DISCRETE CHEMICAL RELEASE FROM A MICROFLUIDIC CHIP

M. Hu[1], T. Lindemann[1], T. Göttsche[2], J. Kohnle[2], R. Zengerle[1,2], and P. Koltay[1]

[1]University of Freiburg - IMTEK, Laboratory for MEMS Applications,
Georges-Koehler-Allee 106, D-79110 Freiburg, Germany
e-mail: minhu@imtek.de
[2]HSG-IMIT, Wilhelm-Schickard-Str. 10, D-78052 Villingen-Schwenningen, Germany

ABSTRACT

Controlled chemical release has many applications, including treatment for diabetes and stimulation of neurons. In this paper we present a discrete chemical release method capable of delivering picoliter volumes of chemical solutions with 100 µm spatial and 20 µs temporal resolution. The releasing mechanism is based on the transfer of discrete picoliter sized liquid droplets from an ejecting nozzle to a receiving aperture, through an air-trapped hydrophobic chamber. This new method could be a key enabling technology for the precisely controlled release of biochemicals, like potent drugs and neurotransmitters, for modern clinical therapeutics and biological research.

1. INTRODUCTION

Controlled release techniques play an important role in drug delivery and chemical stimulation. For this purpose tools capable of delivering precise dosage of drug/chemicals at the right time and as close to the treatment (or stimulation) site as possible are required [1].

In the last decade, numerous controlled release techniques have been reported, ranging from core-shell nanoparticles for stimuli-sensitive cancer therapy [2] to novel microfabricated chips for repetitive chemical stimulation of cells [3]. Most of these recent techniques fall into two categories: polymer-based systems and microdevice-based systems. While the polymer-based systems can be biodegradable which means no surgery is required to implant or remove the systems, microdevice-based systems can provide greater temporal and spatial control over the drug release process [4]. For instance, a solid-state silicon microchip has been presented by John T. Santini Jr and his co-workers [5], which could release single or multiple chemical compounds in small volumes at multiple, well-defined locations.

In this paper we present a new approach to release chemical solutions on demand in discrete liquid plugs. This technique outperforms the existing solutions by far, especially regarding the volume and spatial resolution as well as the temporal control of the release profile.

2. METHOD

The main technological challenges for temporal and spatial control of drug or chemical release are, how to swiftly switch on and off a tiny array of delivery apertures, as well as how to effectively block any possible leakage and diffusion when the drug or chemical is not demanded. The latter is an especially critical issue for chemical stimulation in cell biological studies.

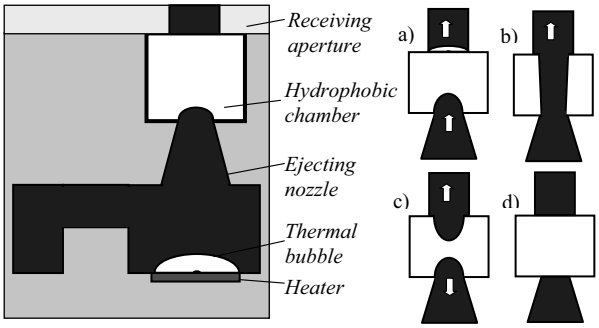

Figure 1 Working principle of discrete chemical release based on thermal bubble actuation. a) - d) shows how the hydrophobic chamber allows a pulsed liquid plug or droplet to pass through it.

To avoid continuous chemical stimulation as a consequence of diffusion, it is proposed that the drugs and chemicals are released by burst liquid ejection. The micro device considered for this purpose consists of a pulsed thermal bubble generator combined with an ejecting nozzle, a leakage-blocking hydrophobic air chamber and a receiving aperture (Figure 1). The pulsed thermal bubble generator produces discrete liquid plugs or droplets with high speed and on demand at the ejecting nozzle. Alternatively also a micro piezoelectric actuator known from inkjet print heads could be applied. The hydrophobic air chamber - the key element of the device - works as a reversible burst valve. It normally prevents liquid passing through, thus preventing any leakage by diffusion. Only ejected liquid plugs with sufficient kinetic energy to overcome the surface tension can cross the air gap and reach the receiving aperture on the other side of the hydrophobic chamber. As the air in the chamber is not escaping during the liquid ejection, the blocking effect of the hydrophobic chamber can be sustained permanently.

Due to its fast dynamic and on demand characteristics (similar to inkjet printing), this chemical release method has many advantages, which include but are not limited to: 1) Accurate delivery. The delivered chemical volume can be

precisely controlled; the resolution can be in the picoliter range. 2) Versatile controllability. Nonlinear, time-varying and even arbitrary delivery profiles can be easily implemented with this rapid and discrete approach. 3) Fast response. The chemical release process can be completed within microseconds. 4) Repeatable release. Chemical doses can be repeatedly delivered on demand. 5) Leakage free performance. The delivery aperture is completely cut-off by liquid surface tension when the chemical is not demanded. As long as the static pressure in the fluid channel does not exceed the threshold value, no leakage will occur. 6) Efficient delivery. The release of drugs is very effective, no liquid suck back, no extra drug and buffer are lost like in a negative pressure system. 7) Easy integration. The simple design is very suitable for system integration (e.g. for in vivo applications), as the pulse pressure generators can be micro fabricated with established techniques. 8) Multiple applications. Based on the same working principle, new microfluidic devices and platforms can be built for e.g. biomedical diagnostics and analytical chemistry.

3. DESIGN

Based on the described working principle, a microfluidic chip for fluid delivery into an aqueous medium via an integrated air-gap was designed by applying a thermal bubble actuation (Figure 2).

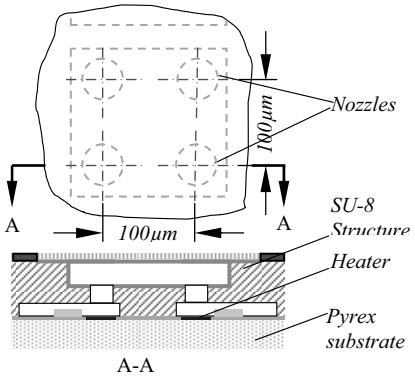

Figure 2 Design of microchip with integrated air-gap. On the top center of the chip is a 10 x 2 aperture array with a pitch of 100µm and a diameter of 30µm for each nozzle.

The microchip comprises fluid channels with 20 individually addressable delivery units. These delivery units are evenly deployed, forming a 10 x 2 release array with pitches (spatial resolution) of 100 x 100µm. Each delivery unit has a short structured microfluidic channel connecting to the main chemical supply. At the end of this connection channel a micro heater is located. Directly on the top of the micro heater there is the ejecting nozzle, which is 30µm in diameter and 35µm high. On top of each ejecting nozzle a hydrophobic air chamber, with 70µm diameter and 300µm height is realized. Depending on the application, the microchip surface can be covered either with a layer containing a micro machined receiving aperture, a nanoporous membrane or – as in the experiments presented later on - with a cell culture insert with a porous membrane at the bottom to form the receiving area (Fig. 6).

4. SIMULATION

To verify the working principle and check the feasibility of the presented chip design, a numerical simulation based on a single delivery unit was performed to show the dynamic process of a pulsed liquid plug crossing the hydrophobic chamber.

The commercially available software CFD-ACE+ was chosen for this numerical modeling. CFD-ACE+ uses numerical methods to solve the Navier-Stokes equation and mass continuity equation and adopts the volume-of-fluid (VOF) method to model free boundary surfaces. Therefore, it can simulate three-dimensional and complex fluid flows like a liquid plug flying through a narrow air gap. The CFD model (Figure 3) was built based on the geometry of the delivery unit. To simplify the simulation, we used an equivalent receiving nozzle instead of a porous aperture as the receiving surface. The thermal bubble actuation at the micro heater area was modeled as inlet boundary condition as proposed by A. Asai et al [6]. The bubble growth and collapse is thus approximated by an appropriate airflow through the heater area.

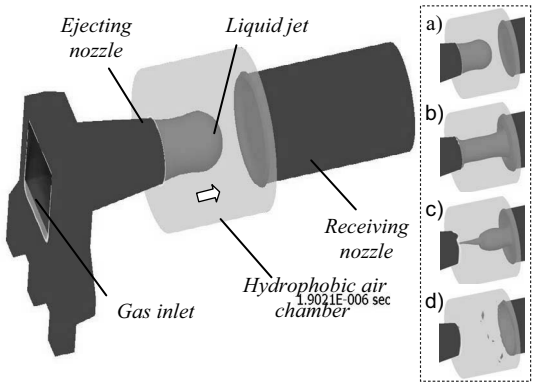

Figure 3 Schematic CFD model and simulation of micro liquid plug flying over a hydrophobic air chamber. a) liquid ejecting at t = 2 µs; b) liquid bridging the air gap at t = 4µs; c) breakup of the liquid plug at t = 14µs; d) transportation process at t = 28 µs.

The simulation results show that corresponding to the growing bubble, a discrete liquid plug can be generated from the ejecting nozzle. Due to the fast dynamics behavior of the bubble actuation, the speed of ejected liquid plug can be very high (about 10m/s). The liquid plug subsequently flies over the hydrophobic chamber and impinges onto the liquid meniscus in the receiving nozzle and forms a liquid bridge. Meanwhile, the collapse of the thermal bubble cuts off the ejected liquid column. After that the tail of the liquid plug retracts into the receiving nozzle. Within a single ejection, a liquid amount of 20pl could be transferred in 20 microseconds.

5. FABRICATION

We have chosen SU-8 to fabricate the microfluidic structures because of its excellent resistance to chemical treatments and good biocompatibility. As SU-8 is a negative tone resist, however, we could not directly obtain the embedded channels, nozzles and air chambers by sequentially spin-coating and patterning SU-8 layers. We had to use bonding technologies to realize these embedded microstructures. Correspondingly, the fabrication process (Figure 4) consists of three aspects: 1) fabrication of chip lower part with micro heaters, electronic interconnections and open fluidic channels on the Pyrex substrate; 2) preparation of chip upper part with ejection nozzles and hydrophobic air chambers; 3) bonding of the two parts with adhesive epoxy.

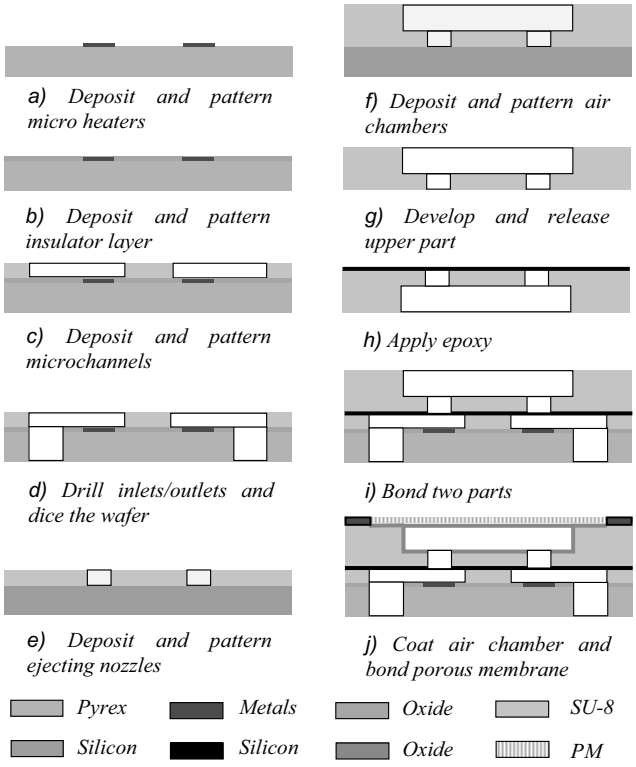

Figure 4 Schematic diagram of microfabrication process

For the fabrication of the lower part of the chip, first a 100 nm thick titanium layer and a 500 nm thick gold layer respectively were magnetically sputtered and wet etched to form the micro heaters and electrical interconnections on the Pyrex substrate. Then, a 2μm thick LTO was deposited and patterned on the micro heaters and interconnection lines as an insulation layer. After that, a 20μm thick SU-8 2025 layer was spin-coated and patterned with top-open microfluidic channels. Finally, the wafer was diced to chips after the mechanical drilling of the fluidic inlets and outlets on the Pyrex substrate.

The chip's upper part was initially fabricated on a silicon wafer by spin coating and patterning of multi layers of SU-8. First, a very thin layer of OmniCoat was applied to the wafer surface by spin coating for the later release of the SU-8 structures as described in [7]. Then, a 25μm thick layer of SU-8 2025 and a 300μm thick layer of SU-8 2100 were sequentially spin-coated and lithographically patterned to form the ejection nozzles and air chambers. After that, the wafer was put into SU-8 developer in an ultrasonic bath. Due to the internal stresses of the baked layers the patterned SU-8 structures could be easily released from the silicon substrate.

For the bonding of the two separately fabricated parts, first a very thin (about 5μm thick) layer of adhesive epoxy was evenly applied to the bonding surface of the upper SU-8 structure by a roller (custom made by NMI, Germany). Then the two parts were held, aligned and pressed together with a chip-bonding system (Fineplacer Lambda from Finetech GmbH). After that, the bonded chips were put into an oven and dried at 80°C for 30 minutes. Here, control of the thickness of epoxy is critical for the success of this bonding process. Due to the capillary action of microchannels, the adhesive epoxy could have flown into and totally block the microfluidic channels during the bonding or drying process, if the applied epoxy would not have been thin enough.

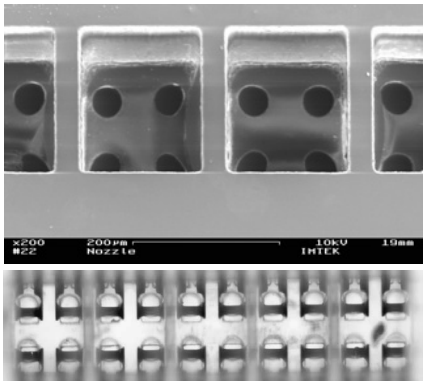

Figure 5 SEM image for the air chambers of the microchip (top) and microscope image for the micro heaters through the SU-8 micro nozzles and air chamber (bottom).

The hydrophobic coating of the air chambers was performed as last step. Perfluorodecyldimethyl-chloro-silane (PFDMS) was dropped to the air chambers and then blown away while the microfluidic channels and nozzles were filled with photo resist for protection. Figure 5 shows an SEM image of the air chambers of the microchip (top) and microscope image for the micro heaters through the SU-8 micro nozzles and air chamber, before it was glued and wire-bonded to a printed circuit board for testing.

6. EXPERIMENT

To facilitate the testing, we directly attached a cell culture insert (PICMORG50 from Millipore) with double-sided type rather than a single layer of porous membrane on the top of the microchip (Figure 6). The insert has a porous membrane bottom (with pore size of 0.4 micron). After filling black dye to the chip inlets and DI water to the cell culture insert, the microchip was put under a stereo stroboscopic camera. Two

arbitrary waveform generators (Agilent 33120A) were connected in burst mode to trigger the micro heaters through a drive circuit for power amplification. In this way, both the energizing (heating) time and frequency of the heater (and delivery unit) under test could be precisely controlled. At the same time, the triggering signal was also used as synchronizing input for the stroboscopic camera.

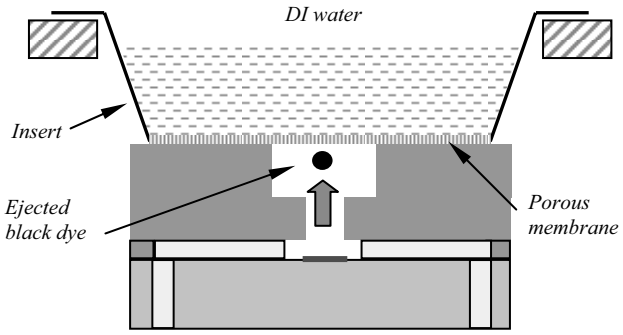

Figure 6 Experimental setup.

For the first test, we triggered the micro heater under test at a frequency of 5 kHz to observe the burst release of different amounts of black dye within a very short period (Figure 7). The delivery unit could continuously work at extremely high speeds, and the amount of released black dye is increasing with the number of triggered droplets. Therefore, time-varying and non-linear delivery profiles can be realized this way easily.

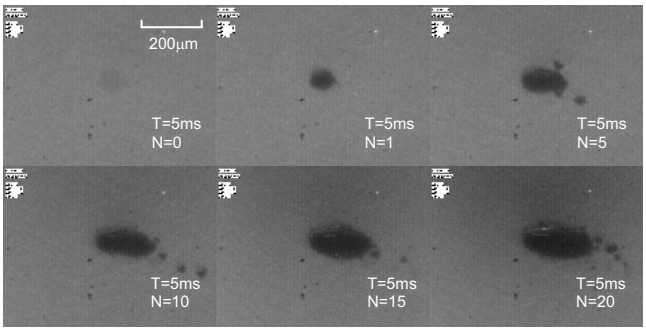

Figure 7 Top view of the porous membrane. T is the delay time for the stroboscopic image recording that was counted from the first triggering pulse; N stands for the number of trigger signals sent to the heater (at 5 KHz).

For the second test, the time-resolved concentration of black dye around a delivery aperture was measured. The experiment was performed by releasing one drop of black dye at the beginning. Then every second a picture was taken and from the grey scale values the concentration of black dye in the DI water was deduced. The black dye diffused over time within the DI water and the concentration decayed as expected (Figure 8).

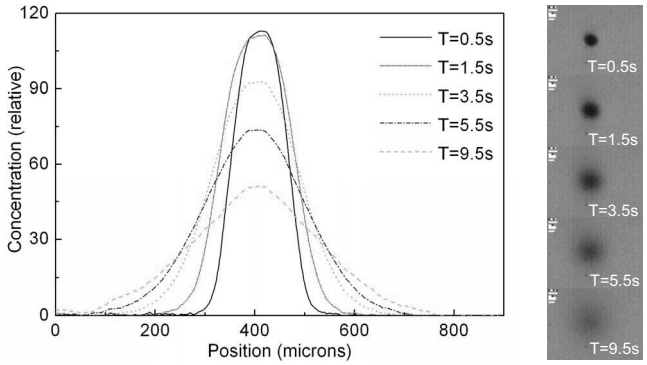

Figure 8 Time-resolved concentrations of dye (inverted grey level) around a delivery aperture.

7. CONCLUSION

A novel microfluidic method for temporal and localized delivery of liquid chemicals has successfully been demonstrated. Significances of this on-chip drop-on-demand technology include versatile controllability, leakage free operation, high resolution and fast response. Future work will be dedicated to the application of the presented device for stimulation of living cells.

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