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TECHNICAL PAPER

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A microfluidic gel valve device using reversible sol–gel transition of methyl cellulose for biomedical application

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Abstract We have fabricated a microfluidic gel valve device that used reversible sol–gel transition of methyl cellulose (MC). A microheater and a microtemperature sensor were implemented in each microchannel in the gel valve device. Before evaluating the performance of the gel valve device, various properties of the MC solution were investigated using viscometer, spectrophotometer, and NMR. Gelation temperature was increased as the MC concentration was increased. Clear gel, an intermediate state between clear sol and turbid gel, was found at the temperature range from 30–40°C to 50–60°C. Temperature at each microchannel of the device was measured and the effect of the temperature difference on the valve operation was elucidated. In order to have normal operation of the gel valve, it was important to keep the temperature of the heated microchannel around 60°C while keeping the temperature of the flowing microchannel below 35°C. The temperature difference between two microchannels was about 23 K when fan forced cooling (FFC) method was used. For normal performance of the gel valve device, a temporary pause of fluid flow for at least 5 s was required to complete the local gelation in the microchannel. Stable gel valve performance was obtained at the flow rates larger than 5 μl/min. The gel valve device showed no leakage up to 2.07×10^4 Pa.

Keywords Methyl cellulose · Sol–gel · Gel valve · BioMEMS

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1 Introduction

Methyl cellulose (MC) has a unique property that it shows reversible sol–gel transition under periodic temperature change (Carlsson et al. 1990; Desbrieres et al. 2000; Hirrien et al. 1998; Hussain et al. 2002; Kundu and Kundu 2001; Lindman et al. 1990; Sarkar 1995). This peculiar physical property has been actively investigated by many researchers (Carlsson et al. 1990; Desbrieres et al. 2000; Hirrien et al. 1998; Hussain et al. 2002; Kundu and Kundu 2001; Lindman et al. 1990; Sarkar 1995). The MC is an alternate block co-polymer with highly substituted hydrophobic region and less substituted hydrophilic region (Kundu and Kundu 2001). The MC block copolymer prefers to form micelle structure having hydrophilic part associated with water. This micelle formation was suggested as a mechanism of the gelation of MC (Kundu and Kundu 2001).

Many attempts have been made recently to manufacture various microfluidic devices utilizing local polymerization or gelation of polymers (Tashiro et al. 2001a, b; Beebe et al. 2000; Rehm et al. 2001; Unger et al. 2000). This approach can drastically simplify the fabrication process of the microfluidic chip because no extra photomasks are needed for forming actuators or valves. Most researchers used photosensitive solutions as working fluids. Beebe et al. (2000) has made active hydrogel components in which a photosensitive fluid was injected into a microchannel and locally hardened by photo-patterning. These components could be implemented to have various functions such as sensors and actuators simultaneously. Rehm et al. (2001) has produced a polymeric monolith by inserting monomer–

solvent–initiator mixtures into a microchannel and hardening only the desired area. An on-chip check valve was implemented by adopting a bypass channel around this monolith.

Tashiro et al. (2001a, b) has fabricated a microfluidic gel valve device using the reversible sol–gel transition of MC. The MC has been widely used in the field of biomedical industry, since it has remarkable biocompatibility. In Tashiro's work, the MC solution was injected into a microchannel and locally hardened. A gel monolith in the specific part of the microchannel was formed by IR laser heating. A microfluidic valve operation for cell sorting was demonstrated by the alternate irradiation of the IR laser on both outlets of Y-branch type microchannels.

The study of cell sorting using MC is the most intriguing work among a few studies mentioned above, because the gel monolith can be transformed into sol as its original state with changing the temperature. In addition, MC has a sol–gel reversible transition property, which enables a microfluidic component (e.g., a valve) to perform multiple cyclic process. In other cases except for Tashiro's work, however, monoliths would not go back to their original fluid states after the polymerization occurred. The MC solution from Tashiro et al. (2001a, b) work is capable of reversible sol–gel transitions by simply controlling the temperature of the chip. In other words, one can allow a specific location of the microchannel to act as a valve while moving the fluid from place to place within the chips. This is a very useful property that can dramatically simplify the structure of microfluidic chips. Even though Tashiro's work suggested very interesting and useful function, it is somewhat difficult to further develop a fully integrated system because a large laser system is required to operate. Moreover, the thermal characteristics of the used MC solution were not fully elucidated.

In this study, we have fabricated a microfluidic gel valve device using a standard Si bulk micromachining process for biomedical application. A microheater and a microtemperature sensor were implemented in each microchannel in the gel valve device. As a result, heat generated by the heater could transfer directly to the fluid, and the temperature of the solution was directly measured.

Aqueous MC solution is used as a working fluid because it shows remarkable biocompatibility and reversible sol–gel transition, as explained before. To have better understanding of the rheological properties of the MC solution, the shear stresses with respect to the temperature were measured using a cone-type viscometer. Temperature at both microchannels of the device was measured and the effect of the temperature difference on the valve operation was elucidated. Correlation between thermal properties of MC and the temperature distribution of the gel valve device was also discussed in terms of the valving performance. Finally, we report a guideline that would help to implement a more compact gel valve device with high performance.

2 Experimental

Powder MC [9004-67-5], laboratory grade was purchased from Aldrich Chemical Co. (MO, USA). According to the manufacturer, the viscosity of 2% MC solution is 400 cP at room temperature. Average molecular weight is 130,000 g/mol and polydispersity index is 1.8. Average substitution of methyl radical is 2.1. The 0.5, 1.0, 1.5, and 2.0 wt.% MC solutions was prepared by dissolving a desired quantity of MC powder in deionized water at 4°C and keeping at least for 24 h to ensure complete dissolution.

Rheological properties of the solution were measured as a function of the temperature and the MC concentration. The rheological measurement was conducted using a stress-controlled viscometer (Carrimed CS50). The gelation temperature was also measured using a Shimadzu multispec-1501 UV/Vis spectrophotometer. The gelation of the MC solution is caused by the phase separation, which greatly affects the turbidity of the MC solution.

Figure 1 shows a layout of the fabricated gel valve device. The fabrication process for the gel valve device consists of two photolithography steps for silicon and glass respectively. Figure 2 shows a flow diagram of the fabrication processes of the gel valve device. The starting wafer was double-sided polished silicon (100) substrate with a diameter of 4 in. and a thickness of 300 μm. A silicon dioxide layer with a thickness of 700 nm was grown on the substrate by wet oxidation. The silicon dioxide layer was photolithographically patterned and wet etched down to the silicon. After removing the photoresist, the silicon was etched to 100 μm depth by 25% tetramethylammonium hydroxide (TMAH) solution to generate the microchannels.

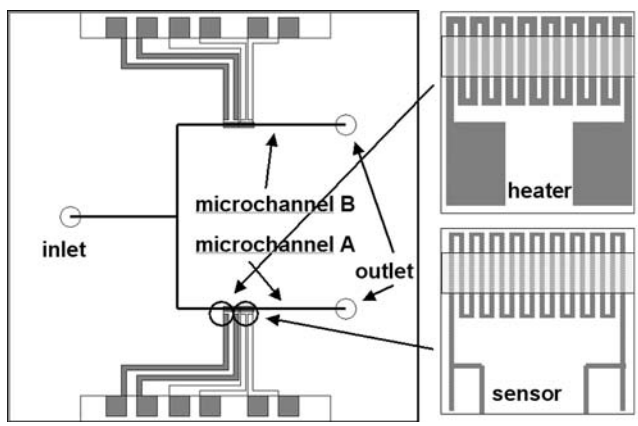
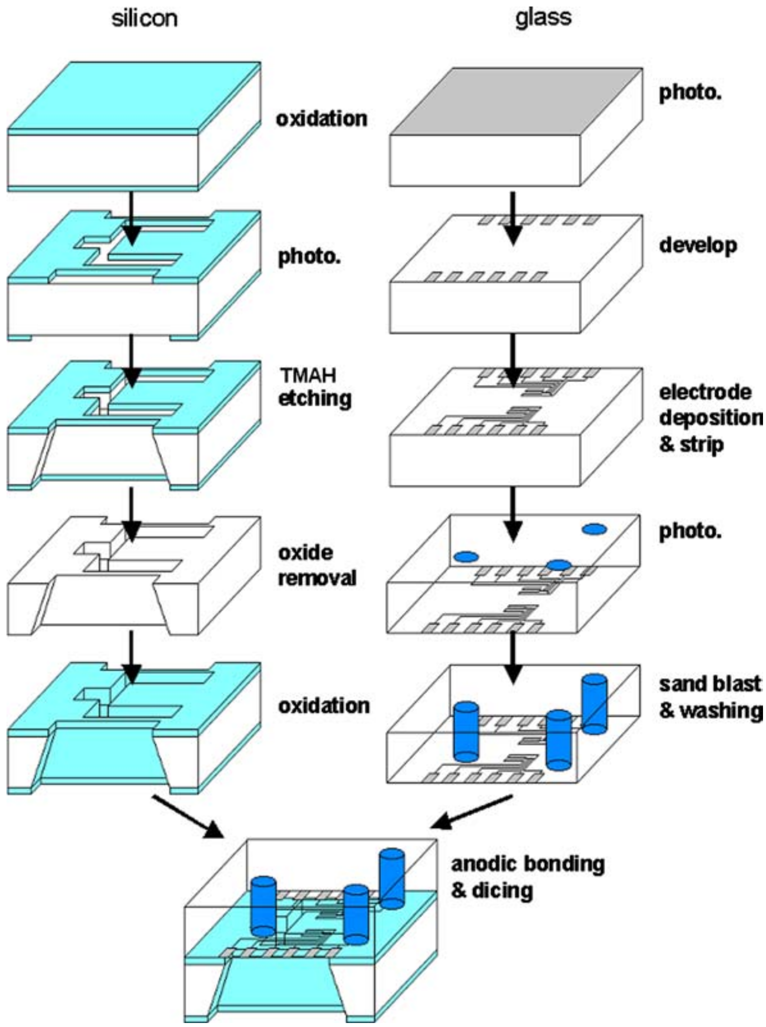


Fig. 1 A layout of the gel valve device having the Pt thin film heater and the temperature sensor. The thin film heater and the temperature sensor were located at the interface between the glass and the silicon substrate. Therefore, the fluid in the microchannel was directly heated by the microheater and the temperature of the fluid was directly monitored by the temperature sensor. The resistance values of the heater and the sensor were 100 and 200 Ω, respectively

Fig. 2 A flow diagram of the fabrication processes of the gel valve device. The fabrication processes consist of Si processing, glass processing, and Si/glass hybrid processing including anodic bonding and dicing

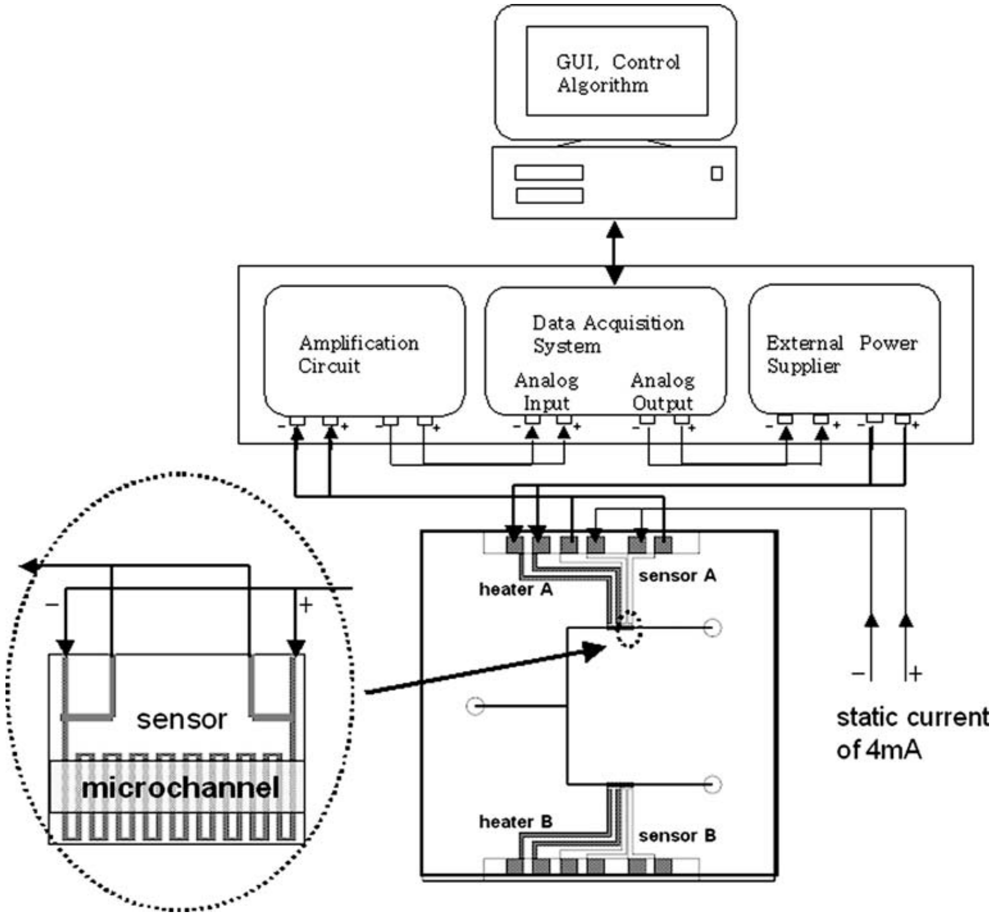


The glass substrate with a diameter of 4 in. and a thickness of 300 μm was cleaned. The photoresist was coated on the glass substrate by spin coating. The photoresist was photolithographically patterned for the Pt thin film heater and the temperature sensor. Ti film of 30 nm and Pt film of 200 nm were deposited on the patterned bottom side of wafer by DC off-axis magnetron sputtering. Finally, the heater and the sensor patterns were developed by the lift-off technique. The glass substrate was rinsed with deionized water and laminated by BF410 film photoresist (Tokyo Ohka Kogyo Co. Ltd., Tokyo, Japan). The photoresist was photolithographically patterned for the formation of holes with a diameter of 1 mm. The holes that served as the inlet and outlet fluid passages were formed by using a sand blast apparatus (Nicolis Co.). After alignment, the etched silicon wafer was anodically bonded with the glass substrate. Finally, the wafer was diced into individual gel valve devices.

The Pt thin film sensors on the chip are used to measure the temperatures of the microchannels. The operation principle of the Pt temperature sensor is illustrated in Fig. 3. Four electrodes exist in the Pt temperature sensor. A static current of 4 mA is applied to two electrodes and an induced voltage between the other two electrodes was measured. The measured voltage of platinum sensor is amplified by the amplification circuit and transferred to the analog input of the data acquisition (DAQ) system. The amplification contributes to increasing the resolution in reading the temperature and suppresses the measurement noise due to the low resolution. The resolution of the AD converter is 14 bit for the full input range of 0.0–2.5 V. But, the actual voltage range of the platinum sensor corresponding to the operating temperature range is very small compared to the full input range of the AD converter if we don't use the amplification circuit. Then, the net available resolution in reading the operating temperature range is seriously degraded, resulting in measurement noises due to the severe quantization errors. So, the actual voltage variation of the sensor should be amplified to the full input range of the AD converter to fully use the whole 14-bit resolution.

The thermal characteristics of the chip were evaluated to operate the microfluidic gel valve device. Two power supplies were used to apply the static voltage to each heater in the microchannel. The temperature was

Fig. 3 Experimental set-up for temperature calibration of the Pt thin film temperature sensor integrated in the gel valve device



measured using an Agilent 34970A DAQ system connected to the microheater. A digital video camera (SONY DCR-TRV40) was used to monitor the valve operation.

3 Results and discussion

3.1 Reversible sol–gel transition of MC

In order to use the MC solution as a working fluid of the gel valve device, temperature dependency of the rheological properties of the MC solution was first evaluated. The MC solutions were prepared with various MC concentrations. Dynamic rheology of each solution was investigated as a function of temperature. Figure 4 shows that the shear stress is increased at higher temperature. Initial gelation began at about 35°C. Abrupt transition from low shear stress to higher shear stress occurred for the solutions of over 1.0 wt.% of the MC at about 35°C. However, the transition was rather slower for 0.5 wt.% of MC solution.

Hirrien et al. (1998) reported that MC solution has phase transition from clear sol to turbid gel through a clear gel state. Micelle formation by phase separation was the main cause of the formation of the turbid gel. Strong light scattering of the turbid gel allows one to estimate the gelation temperature by measuring the absorbance spectrum of the solution. Figure 5 shows the temperature dependence of the absorbance data of the MC solutions with different concentrations at the wavelength of

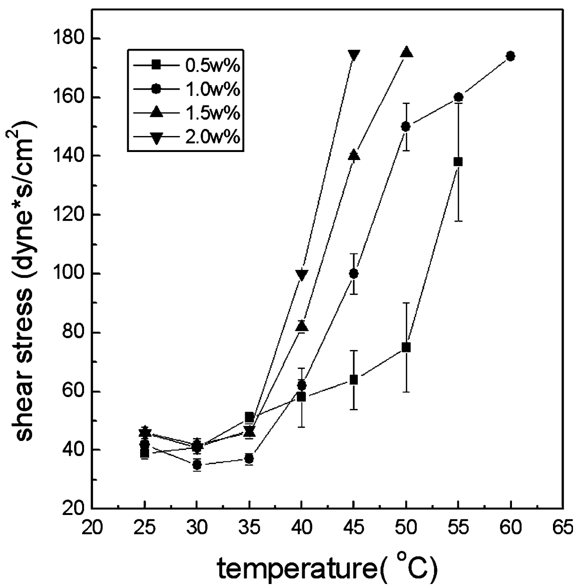


Fig. 4 Shear stress of the solutions with various MC concentrations: 0.5 wt.% (*squares*), wt.% (*circles*), 1.5 wt.% (*up triangles*), and 2.0 wt.% (*down triangles*) as a function of temperature. Sol–gel transition was initiated at about 35°C

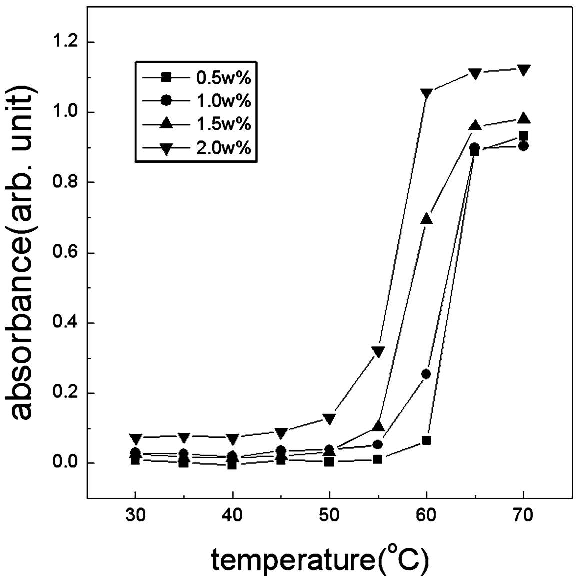


Fig. 5 Absorbance data of the MC solutions with different MC concentrations: 0.5 wt.% (*squares*), wt.% (*circles*), 1.5 wt.% (*up triangles*), and 2.0 wt.% (*down triangles*) as a function of temperature. All absorbance values were measured at the wavelength of 700 nm

700 nm. The absorbance was increased at higher temperature and concentrations, which is consistent with the previous report (Hirrien et al. 1998). However, it is worthwhile to note that there is a big difference between gelation temperatures estimated by rheological measurements and the optical measurements. In the case of 0.5 wt.% solution, the gelation temperature measured by shear stress was estimated to be about 35°C, while the optical measurements suggested about 60°C. The difference from two independent measurements was about 25°C. These measurements suggest that the viscosity continues to increase while the absorbance remains constant at certain range of temperatures. This can be a strong evidence that there is an intermediate clear gel state in the sol-gel transition. Therefore, rheological measurements may suggest better insights for the gel valve operation.

We also investigated temperature dependency of the chemical structure of the MC gel using NMR. Figure 6a shows ^{1}H NMR spectra of the MC solution at different temperatures. A decrease of the peak intensity was observed at the temperature higher than 35°C. This peaks (in the range of 3–4 ppm) are attributed to the proton atoms from the methyl groups. Decrease of the peak intensity indicates a progressive decrease of the mobility of the MC chains. Gelation temperature was defined as the temperature when the peak area decreased to 20% of the NMR peak area at 25°C. Because most of the biological solution contains some amount of salts, we also investigated the effect of the salt concentrations on the gelation temperature of the MC solution. As shown in Fig. 6b, the gelation temperature was decreased as the salt concentration was increased. The effect of NaCl addition on gelation time was significant between 0.5 and 1% and only minor above 1%. This is consistent with the previous report (Kundu and Kundu 2001). The addition of salt lowers the gelation temperature of MC due to its dehydration. Most electrolytes depress the gelation temperature due to its greater affinity to water. As the salt concentration was increased, the cation of the salt associates with water reducing the intermolecular hydrogen bonds between water and hydroxyl group of MC. Therefore, the

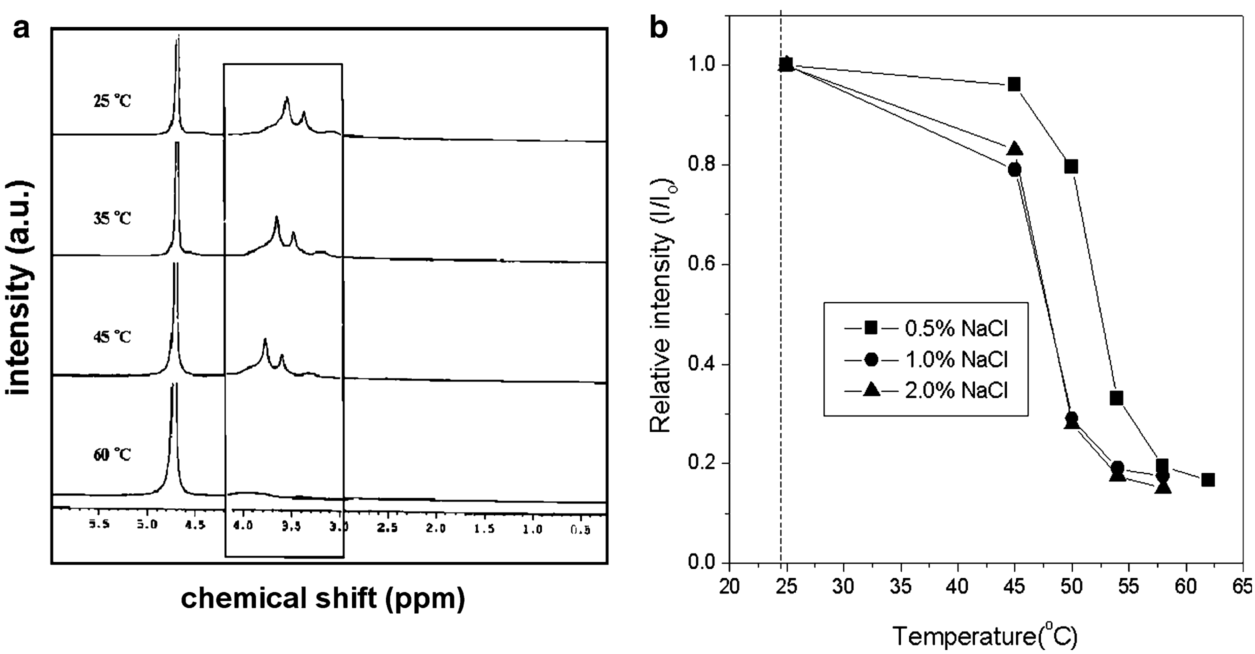


Fig. 6 **a** ^{1}H NMR spectra of the MC solution with 0.5 wt.% MC and 2.0% NaCl, measured at different temperatures, and **b** temperature dependence of the peak intensity normalized by peak intensity at 25°C for 0.5 wt.% MC with various NaCl concentrations

hydrophobic interaction is enhanced and thus the gelation temperature is decreased (Kundu and Kundu 2001). These measurements suggest that one can adjust the operation temperature of gel valve device by changing the salt type and the concentration.

3.2 Evaluation of the performance of the gel valve device

Before the performance test of the gel valve device, the performance of the temperature sensor integrated in the gel valve was evaluated to precisely control the temperature of the microchannel in the chip. The resistance values of the sensor are also measured at various steady state temperatures using the DAQ system. From Fig. 7, the resistance of the sensor shows a good linearity in the entire temperature ranges. The linear property of the sensor can be represented by the following equation:

$$R = R_0 \times [1 + \alpha(T - T_0)], \tag{1}$$

where R is the resistance of the sensor (Ω) at temperature T (°C), R_0 is the resistance (Ω) at reference temperature T_0 (°C) and α is the temperature coefficient of resistance (TCR) of Pt thin film. The TCR of Pt thin film was estimated to be 2.48×10^{-3}/K. Once calibrated, the instrument is capable of in situ temperature measuring for the reaction chamber temperature based on the sensor voltage.

The basic thermal response of the gel valve device was first evaluated. There should be a certain temperature difference between the microchannels A and B to switch the fluid direction effectively. Figure 8 shows equilibrium temperatures of the microchannels A and B when the electrical power was applied to the microchannel A heater. As the applied electrical power was increased, the

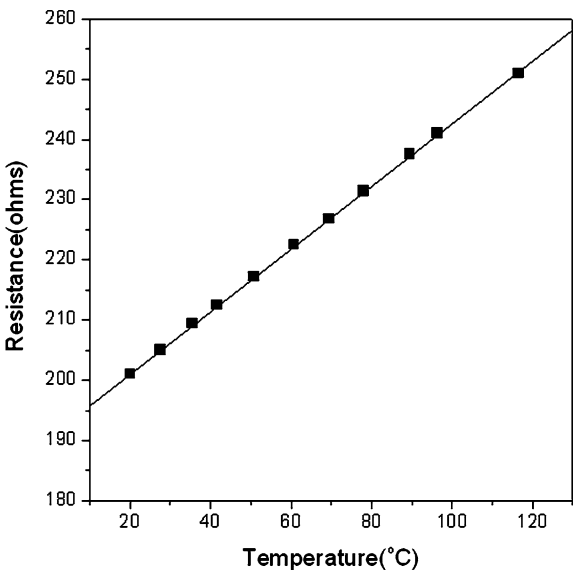


Fig. 7 Resistance variations of Pt thin film temperature sensor as a function of temperature

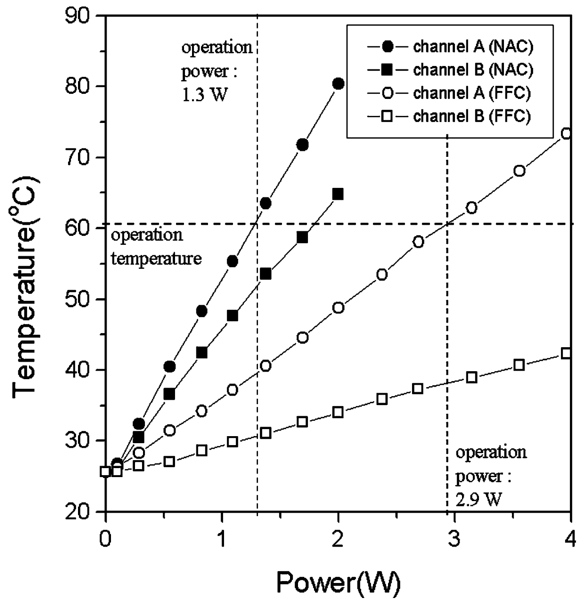


Fig. 8 Equilibrium temperatures of both microchannels A and B under the natural air convection (*NAC, closed symbols*) and the fan forced cooling (*FFC, open symbols*) conditions when the power was applied to the microchannel A only. The corresponding temperature at each microchannel was monitored by the on-chip temperature sensor

temperature difference between the microchannels A and B was also increased gradually. Based on the temperature dependency of the rheological property of the MC solution, the gelation is almost completed at 60°C. Therefore, the microchannel A must be heated until the temperature of the microchannel A reached the equilibrium temperature of 60°C. When natural air convection (NAC) was used for cooling, the electrical power of 1.3 W was required to keep the temperature of the microchannel A at 60°C. In this case, the temperature difference between the microchannels A and B was less than 10 K, which was insufficient to operate the gel valve device. Both the microchannels A and B were blocked with gels and the liquid could not flow through the microchannels.

A larger temperature difference between the microchannels A and B was required in order to switch the flow direction using the gel valve device. As we introduced fan forced cooling (FFC) method, the temperature of the microchannel B was about 37°C when the temperature of the heated microchannel A reached 60°C. The temperature difference between the microchannels A and B was measured to be 23 K. Based on the rheological measurements, the solution in the microchannel A would be turbid gel while the MC solution at the microchannel B was in clear sol state.

The rapid operation of the gel valve device requires fast heating and cooling rates. Figure 9 shows the temperature profiles of the microchannels A and B when the electrical powers of 1.3 W (NAC) or 2.9 W (FFC) were alternately applied to each microchannel with the time interval of 65 s. Under the NAC cooling method, the heating and cooling rates were measured to be 2.4

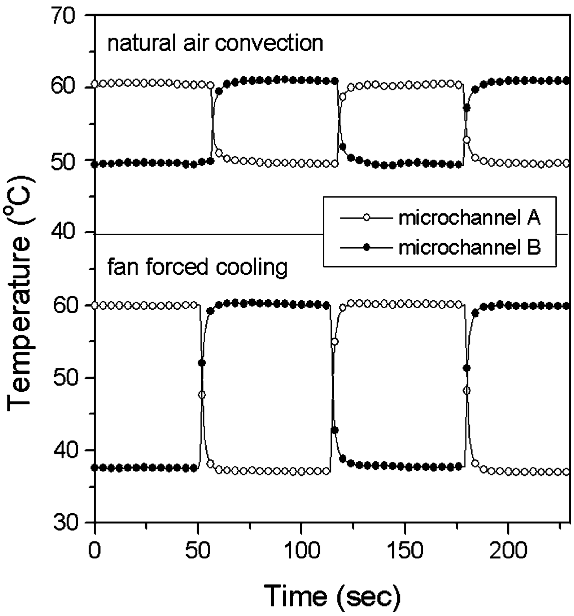


Fig. 9 Temperature profiles of the microchannels A and B under the NAC (*top panel*) and the FFC condition (*bottom panel*). With regulating the electrical power of each microchannel alternatively, the corresponding temperatures at the microchannels A (*open symbols*) and B (*closed symbols*) were monitored by the on-chip temperature sensors

and 2.7 K/s, respectively. On the other hands, the initial heating and the cooling rates were evaluated to be 5.7 and 5.8 K/s, respectively, for the FFC method. This experiment revealed that the FFC is advantageous not only because there is big enough temperature difference between both microchannels but also because it has higher ramping rate.

We conducted the flow switching experiment using the gel valve device. 0.5% MC solution was used as a working fluid. The operation power was fixed at 2.9 W and the FFC method was used. The flow rate of inlet was 10 μl/min. Figure 10a shows the operation schedule of the electrical power to heat the microchannels, and the flow rates of the inlet and the microchannels. Figure 10b shows the snapshots of the device undergoing major operational events such as valve turn-on and turn-off. The reliable switching of the liquid flow from the microchannels A to B requires a pause of flow for about 5 s. Without the pause, allowing a continuous flow during the microchannel switching resulted in poor valve performance. Even if the temperatures of two microchannels were above 60°C, the liquid continuously flew through both microchannels simultaneously. This suggested that the sufficient gelation for valve performance did not take place due to the continued fluid flow. When we heated up the microchannel B and stopped the fluid flow for about 5 s, the liquid could not flow through the microchannel B. A snapshot (c) in Fig. 10b shows that the liquid flew through the microchannel A only. In the work of Tashiro et al. (2001a, b), the valve function was accomplished without the temporary pause of the fluid flow. Compared to our work, the dimension of their microchannels was much smaller, 15 μm wide and 12 μm deep. Even though a narrow microchannel might help easier fluid flow operation, it also has a danger of increasing the fluidic impedance and thus inhibits the high throughput of the fluid processing.

In order to make the valve function, it is important to keep the temperature of one microchannel at below 35°C and the other at higher than 45°C because of the thermoreversible characteristics of the MC solution. The NAC was not sufficient enough to leave one of the microchannels under 35°C, and it left both microchannels blocked resulting in no fluid flow. The situation was quite different when the FFC was used. The FFC brought both microchannels to the equilibrium after 10 s (Fig. 8c), at which the temperatures of the microchannels A and B recorded about 37 and 60°C, respectively. The larger temperature difference between both microchannels generated by FFC helped more accurate and reproducible operation of the gel valve device.

As a result of the performance test of the gel valve device at various flow rates, stable operation condition was obtained when the flow rate was higher than 5 μl/min. Below 5 μl/min, the gel debris was not sufficiently cleaned away and therefore stable reversible operation was not obtained. In addition, the leakage test was performed by measuring the leakage at various pressures while keeping the temperature of both microchannels at 60°C. The leakage test was conducted by following the method suggested by Oh (1999). The valve inlet was connected to a reservoir with a silicone tube. By raising the height of the reservoir from the valve inlet, static pressure was varied. These gel valves could withstand hydrostatic pressures up to 2.07×10^4 Pa without moving.

Powerful advantages of this gel valve device are that the leakage is minimal and the valve design is very simple. Even though mechanical valves using membranes or microacutators are advantageous at high frequency valving operation, they usually have complicated structures. Therefore, it is difficult to fabricate and some amount of leakage was frequently observed. The microfluidic lab-on-a-chip for diagnostics application usually does not require high frequency valving operation because most biochemical reactions such as DNA hybridization or PCR (polymerase chain reaction) (Koh et al. 2003; Yoon et al. 2002) require at least several seconds to hours to complete the reactions. Accordingly, the gel valve with no leakage and simple structure would have wide range of applications. Especially, this gel valve may be favorable for application of PCR chip, which performs multiple thermal cycling of annealing (~55°C), extension (~72°C) and denaturation (~95°C), because 0.5% MC solution has high transition temperature (~50°C). For other biological applications, however, the transition temperature should be adjusted not to deteriorate the activity of biologically relevant fluids in each chip. The transition temperature of working fluid can be controlled through polymer engineering in which the type and the concentration of polymer, ion, and buffer can be surveyed.

4 Conclusion

A microfluidic gel valve device was manufactured using thermoreversible sol–gel transition characteristics of MC. Various properties of the MC solution were investigated using viscometer, spectrophotometer, and NMR. Gelation temperature was increased as the MC concentration was increased. Clear gel, an intermediate state between clear sol and turbid gel, was found at the temperature range from 30–40°C to 50–60°C. In order to have normal operation of the gel valve, it was important to keep the temperature of the heated microchannel around 60°C while keeping the temperature of the flowing microchannel below 35°C. The temperature difference between two microchannels was about 23 K when FFC method was used. The initial heating and cooling rates when FFC method was used were 5.7 and 5.8 K/s, respectively. For normal performance of the gel valve device, a temporary pause of fluid flow for at least 5 s was required to complete the local gelation in the microchannel. Stable gel valve performance was obtained at the flow rates higher than 5 μl/min. Leakage tests showed no leakage up to $2.07{\times}10^4$ Pa. From above results, it was revealed that the gel valve device using the thin film heaters and the thermoreversible sol–gel transition characteristics of MC solution, is applicable to microfluidic chip application. Further systematic study is currently under investigation in order to realize the gel valve device toward commercial microfluidic chip application.

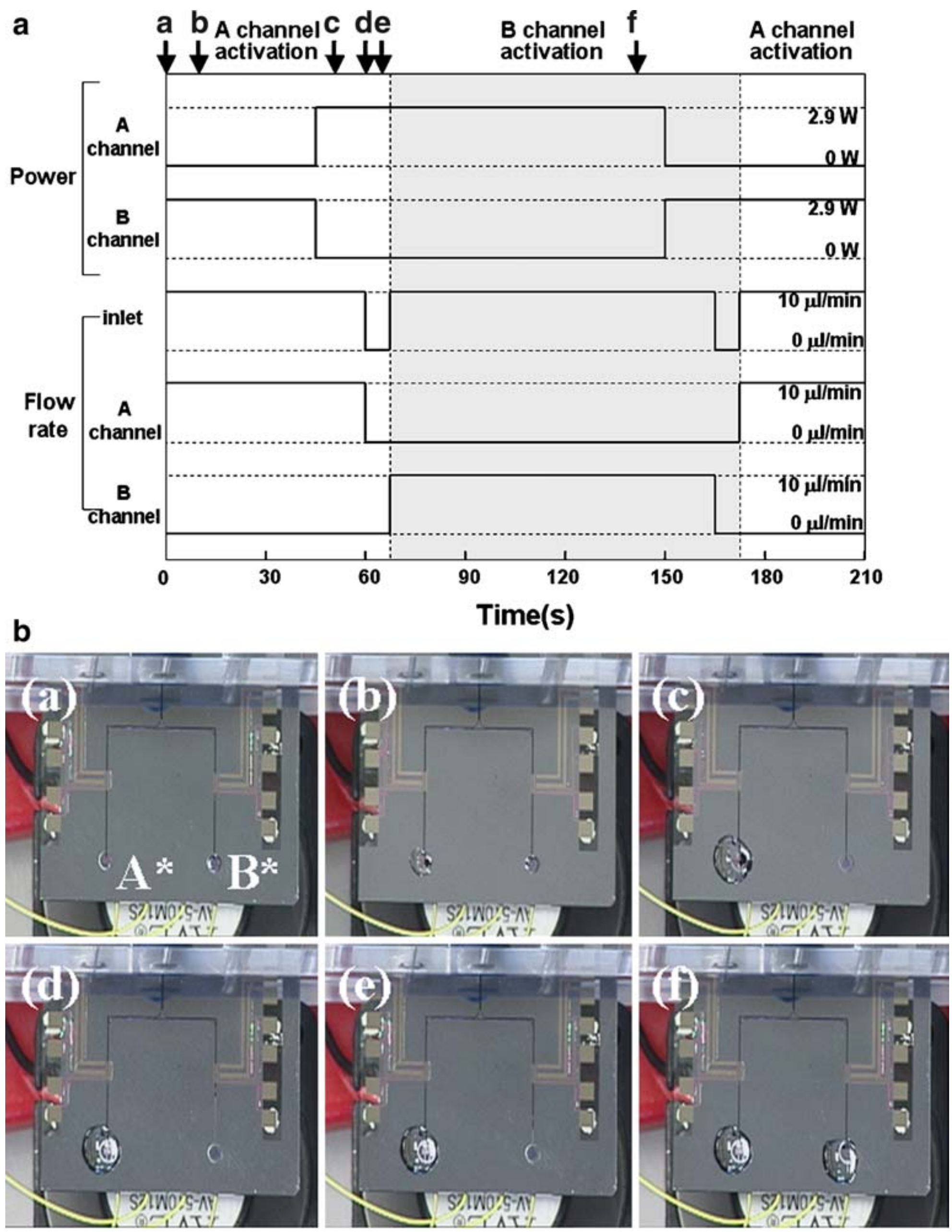


Fig. 10 *Top panel* (**a**) depicts the heating schedule and flow rate employed to operate the gel valve device. Each photo of (a)–(f) at the bottom panel (**b**) captures the snapshots of the gel valve at the corresponding timing marks on the schedule. (a)–(c) represent the turn-on of the valve B and then a fluid flow occurs in the microchannel A. (d) represents the temporary pause of a flow to activate the gelation of MC solution under the turn-on of the valve A. (e)–(f) represent the turn-on of the valve A and then a fluid flow occurs in the microchannel B. Marks A* and B* represent the microchannels A and B

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