

MICROFABRICATION OF FUNCTIONAL GELS AND APPLICATION TO CONTROLLED DRUG RELEASE MICROCHIP

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Introduction

Recently, stimuli-responsive polymer gels attract attention as functional soft materials in the research fields of microfluidic systems. Several applications as a smart microvalve or micropump to switch the direction of flow automatically or extrude fluid are attempted (1, 2). Conventional microvalves made of hard and dry materials such as piezoelectric elements (3), shape-memory alloy (4), etc. are driven by electricity or heat generated from electric energy. In contrast, microvalve made of stimuli-responsive gel can respond to several stimuli other than electricity. And also, there are several advantages such as no heat release, high dust-proof, low power consumption, etc. Consequently, utilization of smart gels will contribute to simplification and miniaturization of device.

For microfabrication or micropatterning of gels, lithography method using a mask has been typically employed (5). In the case of photolithography, additional process to make a photomask is needed. Here we show simple and convenient method to prepare micropatterned gels by use of a microscope without large-scale or special-order experimental setup. UV light focused by an objective lens was locally irradiated to pre-gel solution in microchannel. By moving the sample stage, microgel with any shape can be prepared at any position in the microchannel. This method would be useful for preparing microgel at target position in microchip as a microvalve or micropump. In this study, controlled drug release microchip has been actually fabricated by utilizing this local photo-irradiation method and pulsatile drug release in response to temperature changes were demonstrated (6). In addition to stimuli-responsive drug release, we have also designed oscillatory drug delivery systems to release drug with preprogrammed periods without external stimuli by coupling pH-sensitive gel and pH-oscillating chemical reaction in a continuous-flow stirred tank reactor (CSTR) in the microchip (7).

Experimental Part

For preparation of microgels by photo-polymerization, N-isopropylacrylamide (NIPAAm), acrylic acid (AAc), methylenebisacrylamide (MBAAm), and 2,2-dimethoxy-2-phenylacetophenone as a photo-initiator were dissolved in methanol. The pre-gel solution was injected into speculum plate with a spacer of 70 μ m thickness. The plate was set up on the motor-driven x-y sample stage which was equipped with a fluorescence microscope. UV light from Hg lump (peak wavelength: 365nm) was condensed by objective lens to focus on the stage, and the spotlight was irradiated to the plate for 15sec. The prepared microgels were washed by methanol.

As one of applications to micro-device by using this maskless local photo-irradiation method, controlled drug release microchip using stimuli-responsive gel as a microvalve was designed. The drug release microchip composed of three PDMS layers was fabricated by typical soft lithography method. Each layer was bonded each other after O₂ plasma treatment. The width and the height of microchannel is 500 μ m and 200 μ m, respectively.

The pre-gel solution was injected into the microchannel of the microchip. The UV spotlight condensed by objective lens was locally irradiated to the region around the pillar for 15sec. After gelation, the gel was washed and deswelled by drying. The colored solution of Ru(bpy)₃Cl₂, as a

model drug, was loaded in the drug reservoir by injecting into the microchannel. To close the drug reservoir, the gel was swollen by supplying water to water-flow channel. Pure water was supplied to both of drug-flow and water-flow channel by using HPLC pump with a flow rate of 0.1ml/min. The microchip was inserted into a water-jacketed cell together with water. The temperature was controlled by circulating thermostated water through the water-jacket around the cell. The effluent from the drug-flow channel was introduced to a single path UV detector and the release rates of drug were continuously monitored from the absorbance of 420nm wavelength in response to stepwise temperature changes.

In addition to stimuli-responsive drug release, we have also designed the oscillatory drug release microchip by coupling pH-oscillating reaction with pH-sensitive gels. In order to generate pH-oscillating reaction, a CSTR was used. Two premixed solutions of sulphuric acid, sodium sulphite and potassium hexacyanoferrate (II) trihydrate and sodium bromate solution were continuously supplied to the reactor independently with HPLC pumps at a constant flow rate. The effluent from the CSTR was directly fed into the microchannel. The pH changes in the reactor and the dimensional changes of the microgel were monitored continuously.

Results and Discussion

Microgels can be prepared at any position in the speculum plate by local UV irradiation. By moving the stage continuously and sweeping the spotlight, several shapes of micrometer-sized gels can be easily prepared. In this local photo-irradiation method, array of microgels can be also prepared easily by irradiating UV spotlight without sweeping. Figure 1 shows the fabrication process of microgel array by repeating on-off switching of UV irradiation and moving the sample stage. UV spotlight focused by objective lens was irradiated locally to the monomer solution including a photo-initiator. After 15sec, the spotlight was turned off. Then it was observed that microgel with the diameter of about 100 μ m was formed within the region where the spotlight was irradiated. After that, the sample stage was moved and the spotlight was irradiated again to prepare another microgel next to the first one. By repeating this process, microgels which stand in a line can be fabricated. We can control the size of microgel by changing light volume, magnification of objective lens, composition of pregel solution, etc. Generally, by using objective lens with higher magnification, smaller microgel can be prepared. And also, as the concentration of monomer, crosslinker and initiator decreases, the size of prepared microgel decreases although the gelation time becomes longer. So far, it was found that the diameter of microgel could be reduced to about 20 μ m by this photopolymerization method.

Figure 2 shows the PNIPAAm microgel array obtained by this method. At lower temperature, the microgels are at swelling state (diameter, $d=120\mu$ m) and then there is no gap between the gels. With increasing temperature, the gels deswell ($d=60\mu$ m) and make a gap between them. By decreasing temperature, the gels swell again and the gap is closed. Such gap formation changes of the gels might be useful for application as a microvalve to open and shut the flow automatically in microfluidic systems.

As one of applications to micro-device by using these maskless local photo-irradiation methods, controlled drug release microchip was fabricated. As shown in Figure 3, the microchip is composed of three layers of PDMS. Each PDMS layer was made by conventional microfabrication method using photoresist. The top layer has water-flow channel and the space for fixing the microgel. In the space, there is a small pillar to fix the microgel. The middle layer has diaphragm to open and close drug reservoir by swelling and deswelling of the gel. By employing the diaphragm structure, we can avoid a direct contact of the microgel with the drug solution. The bottom layer has the drug reservoir and drug-flow channel.

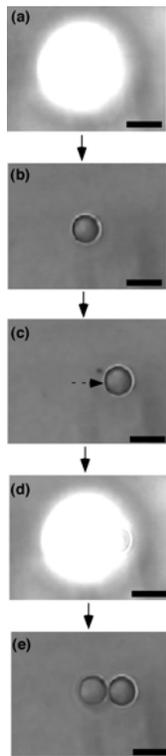


Figure 1. Preparation of PNIPAAm microgel array by local photo-irradiation (scale bars : 100 μ m). (a) 1st irradiation of UV spotlight (15sec), (b) formation of 1st microgel, (c) movement of stage, (d) 2nd UV irradiation (15sec), (e) formation of 2nd microgel.

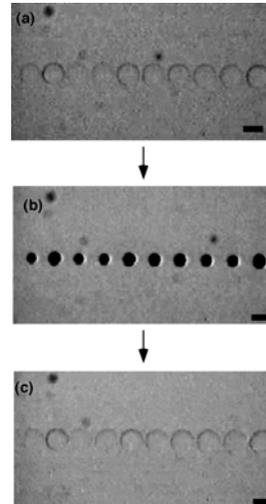


Figure 2. Swelling-deswelling changes of PNIPAAm microgel array in response to stepwise temperature changes between 20 $^{\circ}$ C (a,c) and 40 $^{\circ}$ C (b). Scale bars : 100 μ m.

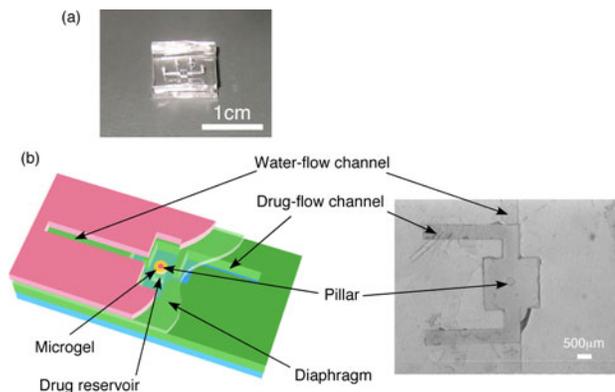


Figure 3. Drug release microchip: (a) general photograph and (b) schematic drawing (left) and the top view around drug reservoir (right).

Thermosensitive microgel was prepared in the microchannel by local UV irradiation. At 20 $^{\circ}$ C, the gel swelled to push the diaphragm and close the drug reservoir (Figure 4(a)). When temperature increased to 50 $^{\circ}$ C, the gel deswelled to open the drug reservoir. Since the gel became opaque, then the drug reservoir could not be observed directly (Figure 4(b)). When temperature decreased to 20 $^{\circ}$ C and the gel swelled again, drug reservoir was already vacant (Figure 4(c)). This means that the model drug was completely released while microgel deswelled. The release profile

of the model drug also shows that the drug was released after increasing temperature. This type of microchip would be applicable as an intelligent and disposable drug delivery patch to release antipyretic only when body temperature increases.

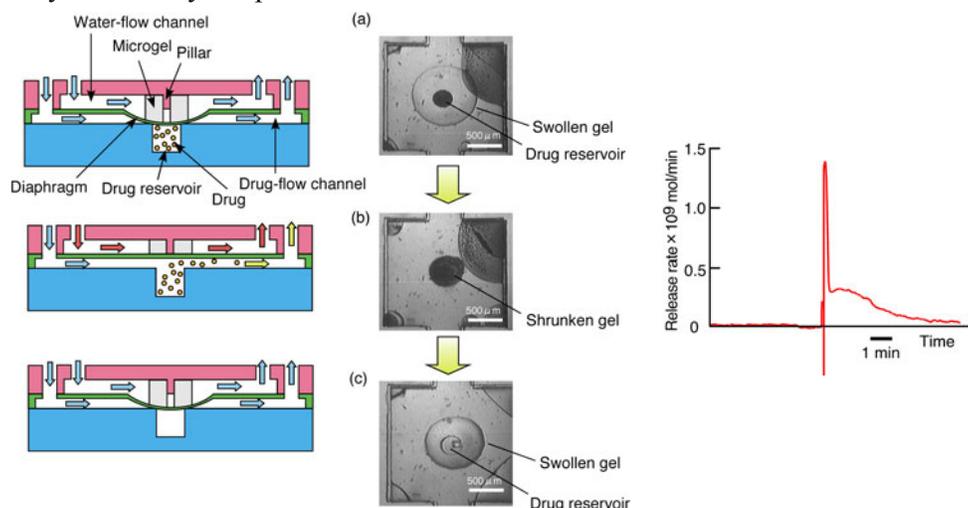


Figure 4. Drug release behaviours from the microchip in response to stepwise temperature changes. Cross sectional illustration (left), photograph of top view (middle) and pulsatile drug release pattern (right). Poly(NIPAAm-co-AAc) microgel valve prepared above drug reservoir. (a) The gel swells at 20°C and the reservoir is filled with model drug. (b) The gel deswells at 50°C. (c) When it falls to 20°C, the gel swells again and the drug reservoir is vacant.

In addition to stimuli-responsive drug release, we have also designed the oscillatory drug release microchip to release drug with preprogrammed periods without external stimuli by using self-oscillating gel. The self-oscillating microgel was designed by coupling pH-sensitive Poly(NIPAAm-co-AAc) microgel with pH-oscillating chemical reaction in a CSTR (Figure 5). Figure 6 shows the pH changes in the CSTR and the dimensional changes of the microgel prepared in the microchannel. The gel demonstrated rhythmic swelling and deswelling changes synchronized with the pH oscillation. Such a self-oscillating behavior of the microgel would act as a micro-valve that periodically opens drug reservoir by itself. It should be emphasized that the oscillation of microgel was achieved with a constant input requiring no on-off switching of pH changes.

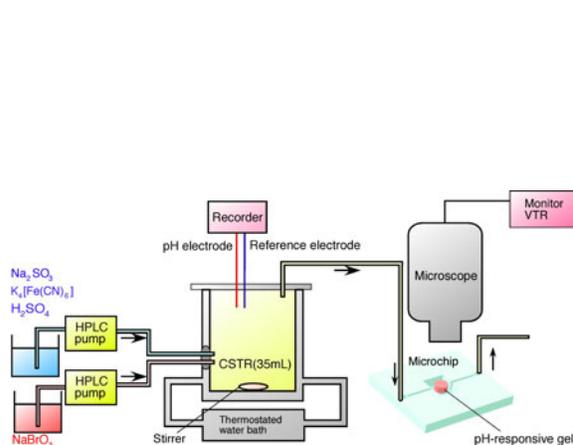


Figure 5. Prototype system to generate self-oscillating swelling-deswelling changes by coupling of pH-oscillating reaction and pH-responsive gel.

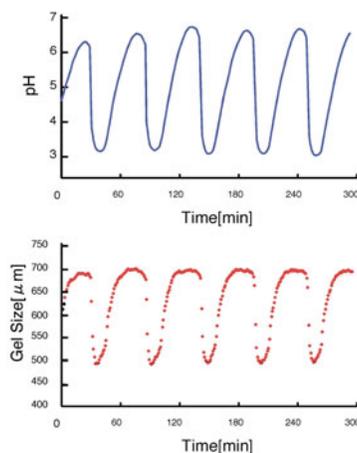


Figure 6. Oscillating profiles of pH in CSTR (upper) and swelling-deswelling changes for poly(NIPAAm-co-AAc) gel (lower).

As the next step, we designed a microchip that has the micro-CSTR (volume: 200 μl) within it (Fig.7). When the same two solutions were continuously supplied to the micro-CSTR by HPLC pump at constant flow rate, pH-oscillation was also generated in the micro-CSTR and swelling-deswelling oscillation was observed (Fig.8). This suggests that the pumps would be only needed as external apparatus for self-oscillation of gel. Recently, hydrogel microdispensing device using an array of responsive hydrogels to deform a flexible membrane above a fluid reservoir was reported (8). Future work will focus on developing such a microdispensing device in the microchannel for the design of a complete stand-alone microchip.

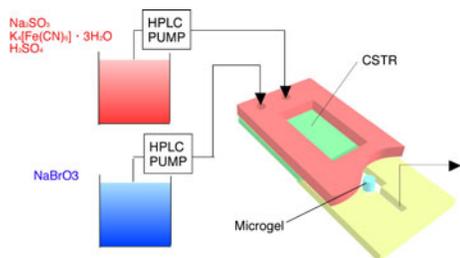


Figure 7. Microchip in which CSTR is built for pH-oscillating reaction.

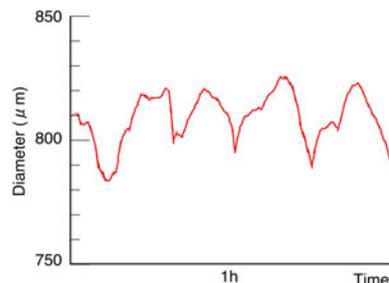


Figure 8. Swelling-deswelling changes of poly(NIPAAm-co-AAc) gel synchronized with pH-oscillating reaction in the built-in CSTR.

For microfabrication of gels, the local photo-irradiation method utilizing a microscope we presented here would be useful as an easy and simple method which does not need another process for making photomask or special-order experimental setup. In particular, this maskless method will be effective for preparing microgel in microchannel because troublesome processes for alignment of photomask to the channel are not needed. Further, several kinds of gels could be placed in the same microchannel by repeating irradiation and replacement of another monomer solution. Since any shape of gel can be also created by this method, application as a new manufacturing method for soft microactuator, microgel valve, gel display, etc. is expected.

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