A MODULAR DISPENSING SYSTEM FOR LEAKAGE-FREE PICOLITER DROPLET RELEASE IN LIQUID ENVIRONMENTS

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ABSTRACT

We present a new tool that can be positioned accurately next to any individual cell for the precisely controlled transfer of individual picoliter (pL) droplets in the range of 150-950 pL ($CV < 3.5\%$) in liquid environment while avoiding any leakage. This is achieved by a low-cost, disposable and biocompatible cap that is placed on top of any pL-dispenser and generates a phase-gap between dispensing agent and target liquid when the dispenser is dipped into the latter thus avoiding diffusive transport. We developed two different working modes: (*i*) the standard mode enables an instant injection (<< 1 ms) of the droplet into the liquid environment and (*ii*) the focus mode further increases the spatial resolution from 100 µm to 50 µm. For the phase-gap we have proven an excellent long-term stability of more than 30 hours against capillary priming and a maximum volume ejection rate of up to 137 nL/s without flooding.

KEYWORDS: discrete chemical release, leakage-free, drug delivery, pL-droplets

INTRODUCTION

Modern therapeutic techniques and chemical cell stimulation are based on highly targeted delivery of chemicals [1]. Current challenges are: 1) precise dosage administration; 2) localized chemical delivery; 3) temporal control of release profile. MEMS devices have been presented that could release chemical compounds in small volumes [2] at multiple, well defined locations [3].

Our motivation is to chemically stimulate individual cells in their physiological environment where a high temporal and spatial resolution of the drug release is required [4,5]. In this paper we present a new approach to release chemical solutions on demand in liquid environments. 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.

MODULAR DISPENSING SYSTEM

We developed a self-aligning hydrophobic PDMS cap (Fig. 1A) that can easily be attached to our novel piezo-stack actuated NanoJet dispenser spanning a large volume range (V = 150-950 pL) with excellent properties ($R^2 = 0.995$, $CV \leq 3.5\%$) (Fig. 1C). Inserting the modular system into liquid traps air inside the cap and forms two stable menisci at the nozzle and the outlet (Fig. 1B). This way, the phase-gap is generated and works as a reversible burst valve that prevents any leakage by

diffusion. Solely ejected droplets are able to overcome the phase-gap which was demonstrated in simulations [6].

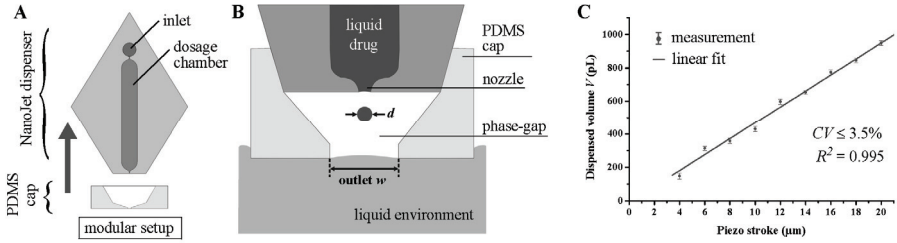

Figure 1. (A) Concept of the modular dispensing system. (B) Working principle of the phase-gap concept. (C) Characteristics of the NanoJet dispenser.

TWO WORKING MODES OF THE PHASE-GAP

We developed two different setups optimized primarily for increased temporal or spatial resolution (Fig. 2). For outlet widths w larger than the droplet diameter d, the whole drug volume is injected into the liquid in a time frame $t_0 << 1$ ms (Fig. 2A). This setup is useful for neural stimulation where highly dynamic neural activity is initiated. If the application demands higher spatial resolution, the droplet with initial diameter d is focused on a smaller outlet area ($d > w$) sticks at the conical, hydrophobic outlet and is slowly released *via* convection forces into the liquid environment. The drug inside the droplet with an initial diameter of $d = 100$ µm is spatially focused to the smaller outlet ($w = 50$ µm) with a temporal delay correlating with the size of the outlet (Fig. 2B). The defined outlets are fabricated by casting a silicon master in biocompatible and hydrophobic PDMS applying a force of $F = 95$ N (Fig. 3A).

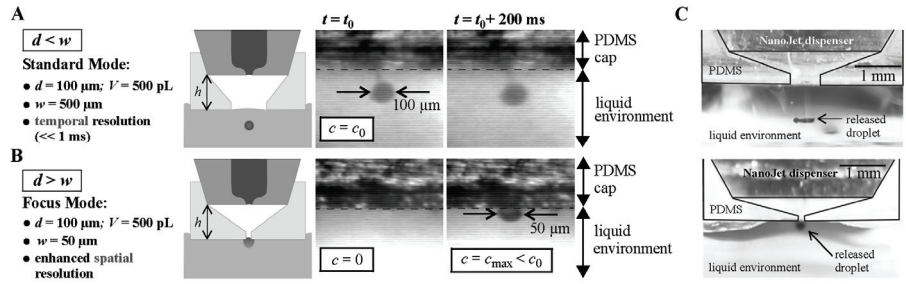

Figure 2. The two working modes of the phase-gap concept. (A) Standard Mode for high temporal resolution. (B) Focus mode for enhanced spatial resolution. (C) Microscopic image of the experiments.

PHASE-GAP STABILITY TESTS

We have proven long-term stability of the phase-gap in liquid environment for more than 30 hours for inactive dispensers. In operation the ejection rate is limited in order to avoid flooding of the phase-gap. Figure 3B shows the maximum volume

ejection rate for various ejection volumes. We achieved up to 137 nL/s at a resolution of 250 pL at 475 Hz (limit of driving electronics) sufficient for typical ejection rates in cell stimulation (< 0.1 nL/s [7]).

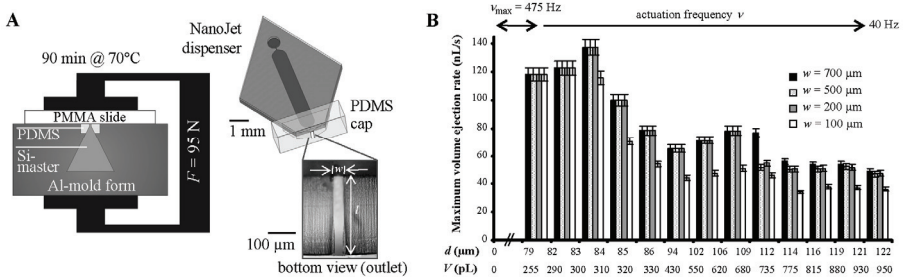

Figure 3. (A) The flexible fabrication process of the disposable phase-gap cap. (B) Maximum volume ejection rates where no flooding of the phase-gap occurs.

CONCLUSIONS

The developed system featuring leakage-free dispensing of chemicals in spatially (100 µm) and time resolved (<< 1 ms) manner. This is promising to be a key technology for chemical stimulation of individual cells in physiological environment. Furthermore, this phase-gap technology could easily be applied to further dispensers, just by adapting the mold master.

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