Fabrication and Evaluation of Polymeric Microvalve using the pH-Responsive Hydrogel Microsphere

J.Y. Park[1,2,3], D.J. Kim[1,2], S.R. Kim[1,2], J.Y. Baek[1,2], K. Sun[1,2] and S.H. Lee[1,2]

[1] Department of Biomedical Engineering, College of Medicine, Korea University, Korea
[2] Korea Artificial Organ Center, Korea University, Korea
[3] Department of Biomedical Engineering, DanKook University, Korea

Abstract— **In this paper, we propose a new fabrication method of pH-responsive microfluidic valves and suggest the feasibility as a microminiature systems without peripheral devices. Conventionally, in-situ photopolymerization method has been employed to build the micro functional structure inside microfluidic channel. Here, we suggest a new method allowing the mass production of stimuli-responsive microsystem through the use of pre-made microstructure as actuating element like assembly of commercial products in the factory. We have massively fabricated pH-responsive microspheres that act as actuating component through the use of PDMS-based microfluidic apparatus and 'on the fly' photopolymerization method. By the incorporation of this microsphere into the microvalve during the fabrication process, we have produced the pH-responsive microfluidic valve in a simple way. The operation and the function of the fabricated microvalve were evaluated through the diverse experiments. The microvalve was successfully fabricated, and functioned well according to the pH change.**

Keywords— **pH-Responsive, Microfluidic, Microvalve, microsphere, drug delivery**

I. Introduction

Microfluidic systems has demonstrated their many potential applications in biology, chemistry, industry and medicine and is making possible the realization of a one-step microscale total analysis system (μTAS)[1-2], and they have many advantages (1) in the handling of micro or nano scale samples, (2) in the production of portable and implantable devices, and (3) in cost effective and parallel processing owing to the devices' highly integrative capacity relative to small areas. Microvalve is the one of microfluidic device's core technology. These miniaturized systems, the delivery of sample fluids are of great importance. Several actuation methods have been reported including electrostatic actuation, piezoelectric actuation, thermopneumatic actuation, electro-magnetic actuation, shape memory alloy actuation, paraffin phase transition actuation and hydrogel based on-chip check valve for high pressurized flow-control [3-5]. These actuation methods have many advantages but they have some limits to be applied in the medical field like implantable, portable drug delivery system. In order to apply these actuation methods to the human body, additional peripheral devices (e.g.: sensor and microprocesor) are required to be able to function according to the body-requirements. Recently, new delivery devices mimicking an actuating process of living systems have been developed for biological and medical applications, and the approach involves the direct conversion of chemical energy into mechanical energy on the basis of materials that respond to external stimuli such as temperature, pH, light, electric fields, chemicals, glucose, antigens, and ionic strength [6-7]. Such stimuli-responsive, or "smart," polymers have been extensively applied in the delivery systems. We apply to the new method drug delivery systems using the reported previously microvalve [8]. By using the PDMS-based microfluidic apparatus, we have fabricated pH-responsive microspheres that act as an actuating component via 'on the fly' photopolymerization [9]. And by incorporating this microsphere into the microvalve instead of by constructing a microstructure via *in-situ* photopolymerization, we have fabricated the pH-responsive valve in a simple way. We expect that our method allows the mass production of stimuli-responsive microsystem through the use of pre-made microstructure as actuating element like assembly of commercial products in the factory. Finally, the operation and the function of the microvalve were evaluated through the diverse experiments.

II. Fabrication and Principle

We have produced pH-responsive microspheres by using a microfluidic apparatus that we fabricated by hybridizing the PDMS substrate and a pulled glass micropipette, as demonstrated in Figure 1 and the details of fabrication process was reported previously [9]. The photopolymerizable solution (85wt% 4-hydroxybutylacrylate (4-HBA) + 3wt% 2,2-dimethoxy-2-phenylacetophenone (DMPA) + 1wt% ethyleneglycoldimethacrylate (EGDMA) + 11 wt% acrylicacid (AA)) was used as a material of sample fluid, while a non-polymerizable solution (mineral oil) was used as a sheath fluid. Generally, the pH responsive hydrogels usually

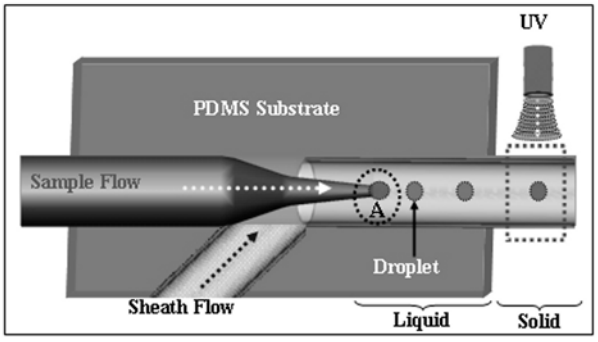

Fig. 1 Schematic diagram of the microsphere generation apparatus, which was fabricated through the hybridization of the PDMS substrate having a preformed main hole and a pulled micropipette.

contain two monomer components, one is the pH-sensitive component that gives rise to the pH sensitivity, and the other one is pH inert component that is related with the mechanical properties of the hydrogel. At the tip of the pulled pipette, the droplets were formed and they moves through the outlet pipette floating among the sheath fluid. To solidify the droplets, we radiated UV light and this light rapidly polymerized the traveling microcapsules. Figure 2(a) shown the scanning electron microscope (SEM) image of microspheres by using our PDMS substrate device. And the SEM image of a divided microsphere is demonstrated in figure 2(b). We constructed a PDMS-based microfluidic valve, into which a pH-responsive microsphere was integrated. We constructed the patterned bas-relief plate by using a replica molding against a master that consisted of photolithographically patterned photoresist (SU-8, Micro-Chem) on a 3-inch silicon wafer. We stacked the 3 thin, patterned PDMS layers (hole-layer, membrane-layer, and upper-layer) and the one PDMS bas-relief plate (thickness: 8 mm), and the top was covered with the cover slip. We fabricated the bas-relief plate by pouring a 10:1mixture of the PDMS prepolymer and a curing agent (Sylgard 184 silicone elastomer kit, Dow Corning, Midland, MI) onto the master mold placed in a Petri-dish. The mixture was thermally cured for 2 hr on a hot plate at 80 ◦C, and separated from the mold. With this plate and these 3 layers, the microvalve was constructed according to an aligning and bonding process. The bonding, both of the surfaces of each layer were exposed to an oxygen plasma, and aligned with a homemade aligning system by using methanol as a lubricant. Each bonding process was cured on the hot plate for 2 hours at 80^{o}C. To fabricate the valve layer, we made the 2-stepped master mold in which the thick center has different thickness. The upper layer that had the entrap post was stacked onto the membrane layer and bonded. Afterward, we picked one pH-responsive microsphere by using the glass pipette whose tip is sharp (diameter: 40 μm), and placed it within the entrap post carefully under the stereoscope. Finally, a No. 2 cover-slip was stacked and bonded. Figures 3(*a*) and (*b*) demonstrate, respectively, the principles of the 'OPEN' operation and the 'CLOSE' operation. At the application of the acidic solution, the microsphere inside the entrap post shrinks, as shown in figure 3(a), and the thick-centered membrane moves upward because of the pressurized inlet flow, and the fluid passes through the hole and moves out to the outlet. When the basic solution is introduced(figure 3(b)), the microsphere swells and presses the thick-centered membrane, and the bended membrane seals the hole. So the flow path from the inlet to the outlet is blocked. The fabrication procedures are as follows. For the measurement of swelling ratio, we placed microspheres into the microfluidic chamber, and their changes in shape relative to the pH variation were captured on video camera, and the variations of diameter were measured. The performance

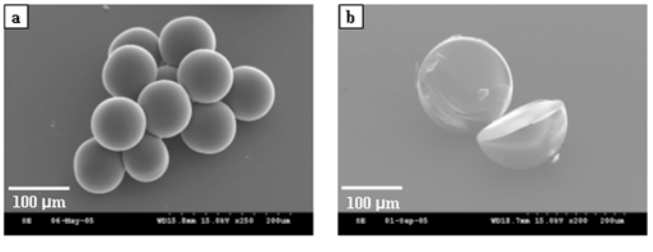

Fig. 2 (a) The scanning electron microscope (SEM) image of microspheres, (b) The SEM image of a divided microsphere.

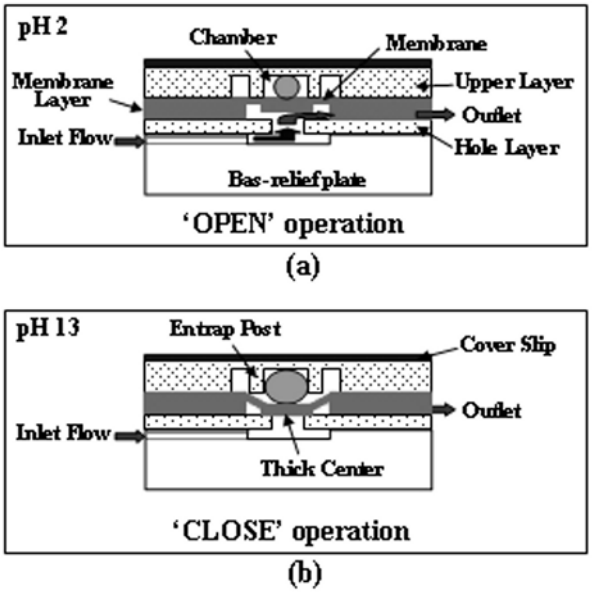

Fig. 3 The principle of (a) the microvalve's 'OPEN' operation and (b) the microvalve's 'CLOSE' operation.

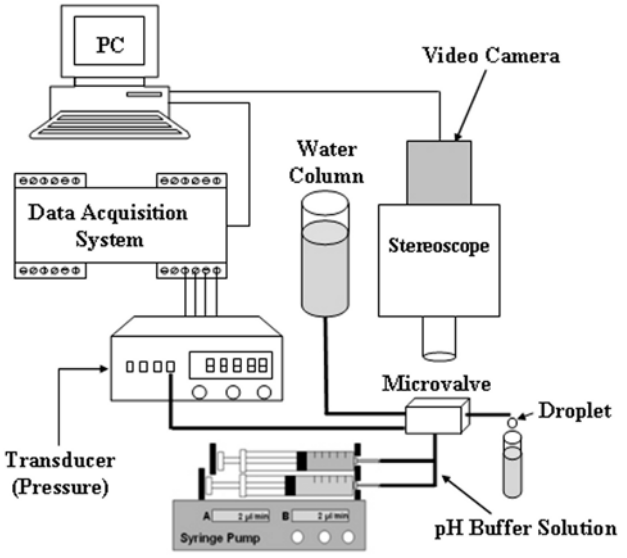

Fig. 4 Set-up for the performance evaluation of the microvalve. The pressure at the inlet port was measured by a pressure transducer (PX217A, OMEGA) and stored at the computer via the data acquisition system (Dasylab, NATIONAL INSTRUMENTS). Both the water column (constant pressure source) and syringe pump (increasing pressure source) are used as a delivery system of pressurized fluid.

of the fabricated microvalve was evaluated under the experimental configuration shown in figure 4. We introduced into the inlet the fluid that was pressurized through the use of a water column, while the acidic and the basic solutions were introduced through the use of syringe pumps. The operation of the valve was visually monitored under a microscope equipped with a digital camera, and the captured images were sent to a personal computer. The pressure at the inlet port was measured with a modular pressure transducer (PX217A, OMEGA), and the pressure signals were sent to the personal computer via a data acquisition system.

III. Result and discussions

We estimated the polymerization time by measuring the moving speed of microspheres at the outlet pipette, and the value was approximately less than 200 ms. Such fast polymerization time enables the liquid droplet to be solidified as it travels through the outlet pipette. The swelling ratio to the alternative variation of pH was measured, and the results are shown in figure 6. Figure 6(a) plots the swelling ratio for every 20 s according to the pH variation. When there was a step increase of pH value (from pH 2 to pH 13) and a step decrease of pH value (from pH 13 to pH 2), the microsphere swelled and shrank within almost 1 min, and we assume that this fast response was mainly due to the size

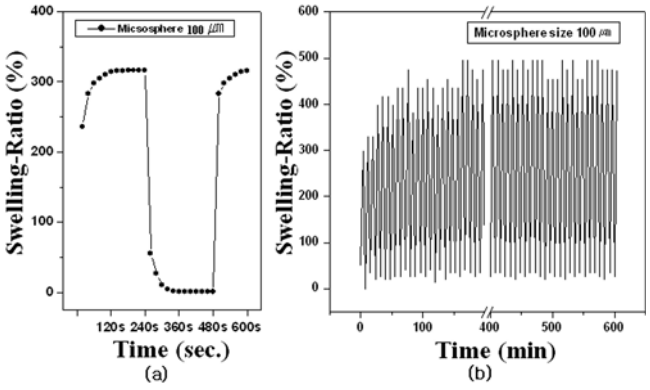

Fig. 5 (a) The swelling ratio to the alternative variation of pH (pH 2–pH 13). The swelling ratio was measured every 20 s. (b) The change of swelling ratio for 10 h (pH was changed for every 4 min and the corresponding swelling ratio was measured after the volume transition)

and the shape of the microsphere (spherical shape has a higher surface-to-volume ratio and this is more advantageous in the better ionic diffusion). Figure 6(b) illustrates the change of swelling ratio for 10 h (pH was changed for every 4 min and the corresponding swelling ratio was measured after volume transition). The microsphere illustrated stable and reproducible volume changes to the pH variation, and this finding indicates that, in part through the regulation of pH, the fabricated pH-responsive microspheres can be employed as reproducible actuating elements. Figures 7(a) and (b) demonstrate the micrograph of the 'OPEN' operation and the 'CLOSE' operation of the fabricated microvalve, respectively. At the appearance of the acidic solution, the microsphere shrank and the channel is opened, while the channel is closed at the appear ance of the basic solution. We have measured the flow rate by according to the variation of pressurized inlet flow as change the height of the water column and to the Base:Acid ratio, and the results are plotted in Figure 8. Inlet pressure was from 5.9kPa to 11.8kPa, measured the pressure by pressure

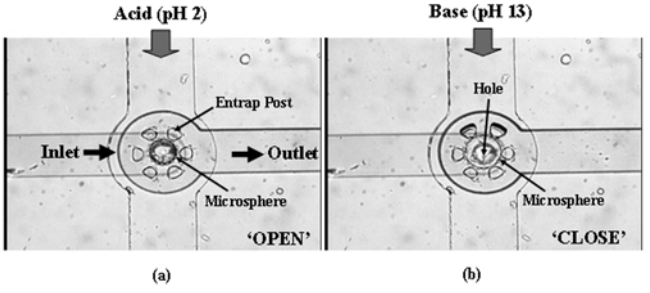

Fig. 6 Micrograph showing the fabricated microvalve's (*a*) 'OPEN' operation and (*b*) 'CLOSE' operation

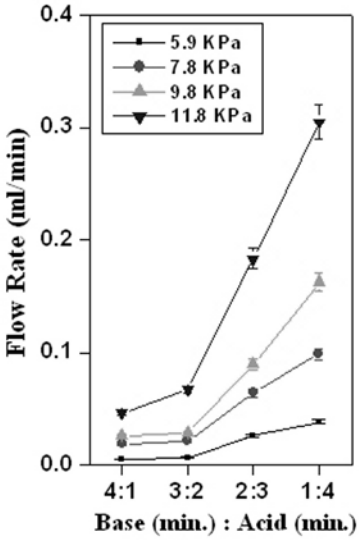

Fig. 7 Mean flow-rate change according to (1) the variation of the pressurized inlet flow (5.9, 7.8, 9.8 and 11.8 kPa) and of the base:acid ratio

sensor. In relation to the increase of inlet pressure and the acid-injection duration (from 3:2 to 1:4), the mean flow rates increased almost linearly. At 4:1, the mean flow rates were saturated, and the reason seems to be that the microsphere was not fully exposed to the acidic solution during the opening phase of the valve.

IV. Conclusions

This paper shows firstly the possibility that the microfluidic device can be fabricated by assembling the separately-fabricated microspheres into a microvalve. Via our 'on the fly' photopolymerization, diverse qualified stimuli-responsive microspheres (involving sensitivity to temperature, pressure, chemicals, or biological materials) can be massively produced. On the basis of our assembly-methods, diverse microvalves, which are operated by the physical, chemical or biological stimuli, can be fabricated in any laboratory without complicated devices and laborious skills required for the in-situ photopolymerization. These stimuli-responsive microvalves do not use any electrical or mechanical components, and have many potential applications as a implantable stimuli-responsive sample or drug-delivery device that are 'responsive' to the patient's therapeutic requirements and deliver certain amount of a drug in response to a biological stimulus.

Acknowledgment

This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health&Welfare, Republic of Korea (0405-ER01-0304-0001)

References

1. Smith J, Jones M Jr, Houghton L et al. (1999) Future of health insurance. N Engl J Med 965:325–329
2. Auroux P. A., Iossifidis D., Reyes D. R. et al. (2002) Micro Total Analysis Systems. 2. Analytical Standard Operations and Applications Anal. Chem. 74: 2637-2852
3. Hong J. W., Studer V., Hang G. et al. (2004) A nanoliter-scale nucleic acid processor with parallel architecture. Nature Biotechnology 22(4) : 435-439
4. Kataoka D E, and Troian S M (1999) Patterning liquid f low at the microscopic scale Nature 402 : 794-797
5. Feustel A, Krusemark O, Lehmann U et al. (1996) 1996 Electromagnetic membrane actuator with a compliant silicone suspension Sperling T. Actuator' 96 (Bremen, 26-28 June) 76
6. Peirs J, Reynaerts D and Brussel H V (2001) The 'true' power of SMA micro-actuation Proc. MME 2001: 217-220
7. Chen G, Imanishi Y and Ito Y (1998) PH-Sensitive thin hydrogel microfabricated by photolithography Langmuir 14 : 6610–6612
8. Tanaka T, Nishio I, Sun S T et al. (1982) Collapse of gels in an electric field Science 218 : 467–469
9. Eddington D.T, Beebe D.J (2004) Flow control with hydrogels Advanced drug delivery reviews 56 : 199-210
10. Jeong W J, Kim J Y, Kim S J, Lee S H et al. (2004) Hydrodynamic Microfabrication via "on the fly" Photopolymerization of Micro Scale Fibers and Tubes. Lab on a chip 4 : 576-580

Address of the corresponding author:

Author: Ji Young Park
Institute: Korea Artificial Organ Center, Korea University
Street: 126-1, Anam-dong 5ga, Seongbuk-gu, 136-705
City: Seoul
Country: Korea
Email: taein2302@dankook.ac.kr