COMBINATION OF OPTICAL MANIPULATION OF PARTICLES AND PATTERNING OF HYDROGELS FOR DEMONSTRATION OF DIGITAL DRUG COCKTAILS

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ABSTRACT

This study presents an integrated microfluidic system combining two techniques, including an optically-induced dielectrophoresis (ODEP) module for manipulation of drug particles and an UV-direct-writing module capable of patterning of hydrogel, for applications of digital drug cocktails. This system was able to provide an automatic and customized production of drug cocktails. Experimental results showed that poly (ethylene glycol) diacrylate (PEGDA) hydrogel performed well under the ODEP operation which made it possible to be manipulated and UV-cured to form the drug particles. Moreover, a drug cocktail could be formed in less than 30~60 seconds. With a digital micromirror device (DMD) to form an UV-direct-writing module, the UV-curable pattern could be easily designed and formed, thereby allowing the formation of drug cocktails patterned in different shapes.

INTRODUCTION

Drug cocktail is a promising therapy which uses specific combinations of various drugs to improve the efficacy of therapies [1]. However, reducing the time required for fine-tuning the ratio of drugs in the combination is of great need. The most commonly used method for drug cocktail formulation is the liposome or the so-called lipid vesicles approach [2]. Although it shows great promise as a drug carrier, the time required for forming liposome spheres carrying drug combinations may be as long as 2 to 20 hours, depending upon the size of the liposomes. Recently, a study reported the use of UV-curable hydrogel for developing digital drug cocktails [3]. UV light was used for curing the hydrogel for the test of cancer cells. However, this platform did not completely automate the whole process and the ratio-changing process needed extensive manual steps. In this work, we cleverly integrated an ODEP module to optically manipulate drug particles such that drug cocktails with pre-set ratios could be formed. Then an UV-direct-writing module using a UV-DMD device was used to cure the hydrogels containing these drug cocktails. With this approach, seamless integration of drug particle manipulation and drug cocktail formation could be demonstrated.

MATERIALS AND METHODS

Figure 1 illustrates experimental process for formation of drug particles with different combinations. The particles were first selected and assembled by ODEP force, which could be generated from optically-induced dielectrophoresis by projecting light patterns on indium tin oxide (ITO) glass layers surface-coated with a photoconductive layer [4]. With different dynamic and moving light patterns, specific particles could be selected and assembled accordingly. Then an UV-direct-writing module which was composed of an UV-LED (BUV-6BK, OPTO-IN CO., Ltd., Taiwan) and a UV-DMD device (DLP7000UV, Texas Instruments, USA) was used to cure the PEGDA (Catalog number 455008, Sigma-Aldrich, USA) to form a specific pattern containing pre-assembled particles. The UV-LED device had a wavelength of 365 nm and a power of 30W with a light spot diameter of 10 mm. The UV-DMD device was used to provide dynamic and moving UV light patterns by using UV-LED as a light source. Note that the UV-DMD was able to switch the angle of each and every micro-mirror between on and off states so that the reflection of the UV-beam could turn into a specific light pattern in less than 0.1 seconds. Therefore, a digital drug cocktail demonstrating combination drugs with selected drug particles could be realized.

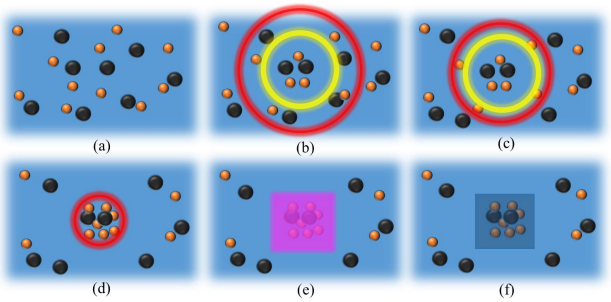

Figure 1: A schematic illustration showing the total operating procedure performed on the microfluidic chip for formation of drug cocktails in hydrogels. (a) Initial condition of medium with different sizes of drug particles. (b) ODEP manipulation of particles by using dynamic and moving light patterns. (c) Selection of the chosen particles. (d) Assembly of a combinational drug containing different drug particles. (e) Exposure of an UV light with designed light pattern. (f) Formation of digital drug cocktail after the UV exposure to cure hydrogels.

Figure 2 shows an exploded view of the microfluidic chip for ODEP operation and a photographed of the assembled chip. It was composed of polydimethylsiloxane (PDMS) inlet/outlet, top ITO glass, a double-side tape and a bottom ITO glass with hydrogen-rich amorphous silicon layer and a thin molybdenum layer. The dimensions of the chip were measured to be 56 mm x 28 mm.

As shown in Figure 3, the integrated microfluidic system was composed of three modules, including a charge-coupled device (CCD) module, a UV-direct-writing module and an ODEP module. The ODEP forces were generated while the optical patterns were provided from the bottom and UV light patterns were provided from the top to cure the hydrogels.

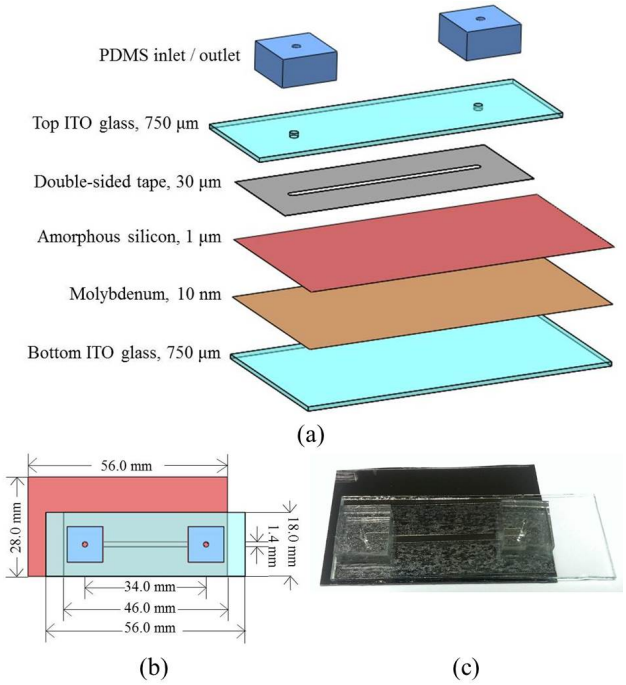

Figure 2: A schematic illustration of the ODEP chip for manipulation of drug particles. (a) An exploded view of the chip. There were six layers in the chip. From top to bottom were PDMS inlet/outlet, top ITO glass substrate, double-sided tape channel layer, amorphous silicon layer, molybdenum layer (adhesive layer) and a bottom ITO glass substrate. (b) The assembly of the chip showing the detailed dimensions. (c) A photograph of the chip. It could be used for the ODEP module to select and assemble particles.

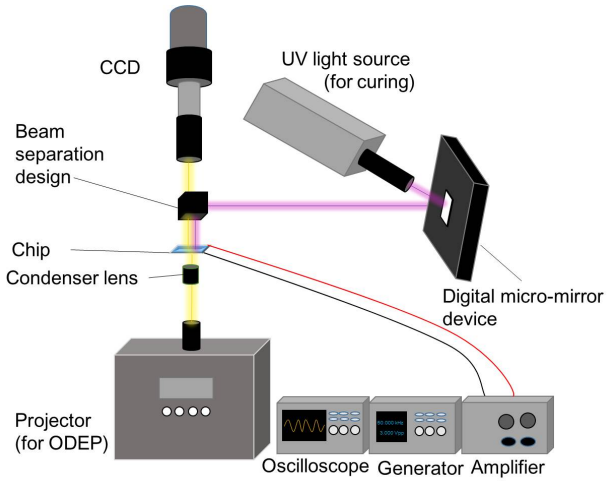

Figure 3: Experimental setup of the integrated microfluidic system. It was composed of three modules, including a charge-coupled device (CCD) module, a UV-direct-writing module and an ODEP module. The ODEP forces were generated while the optical patterns were provided from the bottom and UV light patterns were provided from the top to cure the hydrogels.

RESULTS AND DISCUSSION

PEGDA in ODEP operation

In order to demonstrate the feasibility of the proposed system, the optimal ratio of PEGDA and 0.2M sucrose solution (for ODEP operation), which could generate reasonable UV curing and could be induced with excellent ODEP operation simultaneously, was first explored. ODEP force was found to be well induced in 0.2M sucrose solution as the medium with an acceptable biocompatibility [5]. This is the first time that PEGDA was used as the medium of the ODEP module. Since a photo initiator (PI) needs to be added while PEGDA was UV-cured, the effect of the addition of the PI in PEGDA on the generation of the ODEP force was investigated such that one could verify whether it had any adverse effect on ODEP performance. As shown in Figure 4, the results showed that it only caused about 1% decrease on both ODEP repelling force and beads movement velocity. Note that PEGDA solutions with different concentrations (10%, 15% and 20%) were tested at an AC frequency of 50 kHz and an AC voltage of 15 Vpp.

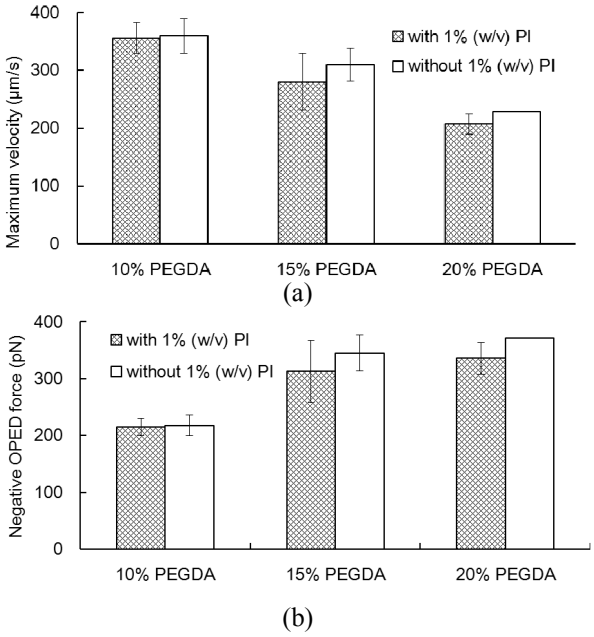

Figure 4: Comparison of (a) the maximum velocity and (b) the corresponding ODEP force for different concentrations of PEGDA and the addition of the photo-initiator (PI).

Next, the optimization of the ODEP force by using PEGDA with different concentrations (10%, 15% and 20%) was performed. As shown in Figure 5, a biggest force of 335 pN and a fastest bead movement velocity of 356 µm/s could be provided at a driving frequency of 50 kHz and a voltage of 15 Vpp. The ODEP force could be then used to manipulate the drug particles, including separation and accumulation. When compared to a previous study [4], this result is almost two times better in terms of ODEP performance.

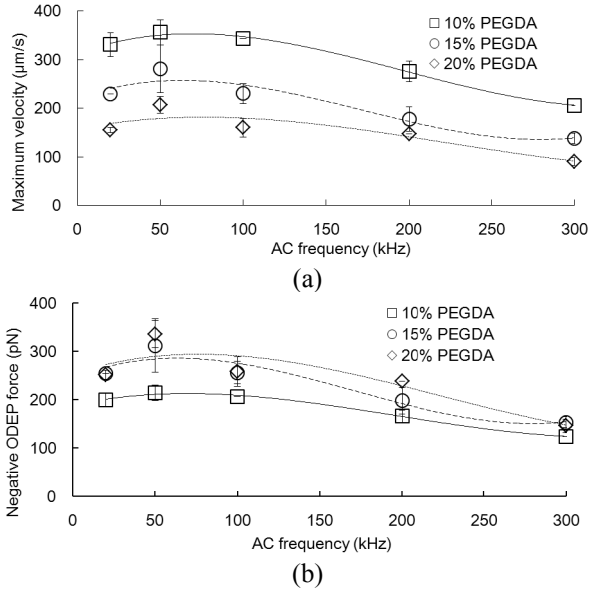

Figure 5: Comparison of (a) the maximum velocity and (b) the corresponding ODEP force for different concentrations of PEGDA at different driving frequency. The driving voltage was 15 Vpp.

Collected particles in PEGDA

The manipulation process of particles in PEGDA medium was further demonstrated. In Figure 6(a), a simple diminishing, moving circular light pattern was used to collect the particles to a specific area, then gathering more than 40 beads in only 18 seconds, while using a PEGDA solution of 15% (m/v) operating at 50 kHz, 15 Vpp. In Figure 6(b), a ring-shape diminishing, moving pattern was used to perform a stronger manipulation for drug cocktail fabrication, thus gathering more than 60 beads in a ring arrangement in only 22 seconds with an automatic process. It shows that ODEP operation is feasible in a medium containing PEDGA, which is ready for us to form digital cocktails.

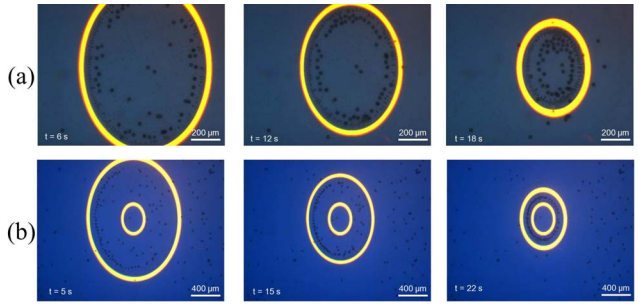

Figure 6: A series of snap-shots for the dynamic optical patterns generated from the ODEP module projecting to assemble particles.

Demonstration of patterned hydrogels after ODEP manipulation

With the capability of manipulating particles by using the ODEP module, the formation of patterned hydrogels by using a photomask was first demonstrated. With this approach, we could simply demonstrate the whole process to prove that this method was feasible on the microfluidic chip. For the particle manipulation, we chose ring-shape pattern to prove the ability to collect the particles. Similarly, for the curing process, we used two patterns (circular and rectangular) to show the ability to control the resulting shapes, which were shown in Figure 7. Preliminary results using a UV-DMD and a UV-LED showed that similar results could be generated.

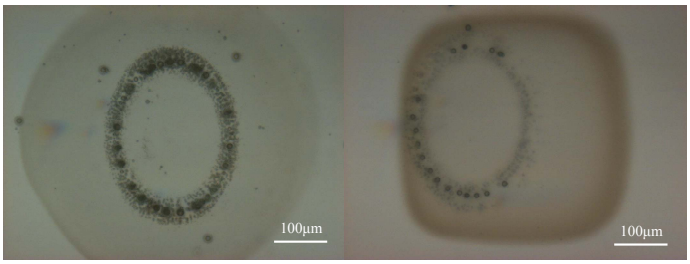

Figure 7: Beads embedded by UV direct writing after ODEP manipulation. More than 40 beads were assembled into a ring by ODEP force and cured into (a) circular and (b) rectangular shapes by UV exposure in 30 seconds

CONCLUSIONS

In this work, a new approach using an integrated microfluidic system combining two techniques, ODEP and UV-direct-writing, could be useful for the formation of drug cocktails. The ODEP force could be successfully generated in a hydrogel such that strong force could be used to select and assemble the particles. Then, a seamless integration of an UV-direct-writing module could be used to cure the hydrogel such that specific shapes containing pre-set drug particles could be formed. With this approach, digital drug cocktails could be realized.

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