area of 250×250 µm². A pearl chain-like fluidic structure with spherical segments was developed which stores and predefines the required drug liquid portions for the whole time of operation. The micropump principle for liquid delivery is based on the local, irreversible thermal expansion of microspheres embedded into polydimethylsiloxane (PDMS).

INTRODUCTION

Neural drug delivery by microprobes is considered to be one of the most promising methods for treating brain related diseases since the liquid drug can be directly infused into a specific brain region. However, whereas chronically implanted silicon-based microprobes with electrodes are meanwhile already used in humans [1], multifunctional probes which combine electrode recording and stimulation with microfluidic drug delivery are still under development or are mainly limited to acute applications [2,3]. The main reason for this is the increased complexity of integration of a microfluidic probe assembly in comparison to a pure electrode system. Electrodes can easily be connected to electric micro connectors to achieve a highly miniaturized, pluggable, chronic system. However, there is no pluggable microfluidic connector compatible with volume deliveries on the order of sub-microliters. Consequently, a permanent fluidic connection of the microprobes either to a macroscopic pump or a miniaturized drug delivery system which can be placed directly next to the probes is required. Considering mobility aspects, the latter is definitively more desirable. Therefore, the NeuroMedicator combines a novel small-scale drug-delivery system with existing fluidic microprobes for neural drug delivery reported previously [4]. Since the required drug for the whole time of operation is stored directly in the device, electrical connection is only required during operation. For actuation we extended a technology presented earlier by the Stemme group at Royal Institute of Technology Stockholm, Sweden. The technology is based on thermally expandable microspheres embedded into PDMS [5]. The microspheres combine large volumetric phase change expansion with irreversible behavior.

PRINCIPLE OF OPERATION

The micropump principle of the device is illustrated in Fig. 1a. Liquid chambers in a pearl chain-like arrangement with a dead end are first filled with liquid. Afterwards, sequential heating of the heat-expandable material underneath the liquid chambers displaces the liquid stored in the chambers. Since the expansion of the material is irreversible, no backflow occurs. Hence, each actuation cycle pumps precisely the liquid volume predefined by the chambers without the need for additional sensor control.

The design of the NeuroMedicator is shown in Fig. 1b. The device consists of a fluidic chip with an attached micro connector and fluidic silicon microprobes. The fluidic chip is based on a compound of three different materials: (i) a microstructured printed circuit board (PCB), (ii) a layer of thermally expandable material, and (iii) a microfluidic structure. Each of the two microprobe shafts is fluidically connected to eight liquid chambers of 0.25 µL in a pearl chain-like arrangement. When the device is mounted on the skull of the subject, the microprobe shafts penetrate the brain region of interest. Immediately after electri-

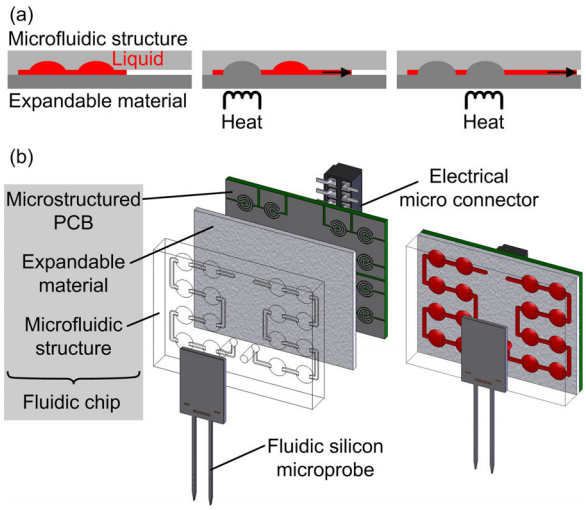

Figure 1: (a) Micropumping principle for liquid delivery. (b) Schematic drawing showing the different components of the NeuroMedicator.

cal connection, drug liquid volumes can be individually infused through the two microprobes into the tissue.

FABRICATION AND ASSEMBLY

The complete fabrication and assembly sequence of the NeuroMedicator is schematically shown in Fig. 5. Thereby, the microstructured PCB, the microfluidic structure, and the fluidic silicon microprobes are first fabricated as individual components. The following subsections describe the fabrication of the components followed by the assembly of the entire device.

Microstructured PCB

A microstructured multilayer PCB serves as the backbone of the NeuroMedicator. The PCB technology combines the advantages of an established electrical via-technology with a relatively low thermal conductivity. The latter is important to keep the power requirements of the microheaters low. However, if microheaters are directly implemented in the copper (Cu) layers of standard PCBs, the thickness and good conductivity of Cu require currents of a few hundred milliamperes at voltages far below 1 V during operation. This can complicate stand-alone-operation when power is only available from 3 V button cells. To overcome this, microheaters have been fabricated by thin film processing of sputtered titanium (Ti) films on custom-specific multilayer PCBs (ANDUS Electronic, Berlin, Germany) as shown in Fig. 2. The Ti tracks of the heaters have a width of 150 µm and a thickness of 400 nm. To facilitate lithographic processing, the PCBs have been designed as 100-mm-discs. Each disc is 500 µm thick and contains 16 NeuroMedicator backbones of 11×14.5 mm². The PCB

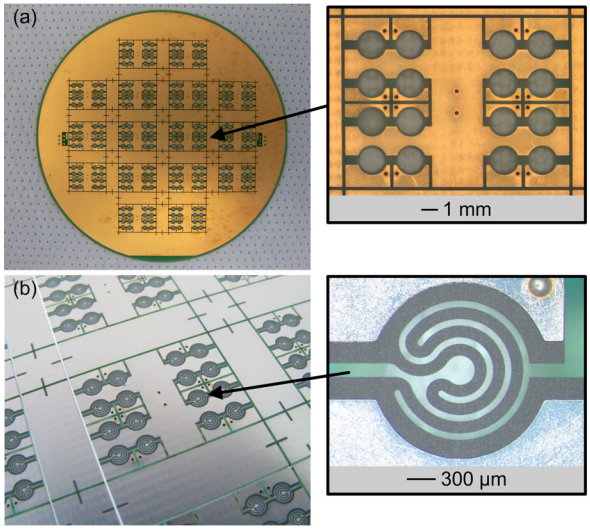

Figure 2: Thin film fabrication of microheaters. (a) Multilayer PCB 100-mm-disc. (b) Fabricated microheaters after deposition and etching of Ti.

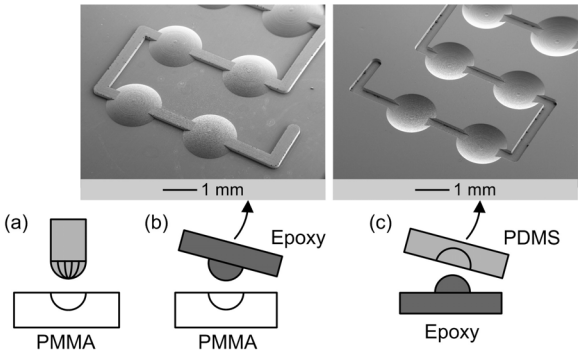

Figure 3: Three-step fabrication process of the microfluidic structure. (a) Milling of a positive PMMA master, (b) casting of a negative epoxy mould, and (c) PDMS replica moulding of the fluidic structure.

substrate underneath the microheaters is selectively thinned to a thickness of 150 µm for better thermal isolation of the heaters. After thin film processing, dicing of the backbones is performed on a standard wafer saw.

Microfluidic Structure

The microfluidic structure is fabricated by replica moulding of biocompatible PDMS RTV 615 (Momentive). To ensure complete delivery of the liquid volumes, the chambers of 0.25 µL are designed as spherical segments which are connected by 300×150 µm² channels. Since PDMS exhibits certain shrinkage after thermal cure, this has already been accounted for in the design process. The corresponding three-step fabrication process is illustrated in Fig. 3. First, a positive master of the microfluidic structure is milled in poly(methyl methacrylate) (PMMA). Afterwards, a negative mould is casted with epoxy. The 2-mm-thick microfluidic structure is created by PDMS replica moulding. Finally, through holes are punched-out by using sharpened steel capillaries.

Fluidic Silicon Microprobes

Fluidic silicon microprobes are fabricated in a two-wafer silicon fusion bond process applying standard 300-µm-thick 4-inch silicon (100) wafers, deep reactive ion etching (DRIE), wafer grinding, and thin film processing as described in [4]. Each probe comprises two 8-mm-long shafts with a cross-sectional area of 250×250 µm² attached to a common platform of 6×4 mm² as shown in Fig. 4. The fluidic inlet ports of Ø 300 µm as well as the outlet ports of Ø 25 µm are oriented out-of-plane on opposite sides of the probe. The microfluidic supply channel narrows starting at the inlet to a cross-section of 50×50 µm² in the probe shaft.

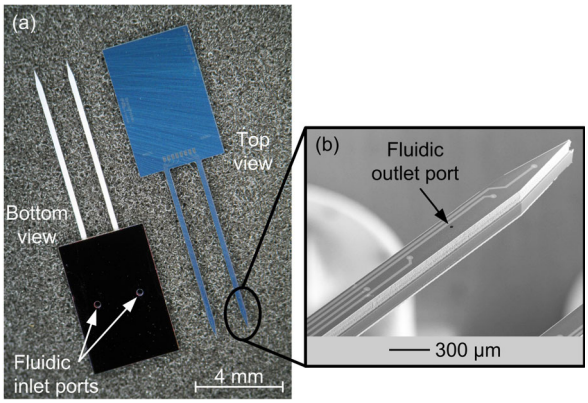

Figure 4: Fabricated fluidic silicon microprobes. (a) Top and bottom view of microprobes. (b) SEM picture of the probe tip.

NeuroMedicator Assembly

In the assembly process, a micro connector is first attached to an individual, microstructured PCB backbone by reflow soldering (Fig. 5c). Afterwards, the expandable material is prepared by mixing PDMS RTV 615 with Expancels 820 DU 40 (Expancel, Sundsvall, Sweden) at a weight ratio of 2:1. A 500-µm-thick expandable layer is spincoated on the topside of the PCB and cured at 60°C (Fig. 5d). An additional 100-µm-thick layer of pure PDMS separates liquids from the expandable material and promotes subsequent bonding of the microfluidic structure. Then, the microfluidic structure is oxygen plasma bonded on the expandable material (Fig. 5e). Since the fluidic chambers have to be situated directly above the heating elements which are now not visible anymore, a double-sided alignment is required. This

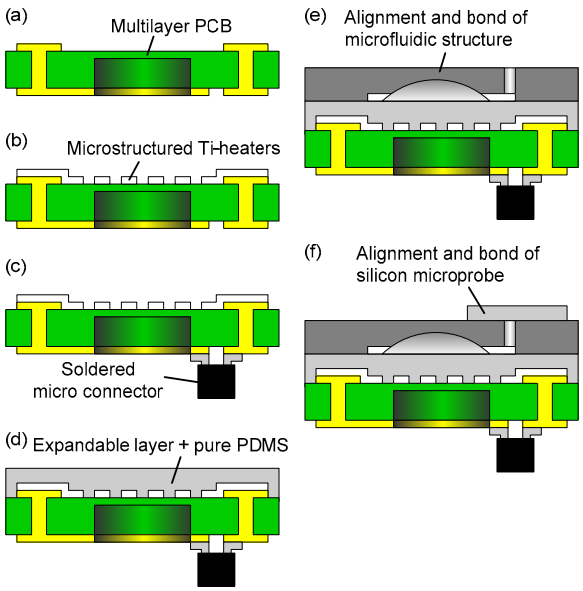

Figure 5: Schematic illustration of fabrication and assembly of the different components of the NeuroMedicator.

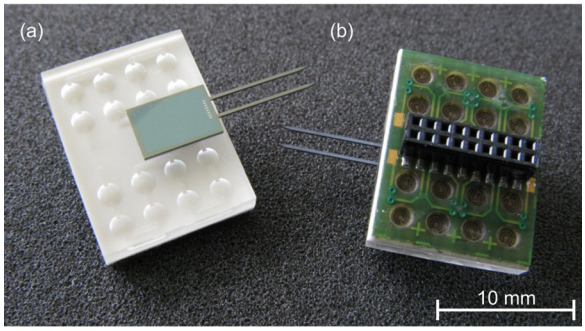

Figure 6: Assembled NeuroMedicators showing (a) the top side with the fluidic chambers and the microprobes as well as (b) the bottom side with the electrical connector.

is realized on a modified fineplacer (Finetech Pico). At this point fabrication of the fluidic chip, which can be operated without silicon microprobes, is finished. For fabrication of the NeuroMedicator, the platform of the fluidic microprobes is additionally bonded on top of the microfluidic structure by using oxygen plasma (Fig. 5f). Since the fluidic inlet ports of the microprobe platform have to match exactly the through holes of the microfluidic structure, a face-to-face alignment is necessary before bonding. This is again performed on a fineplacer. Top and bottom side of assembled NeuroMedicators are shown in Fig. 6.

EXPERIMENTS

All experiments have been performed by first filling the microfluidic structure with liquid under vacuum and subsequent actuation. Since the resistance of the microheaters is increasing with temperature and might additionally vary slightly from device to device, power-controlled heating was implemented. A source meter with microcontroller (Keithley 2602) was programmed to maintain the heating power on the predefined level during the whole actuation time.

First, the fluidic chip without microprobes was characterized. For this purpose fluidic tubing with an inner diameter of 400 µm was inserted into the through holes of the microfluidic structure. After filling the device with water, the delivered liquid volumes (Fig. 7a) as well as the transient delivery characteristics (Fig. 7b) of the fluidic chip were characterized with a microbalance (Sartorius LE26P) and a thermal flow sensor (HSG-IMIT proprietary), respectively. Individual heating with 225 mW for 10 s resulted in an average delivered volume of 0.25±0.02 µL for eight consecutive deliveries. The transient characteristics show a steep increase in delivery rate within half a second followed by a slow descent. All of the liquid is delivered within three seconds. Afterwards, operation of the NeuroMedicator was optically verified by filling the fluidic chambers through the microprobes with concentrated ink and sequential delivery into

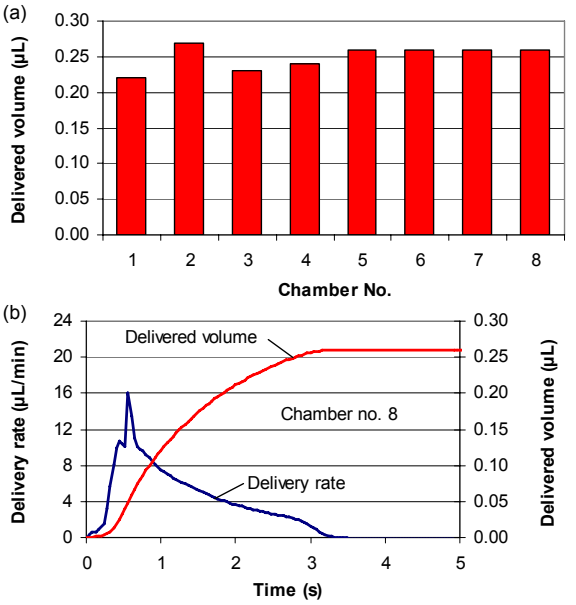

Figure 7: Representative delivery characteristics of a fluidic chip after individual heating with 225 mW for 10 s. (a) Delivered liquid volumes in consecutive order for one half of the device. (b) Transient delivery rate and delivered volume for chamber no. 8.

water as shown in Fig. 8. To achieve complete delivery, the heating time had to be doubled to 20 s. This can be attributed to the increased flow resistance of the microprobe in comparison to the tubing used for characterization of the fluidic chip. Although certain parts of the chambers remained stained due to the concentrated ink, cross sections of actuated chambers proof complete delivery.

CONCLUSION

We presented a novel, compact drug delivery system which enables the precise on-demand infusion of 0.25±0.02 µL portions of liquid drug through silicon microprobes. Experiments showed that the fluidic resistance of the microprobes in conjunction with the observed delivery rate increases actuation time. Hence, slower heating rates resulting in smaller delivery rates should be addressed here. Although the use of PDMS for the microfluidic structure offers the convenience of easy replication and bonding, PDMS is also known as a material with high vapor permeability and liquid absorption. This limits at the moment the liquid storage stability to approximately 24 h at ambient conditions. Therefore, alternative materials are currently evaluated. The current implementation concept of the NeuroMedicator allows further development of the device towards a stand-alone drug delivery system with wireless control.

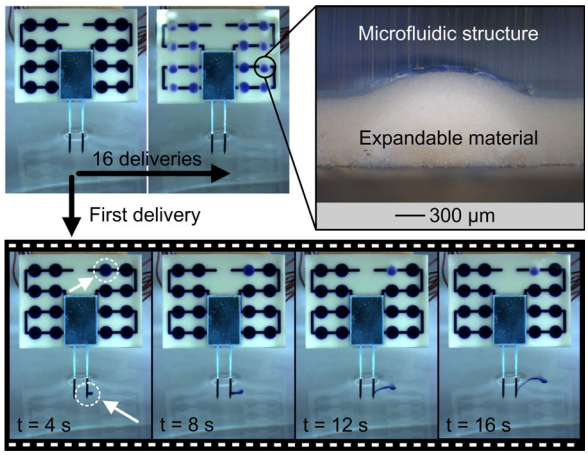

Figure 8: Transient actuation of an ink-filled NeuroMedicator with the probe tips inserted into water. A cross section of an actuated chamber shows complete delivery.

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