A thermoresponsive valve to control fluid flow in microfluidic paper-based devices

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Abstract
Microfluidic paper-based analytical devices (µPADs) have recently attracted the attention of researchers and industry owing to their various advantages. However, µPADs lack a way to control fluid flow; therefore, it is difficult to perform complex immunoassays that use multiple reagents and replace the reagents from the analytical area. We developed a controllable thermoresponsive valve for µPADs by functionalizing a polyvinylidene difluoride porous membrane with plasma-induced graft polymerization of poly(N-isopropylacrylamide) (PNIPAAm), which is a thermoresponsive polymer that changes its hydrophilic properties near the lower critical solution temperature (LCST; 32 °C). Surface analysis by attenuated total reflectance Fourier transform infrared spectroscopy confirmed that the fabricated thermoresponsive valves coated with PNIPAAm. The valve performance was evaluated by sandwiching the thermoresponsive valve between two paper microchannels stacked in a T-shaped paper microfluidic device. The thermoresponsive valve fabricated with a monomer concentration ranging from 2.3 to 3.0 wt% and a polymerization time of 5 h or 2.0 wt% and 20–22 h showed good valve performances. These valves were able to stop the flow at room temperature, and allow the flow by opening within 20 s after heating was initiated using a Peltier element located just under the valve. The valve was successfully closed, thereby stopping the flow, and opened by heating. Although a detailed evaluation of the fluid behavior is necessary, we have demonstrated that our thermoresponsive valve can be opened and closed reversibly by temperature control. We believe that this thermoresponsive valve could potentially be used to control the flow of multiple reagents in µPADs.

Keywords Microfluidic paper-based analytical device · N-isopropylacrylamide · Thermosensitive polymer · Fluid control

1 Introduction

Owing to their various advantages such as small size, easy fabrication, low cost, small sample volumes, and no need for a pump, microfluidic paper-based analytical devices (µPADs) have recently attracted the attention of researchers and industry (Martinez et al. 2007, 2010). They are particularly suited for point-of-care testing (POCT) applications. The advantage of POCT is that minimal effort and manipulation is required by the user. Various quantitative µPADs based on colorimetric, fluorescent, and electrochemical methods have been reported as POCT devices (Cheng et al. 2010; Nie et al. 2010; Mahato et al. 2017; Iwasaki et al. 2020). However, general immunoassays require multiple reagents to be sequentially introduced into the device, which increases the number of manipulation steps rendering the device unsuitable as a POCT. To solve this problem, several flow control methods have been reported (Li et al.
2008, 2013; Fu et al. 2011; Chen et al. 2012; Houghtaling et al. 2013; Shin et al. 2014; Toley et al. 2015). The method of sequentially injecting multiple buffers into the analysis region of a µPAD using the time delay caused by the difference in paper length and the ease of flow of the porous membrane has been widely adopted (Fu et al. 2011; Toley et al. 2013; Shin et al. 2014). Although this method allows multiple reagents that are simultaneously injected into different inlets to sequential flow to the analytical region without the need for additional equipment, the design of the µPADs requires complex calculations (Fu et al. 2011). A switchable valve that could control the opening and closing of the valve by connecting and disconnecting the separated papers in the middle of the paper channel was reported (Li et al. 2008, 2013, 2017; Giokas et al. 2014; Toley et al. 2015; Tu et al. 2021). However, these mechanical valves have a complicated three-dimensional structure and need to be manually switched and manipulated. Other interesting switches and valves have also been reported (Chen et al. 2012; Houghtaling et al. 2013). However, nearly all valves developed to date are passive, open and close only when a certain fluid level is reached, can be used only once, or require the dissolution of unnecessary reagents, such as surfactants; therefore, they are not practical for use in complex immunoassays.

A controllable valve based on a polyvinylidene difluoride (PVDF) porous membrane functionalized with poly(N-isopropylacrylamide) (PNIPAAm), which is a thermoresponsive polymer that changes its hydrophilic properties at approximately 32 °C, has been reported (Iwasaki et al. 2019). PNIPAAm swells when it becomes hydrophilic at temperatures below 32 °C, and shrinks when it becomes hydrophobic at temperatures above 32 °C owing to dehydration. Therefore, at temperatures below 32 °C, the pores of the PVDF membrane are filled with swollen PNIPAAm; thus, the valve membrane closes to liquids and proteins (Fig. 1). In contrast, when the pores of the valve membrane are occupied by shrunken PNIPAAm, liquids and proteins can pass through the valve membrane. Further, with small amounts of PNIPAAm in the valve membrane, the pores are not completely filled and proteins may pass through, while excessive PNIPAAm in the valve membrane causes the pores to remain closed even at temperatures above 32 °C, resulting in an interrupted flow through the valve membrane. Therefore, the amount of PNIPAAm in the thermoresponsive valve is an important factor. We previously performed the free radical polymerization of PNIPAAm using N,N'-methylenebisacrylamide (BIS), ammonium persulfate (APS), and N,N,N',N'-tetramethylethylenediamine (TEMED) (Iwasaki et al. 2019). Upon adding a drop of TEMED, polymerization rapidly progressed from the drop position through the entire monomer solution. However, the extent of polymerization was uneven, which may be attributed to the slow diffusion of TEMED in the porous membrane. On the other hand, in plasma-induced graft polymerization, radicals that initiate polymerization in a chain are homogeneously generated on the surface of the substrate by plasma treatment. Therefore, it is expected that uniformly polymerized PNIPAAm in a porous membrane is obtained by plasma-induced graft polymerization. Therefore, in this study, we performed plasma-induced graft polymerization of NIPAAm to functionalize the PVDF porous membranes, and obtain a good quality thermoresponsive valve membrane. In addition, we investigated the relationship between the amount of PNIPAAm and valve performance by varying the polymerization conditions, and evaluated the responsiveness of the valve by adding a dynamic temperature change.

2 Experimental

2.1 Reagents

Polyvinylidene fluoride (PVDF) membranes (Durapore® membrane filter, HVLP02500), nitrocellulose membranes (Hi-Flow™ Plus HF120), and absorbent pads (SureWick®) were purchased from Merck Millipore Ltd. (County Cork, Republic of Ireland). NIPAAm, BIS, and APS were purchased from Sigma-Aldrich (Tokyo, Japan). Polydimethylsiloxane (PDMS, SILPOT 184) was purchased from Dow...
Corning Toray Co., Ltd. (Tokyo, Japan). We used ultrapure water with a conductivity of 18.2 MΩ-cm in all experiments.

### 2.2 Preparation of a thermoresponsive valve membrane

Plasma-induced graft polymerization of NIPAAm onto PVDF membranes can be performed by immersing PVDF in NIPAAm solution after generating radicals on PVDF by plasma irradiation. Because the polymerization reaction is inhibited by oxygen, it is necessary to immerse the PVDF in the NIPAAm solution without exposing it to the atmosphere after plasma irradiation. We assembled a plasma-induced graft polymerization system that can perform these processes (Fig. 2). The system consists of a glass nipple, which is the plasma production area, a glass bell jar to hold the NIPAAm solution, a gate valve to separate the NIPAAm solution and plasmas, a vacuum pump series consisting of a turbo molecular pump and a diaphragm pump, an argon gas flow control system, a push rod to push out the PVDF membrane, and a radio frequency (RF) power supply to produce plasmas.

Using this system, a thermoresponsive valve membrane was prepared according to the following protocol: the NIPAAm monomers were purified by recrystallization from hexane, and the purified NIPAAm monomers were dissolved in a 50/50 vol% methanol/water solution. The concentration of the NIPAAm monomer ranged from 2.0 to 3.5 wt%. BIS and APS were dissolved in the NIPAAm solution with the respective molar ratios to the NIPAAm monomers of 0.5 and 1%. Then, the NIPAAm solution was poured into a glass bell jar. The PVDF membrane was placed in the glass nipple to ensure it was located at the center of the coil wire. The glass nipple and glass bell jar containing the PVDF membrane and NIPAAm solution, respectively, were evacuated with a diaphragm pump to degas the NIPAAm solution. Next, the gate valve connecting the glass nipple and the glass bell jar was closed, and the glass nipple was evacuated using a turbo molecular pump. Once the vacuum reached below 10⁻⁵ Torr, argon gas was introduced into the glass nipple at a flow rate of 30 sccm, and the PVDF membrane was subjected to 20 W inductively coupled plasma for 30 s. Then, the supply of argon gas and all vacuum pumping systems were stopped, the gate valve was opened, a push rod was used to push the PVDF membrane into the NIPAAm solution, followed by closing the gate valve. Then, the gate valve and the glass bell jar containing the mixture of the NIPAAm solution and PVDF membrane were removed from the apparatus and incubated at 30 °C to initiate NIPAAm polymerization. After incubation, the PVDF-PNIPAAm membranes were immersed in ultrapure water and washed by shaking for more than 3 h. The polymerization time (incubation period) was varied from 4 to 30 h, and the valve performance of each membrane was compared.

### 2.3 Membrane characterization

The surface of the PVDF-PNIPAAm membrane was characterized by Fourier-transform infrared spectroscopy in attenuated total reflectance mode (ATR-FTIR) with a germanium crystal (FT/IR-6300, Jasco Co., Japan) at room temperature. The sample surface was pressed onto the Ge crystal with the active surface. The FTIR spectra were acquired in the range of 4000–350 cm⁻¹ using 16 scans at a resolution of 4 cm⁻¹.

The microstructure of the thermoresponsive valve membrane was investigated using scanning electron microscopy (SEM; JSM-6701F, JEOL Ltd., Tokyo, Japan) in the open and closed states. The membranes were immersed in water at 25 and 40 °C overnight to ensure that the valves were in the closed and open states, respectively. The membranes were removed from the water, immediately frozen by dipping in liquid nitrogen, and then freeze-dried (FD-1000; Tokyo RIKAKIKAI Co., Ltd., Tokyo, Japan). Prior to SEM observation, the membranes in the open and closed states were coated with a thin gold film using a desktop quick coater (SC-701HMCII; Sanyu Electron Co., Ltd., Tokyo, Japan).

![Fig. 2 Photograph (a) and schematic (b) of the plasma graft polymerization apparatus. RF radio frequency power source, TMP turbo molecular pump, DP diaphragm pump, MFC mass flow controller](image-url)
2.4 Evaluation of valve performance in paper microfluidic channel

We evaluated the valve performance of the fabricated thermoresponsive valve using a three-dimensionally stacked paper microfluidic channel (Fig. 3). Two nitrocellulose membranes (Bottom: 50 mm × 5 mm; top: 25 mm × 5 mm) (HF120, Merck Ltd.) were stacked in a T-shape on top of each other, with the thermoresponsive valve membrane (7 mm × 7 mm) sandwiched between the membranes at the junction. All membranes were cut to their respective sizes using a laser cutting machine (Blaster; Hotproceed Inc., Fukuoka, Japan). The stacked T-shaped paper microfluidic channel was covered with polymethylmethacrylate (PMMA) housings. The junction was gently and uniformly pressed using an elastic polydimethylsiloxane block with a torque wrench of 1 N cm to ensure contact for ease of flow (Iwasaki et al. 2015). One edge of the bottom nitrocellulose membrane was held in place using a PMMA jig with an inlet chamber. Absorbent pads were attached to the other edge of the bottom nitrocellulose membrane and the upper edge of the top nitrocellulose membrane. A small Peltier element was placed under the junction as a heating element. This Peltier element, controlled by a microcomputer (Arduino Due), can regulate the temperature of the valve. The open and closed states of the valve membrane can be verified by observing whether the green dye flows to the top nitrocellulose membrane, which is oriented horizontally.

![Fig. 3 Schematic of the experimental setup for the valve performance test](image)

A green dye was used to visualize the flow in the microfluidic channel. First, 50 µL of the green dye solution was injected into the inlet chamber of the bottom nitrocellulose membrane (Fig. 3). Once the inlet chamber was empty, an additional 50 µL of green dye solution was injected. The valve membrane was heated and cooled after a certain time following the injection of the green dye, and the opening and closing behavior of the valve was evaluated.

3 Results and discussion

3.1 SEM observation

A thermoresponsive valve membrane fabricated by polymerization for 20 h with 2.0 wt% NIPAAm monomer and an untreated PVDF membrane were observed by SEM (Fig. 4). The PVDF-PNIPAAm membrane showed polymer adhesion on its surface when compared with the untreated PVDF membrane. The microstructures of open and closed thermoresponsive valve membranes prepared using different polymerization times were also observed by SEM (Fig. 5). For the polymerization time of 15 h, several uniformly distributed pores at both 20 and 40 °C were observed in the membrane. It was also confirmed that the number of pores filled with PNIPAAm proportionally increased with the polymerization time at 20 °C, while they remained open (unfilled) at 40 °C regardless of polymerization time (15, 20, and 30 h). These results show that the uniform polymerization of PNIPAAm on the porous membranes was successful, which was difficult to achieve by free radical polymerization in our previous work (Iwasaki et al. 2019). Further, the closing and opening of the pores by swelling and shrinking, respectively, was observed.

3.2 ATR-FTIR spectroscopy

The results of the ATR-FTIR measurements of a PNI- PAAm sheet and the PVDF membranes before and after graft polymerization for 30 h at 2 wt% NIPAAm monomer concentration are shown in Fig. 6. PNIPAAm sheets were prepared using the method described in the Supporting
Information (SI) for FTIR spectral comparison. Absorption peaks at 835, 878, 1173, 1233, and 1400 cm\(^{-1}\) were observed for both membranes, which correspond to the CF\(_2\) symmetric stretching, CH\(_2\) bending, CF\(_2\) antisymmetric stretching, CH stretching, and CH\(_2\) bending, respectively. The PVDF-PNIPAAm membrane showed new absorption peaks at 1456, 1540 and 1645 cm\(^{-1}\), which correspond to CH\(_2\) bending, N–H stretching and the second amide C=O stretching of the O=C–NH groups in the PNIPAAm chain (Hirashima et al. 2005; Yu et al. 2011; Xiao et al. 2014), respectively. This result shows that PNIPAAm was successfully polymerized on the PVDF membranes.

### 3.3 Valve function of thermoresponsive valve membrane

We compared the behaviors of the opening action of valve membranes prepared using different polymerization times. The Peltier element was heated to 35 °C 240 s after the first injection of the green dye. The thermoresponsive valve membrane showed three patterns of valve performance depending on the polymerization conditions of PNIPAAm. Time-lapse images of the typical flow state for each pattern obtained using the valve membranes fabricated with different polymerization times at 2 wt% NIPAAm monomer concentration are shown in Fig. 7. Videos of these experiments are also available in the SI. The green contrast in Fig. 7 and the videos noticeably increased and became quite visible. For the membrane with a polymerization time of 4 h (Case 1), the green dye passed through the valve membrane and flowed into the top membrane in the horizontal direction prior to heating because the valve membrane remained open even at room temperature. For the polymerization time of 22 h (Case 2), the green dye did not pass through the valve membrane before heating. Approximately 20 s after heating was initiated, the green dye began to flow into the top membrane. Finally, the green dye reached the absorbent pad located at the right edge of the top membrane 240 s after heating was initiated, indicating a good valving performance. For the longer polymerization time of 30 h (Case 3), the green dye did not pass through the valve membrane before heating, as in Case 2. However, even after 240 s of heating, there was no sign of the green dye permeating the valve membrane and flowing into the top membrane. The green dye was only observed to flow to the right edge of the top membrane after 1200 s of heating.

The results of the valve performance test of all the valve membranes and the weight of PNIPAAm obtained from the weight difference of the membranes measured before and after graft polymerization are plotted in Fig. 8. The results of the valve performance test are divided into cases 1, 2, and 3, and are plotted with a cross, circle, and triangle markers, respectively. Since the weight change before and after graft polymerization is minimal, only the PNIPAAm weight should be taken as a reference. Although there was some variation in the PNIPAAm weight and valve performance test results, the weight tended to increase with increasing
polymerization time. As for the valve performance, the short
polymerization time tended to be case 1, the polymerization
time from 20 to 22 h tended to be case 2, and the poly-
merization time of 30 h was case 3. In addition, the extent of
PNIPAAm polymerization also increased depending on the
monomer concentration. With regard to monomer concentra-
tion, less than 2.2 wt% of NIPAAm monomer concentration
exhibited the case 1 scenario, 2.3–3.0 wt% exhibited the
case 2 scenario, and 3.5 wt% exhibited the case 3 scenario.
These results indicate that the amount of PNIPAAm can be
controlled by the polymerization time and monomer con-
centration. Further, with small amounts of PNIPAAm, the
valve cannot be closed, while with large amounts, poor flow
is observed despite an open valve, as expected.

In comparison with the results of the valve performance
test and SEM observation, for the polymerization time of
15 h, it can be understood that the flow could not be stopped
because the pores were barely closed. Although only some
pores were closed in the case of 20 and 30 h, they were suf-
icient to stop the flow. At 40 °C, the pores were open in both
cases (20 and 30 h polymerization time); however, at 30 h,
the pores seemed to be filled more. This slight difference
may have prevented a free flow during heating. Thus, it is
considered that the functioning of the valve is not dependent
on whether the pores are completely filled, but rather on the
extent of open valves. Although it seems difficult to control
the degree of opening, the optimal valve performance was
obtained with a monomer concentration in the range 2.3–3.0
wt% for 5 h of polymerization.

We further evaluated whether the valve could be closed
from an open state using the same T-type microfluidic
channel. In this experiment, the PVDF-PNIPAAm mem-
brane polymerized for 5 h with 2.5 wt% NIPAAm monomer
was used. Heating was initiated 180 s after the injection of
the green dye, cooling was initiated at 330 s, and heating
was performed once more at 540 s (Fig. 9). A video of this
experiment is available in the SI. In this figure, the green
contrast remarkably increased and became quite visible.
The green dye could not penetrate the valve membrane and only
flowed to the lower channel. However, when the valve was
heated, the dye permeated the valve membrane and flowed
to the upper channel (in the horizontal direction). When the
valve membrane was cooled, the lateral flow ceased. The
flow remained stopped as long as the valve was maintained
below the LCST. When the valve was reheated, the dye flow
restarted. These results show that the temperature-respon-
sive valve could be opened and closed reversibly by tem-
perature control.

4 Conclusions

In the present study, we investigated plasma-induced graft
polymerization as a method to fabricate a thermorespon-
sive valve for µPADs by surface treatment of a PVDF
porous membrane with PNIPAAm. The apparatus for
plasma-induced graft polymerization was fabricated, and
the polymerization conditions were varied. Surface analy-
sis by ATR-FTIR confirmed that the fabricated thermore-
sponsive valves were successfully coated with PNIPAAm.
SEM observation confirmed that the pores of the valve
membranes opened and closed in response to tempera-
ture and that the number of pores filled with PNIPAAm
proportionally increased with the polymerization time.
Subsequently, a valve performance test was conducted
to determine the conditions required for an optimal valve
performance. The thermoresponsive valve fabricated by
polymerization with monomer concentration ranging from 2.3 to 3.0 wt% for 5 h of polymerization or 2.0 wt% for 20–22 h of polymerization showed a good valve performance; they stopped the flow at room temperature and opened to allow the flow within 20 s after heating was initiated using a Peltier element located just under the valve. We also demonstrated that this temperature-responsive valve can be reversibly opened and closed via repeated valve heating/cooling experiments. Although a detailed evaluation of the fluid behavior needs to be conducted, we showed that the thermoresponsive valve fabricated by plasma-induced graft polymerization may potentially be used to control the flow of multiple reagents in µPADs. Future investigations may be conducted to demonstrate the effectiveness of our thermoresponsive valve using complex analytical techniques, such as immunoassays with paper analysis chips.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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