

# High-pressure on-chip mechanical valves for thermoplastic microfluidic devices

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Received 18th June 2009, Accepted 3rd September 2009

First published as an Advance Article on the web 6th October 2009

DOI: 10.1039/b912014a

A facile method enabling the integration of elastomeric valves into rigid thermoplastic microfluidic chips is described. The valves employ discrete plugs of elastomeric polydimethylsiloxane (PDMS) integrated into the thermoplastic substrate and actuated using a threaded stainless steel needle. The fabrication process takes advantage of poly(ethylene glycol) (PEG) as a sacrificial molding material to isolate the PDMS regions from the thermoplastic flow channels, while yielding smooth contact surfaces with the PDMS valve seats. The valves introduce minimal dead volumes, and provide a simple mechanical means to achieve reproducible proportional valving within thermoplastic microfluidic systems. Burst pressure tests reveal that the valves can withstand pressures above 12 MPa over repeated open/close cycles without leakage, and above 24 MPa during a single use, making the technology well suited for applications such as high performance liquid chromatography. Proportional valve operation is demonstrated using a multi-valve chemical gradient generator fabricated in cyclic olefin polymer.

## Introduction

A common issue for lab-on-a-chip systems is the need for precise flow control for analyte and reagent delivery. To meet this demand, fluid handling components including valves, pumps, and mixers have been widely integrated within microfluidic chips. In particular, valving is a fundamental requirement for a wide range of microanalytical platforms. A large number of active<sup>1–20</sup> and passive<sup>21–24</sup> microvalves for microfluidic applications have been reported. Active valves are particularly useful for common microfluidic flow control tasks, providing on-demand shut-off or proportional valving using magnetic,<sup>1–3</sup> electrostatic,<sup>4,5</sup> piezoelectric,<sup>6,7</sup> shape-memory,<sup>8</sup> phase-change,<sup>9–13</sup> mechanical,<sup>14,15</sup> or pneumatic<sup>16–18</sup> actuation mechanisms. In particular, elastomeric PDMS valves<sup>16</sup> fabricated using soft lithographic methods<sup>19</sup> represent one of the most widely used classes of microfluidic valve technologies. In a typical PDMS valve, pneumatic control lines deform a thin elastomeric membrane to occlude an underlying microchannel, thereby modulating fluid flow. To simplify the control of PDMS valves and make the technology more amenable to system-level miniaturization, several groups have developed elastomeric valves actuated by alternate mechanisms. Takayama *et al.* utilized a computerized Braille display with its grid of moving pins as linear actuators for programmable valves and pumps integrated with multiple layers of PDMS.<sup>20</sup> Whitesides and co-workers demonstrated a screw-actuated valve using a small machine screw cast into a PDMS substrate directly above a membrane-enclosed channel, allowing the elastomer membrane to be compressed by simply rotating the screw,<sup>21,22</sup> and Wu *et al.* developed an indirect screw-assisted

hydraulic valve in which the screw actuator was used to adjust the pressure applied to a water-filled control channel separated from an underlying microchannel by a PDMS membrane.<sup>23</sup> In this latter example, the machine screws were fixed within a poly(methylmethacrylate) (PMMA) manifold and positioned above the PDMS substrate. However, in each case, the microfluidic system itself was fabricated entirely from PDMS. While PDMS valves are simple to fabricate and actuate, a fundamental limitation imposed by the technology is that the valve elastomer constrains the material options for the overall microfluidic device. In particular, PDMS can impact the mechanical integrity, pressure limits, surface chemistry, gas permeability, and solvent compatibility of the resulting microfluidic system.

Thermoplastics such as polycarbonate (PC), polymethylmethacrylate (PMMA), and cyclic olefin polymer (COP) offer compatibility with high-throughput replication methods, excellent dimensional stability, robust mechanical properties, and rigidity suitable for high pressure applications. However, due to their rigidity, thermoplastics do not directly support the integration of deformable valves. Efforts to adapt PDMS valves to thermoplastics have focused on developing bonding techniques enabling deformable PDMS membranes to be assembled with thermoplastic substrates containing microchannels.<sup>24</sup> However, this hybrid approach still requires the integration of a continuous PDMS layer over the microfluidic channels, and thus does not obviate the underlying disadvantages of PDMS valves. Furthermore, thermoplastic microfluidics are of interest for analytical platforms based on high performance liquid chromatography (HPLC), where high pressures above 10 MPa are commonly required. Elastomeric microvalves are not suitable for this use, with typical pressure limits well below 0.5 MPa.<sup>24</sup> As an alternative to PDMS valves for high pressure thermoplastic microfluidics, thermally-responsive gel valves have been successfully integrated with cyclic olefin copolymer (COC) chips.<sup>11–13</sup> These porous polymer valves operate through

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temperature-controlled swelling and deswelling of the polymer matrix. While leakage pressures of nearly 10 MPa have been demonstrated for these valves, the temperature control mechanism limits the valve response time to at least several seconds,<sup>12</sup> and the valves cannot be used for proportional flow control. The fabrication process, which includes UV photopolymerization and thermoplastic surface modifications to achieve a strong gel/sidewall interface, imposes additional constraints.

Here we report a facile and robust method for fabricating high-pressure proportional valves for thermoplastic microfluidics. Rather than bonding a continuous PDMS membrane over the entirety of a thermoplastic substrate containing embedded microchannels, the valve employs a small PDMS cylinder formed at the base of a threaded access port, with a threaded needle used to deform the PDMS into an underlying microchannel. In this way, the overall microfluidic system retains the mechanical integrity, high-pressure capabilities, and surface chemistry of the thermoplastic substrate, while significantly reducing issues of gas permeability and solvent compatibility by limiting the area of PDMS exposed to the microchannels. Due to its high clarity, UV transmission, and resistance to many common acids, bases, and organic solvents, COP was used as the thermoplastic material. The fabrication process does not require significant instrumentation, and multiple valves can be cast on a single chip with minimal additional fabrication complexity. The use of small-gauge threaded needles yields an exceptionally small footprint for the fabricated valves, while also defining a low dead-volume interface approaching that of pneumatically-actuated PDMS valves.

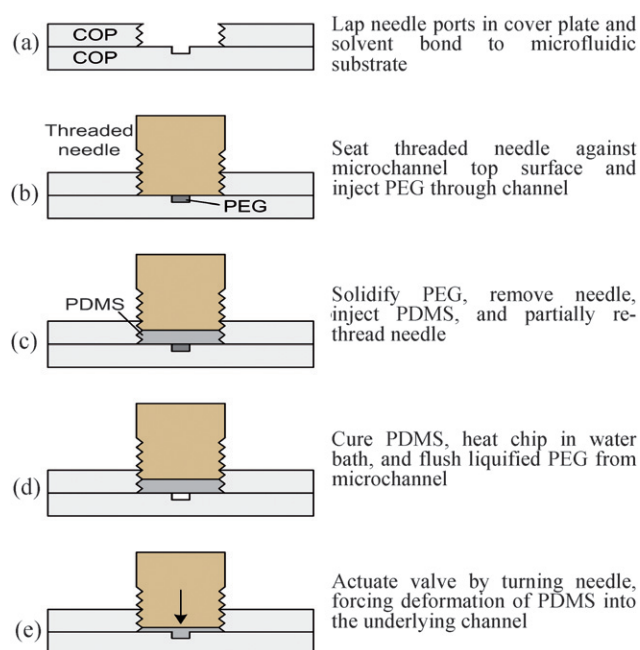
## Experimental

### Chemicals and reagents

Poly(ethylene glycol) (PEG, 1500 MW), cyclohexane and hydrochloric acid were purchased from Sigma-Aldrich (St. Louis, MO). Methanol, 2-propanol and fluorescein sodium salt were purchased from Fisher Scientific (Pittsburgh, PA). Sylgard 184 PDMS was purchased from Dow Corning (Midland, MI). Fluorescent microspheres (1  $\mu\text{m}$  diameter) used for flow visualization were purchased from Polysciences, Inc. (Warrington, PA).

### Microfluidic chip fabrication

The fabrication process of thermoplastic-integrated elastomeric valves is illustrated in Fig. 1. Two pieces of 2 mm thick COP plates (Zeonor 1020R; Zeon Chemicals USA, Louisville, KY) were diced to the desired size. Microchannels were milled in the first COP plate using a 125  $\mu\text{m}$  diameter end mill on a precision computer numerical control (CNC) milling machine (MDX-650A; Roland, Lake Forest, CA). Holes for the valve actuators were formed in a COP cover plate by the same CNC tool using a 533  $\mu\text{m}$  drill bit. Threaded stainless steel needles were prepared from hypodermic needle tubing segments (gauge 22s, 710  $\mu\text{m}$  o.d., 150  $\mu\text{m}$  i.d., 2.5 cm long; Hamilton Syringe, Reno, NV). The needle ends were polished with 1500 grit (3  $\mu\text{m}$  particle size) sandpaper, and a miniature jeweler die (American Science and Surplus, Skokie, IL) was used to form threads with a pitch of 140  $\mu\text{m}$  over a  $\sim$ 4 mm length of the needles. The actuator ports in the COP cover plate were threaded by screwing a needle into each



**Fig. 1** Fabrication process for the thermoplastic-integrated PDMS valves. (a) Before solvent bonding two plates of 2 mm thick COP, with microchannels fabricated in the lower plate, a hole is milled in the upper plate aligned to the lower microchannel, and threads are formed in the hold using a pre-threaded gauge 22s needle segment. (b) An end-polished needle is inserted into the threaded hole to seat against the bottom COP surface, and the channel is filled with heated PEG. (c) After cooling and solidifying the PEG, the needle is removed, the hole is filled with PDMS, and the needle is rethreaded with its end 1 mm above the channel. (d) After fully curing the PDMS, the chip is heated allowing PEG to be flushed from the channel. (e) PDMS occludes the microchannel as the threaded needle is actuated.

hole, using a low-ion detergent during the threading process to reduce friction.

After tapping the holes, the needles were removed, and both COP plates and threaded needles were sonicated for 30 min to remove debris, and sequentially cleaned by methanol, 2-propanol, and DI water, followed by aggressive drying with  $\text{N}_2$ . The cover chip with threaded holes was heated to 95  $^\circ\text{C}$  under 13.79 MPa applied pressure for 2 min to flatten surface swelling which occurred during the tapping process. Before bonding, both COP chips were degassed at 75  $^\circ\text{C}$  under vacuum. The mating COP chips were solvent bonded with vapor-phase cyclohexane by placing the cover chip face down on top of a sealed glass beaker containing cyclohexane, with the chip surface 5 cm away from exposed solvent at 30  $^\circ\text{C}$  for 7.5 min. The chips were aligned and bonded in a hydraulic press (Carver, Wabash, IN) at a 13.79 MPa for 1 min at room temperature. Fabricated chips were held at room temperature for 24 h before use to maximize bonding strength.

### Valve fabrication

Needles were gently inserted by hand until seated against the bottom chip surface. The chip was heated to 70  $^\circ\text{C}$  on a hotplate, well above the PEG melting point of 40  $^\circ\text{C}$ , and liquid-phase PEG was injected through the microchannel network by vacuum, then slowly cooled to room temperature to fully seal the channels

with solidified PEG. After cooling, the needles were removed. PDMS was prepared by combining the Sylgard 184 components in a 10:1 w/w ratio of base to curing agent, and degassed at 20 °C under vacuum for 30 mins. The PDMS was poured into the threaded holes, and the needles were re-threaded to define a 1 mm PDMS height within the hole. Note that the fine thread pitch provides good control over the needle depth during this step. The PDMS was partially cured at room temperature for 24 h, at which point the threaded needles were removed and the PDMS was fully cured at 75 °C under vacuum for 24 h. Finally, the sacrificial PEG was purged by vacuum before allowing the chip to cool, and heated DI water was injected through all channels to flush any residual PEG from the flow path. A capillary fitting was mounted on the end of each threaded needle as a simple knob enabling manual valve operation.

An optical image of a fabricated valve is shown in Fig. 2(a), and electron micrographs in Figs. 2(b) and 2(c) show details of a polished needle tip and a fully-cured PDMS valve seat, respectively. The image of the PDMS surface in Fig. 2(c) was obtained by removing the COP substrate containing the microchannels, revealing the smooth and coplanar COP/PDMS surface achieved using the sacrificial PEG molding process.

### Flow control and pressure measurements

To evaluate flow control and pressure resistance of the thermo-plastic-integrated PDMS valves, three chips were fabricated containing two inlet microchannels (130  $\mu\text{m}$  wide, 70  $\mu\text{m}$  deep) which intersect on-chip and merge into a single outlet channel. A PDMS valve was fabricated between one of the inlets and the

channel intersection. To evaluate valve reproducibility, one flow inlet was connected to a syringe filled with a dilute solution of fluorescent microspheres in DI water. For flow rate measurements, the syringe was mounted vertically with a weight placed on the plunger to produce a constant 0.1 MPa pressure. The initially open on-chip valve was closed in increments of 22.5° from its initial position, and flow of the fluorescent microspheres was monitored within the channel 5 mm downstream from the valve. Flow rates were determined by particle image velocimetry.

For pressure resistance measurements, the same chip design was adopted. One flow inlet was connected to an analytical LC pump (PU-2089; Jasco, Easton, MD) to define a known pressure, and the other flow inlet was connected to a syringe filled with 0.1 mM fluorescein and controlled by a programmable syringe pump (Harvard Apparatus, Holliston, MA). Threaded needle interfaces were used on both flow inlets as high pressure world-to-chip interfaces.<sup>25</sup> The valve was closed by rotating the valve needle in 22.5° increments. Once the valve had been closed, fluorescein was injected to fill the channel. To measure the pressure resistance in each position, a constant DI water flow rate of 10  $\mu\text{L}/\text{min}$  was applied from LC pump to the valve and the LC pump back pressure was monitored, with failure defined by a sudden drop in applied pressure corresponding to PDMS deformation or failure that allowed fluid to pass, resulting in a loss of fluorescence within the outlet channel.

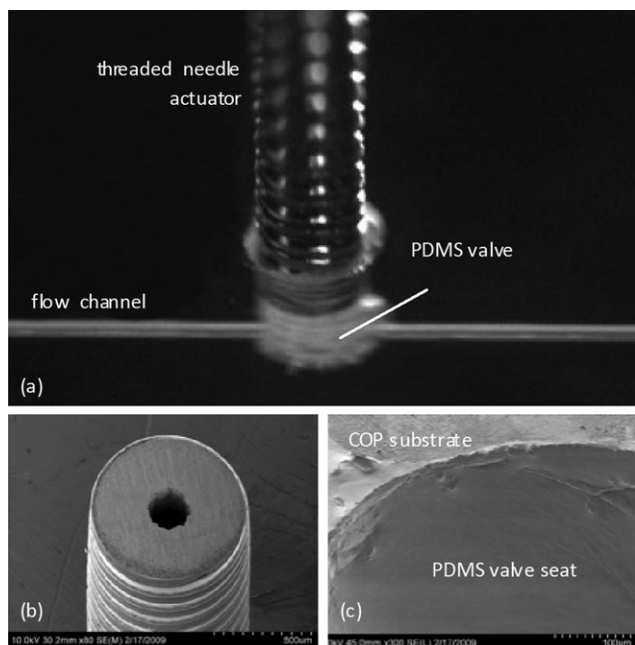
### Chemical gradient reactor

To demonstrate the utility of the valve technology, a microfluidic chemical gradient reactor was fabricated in a three-layer COP chip using four PDMS valves and an array of chaotic micro-mixers (Fig. 3). In this reactor design, the valves are used to generate two different flow rates for each of two inlet streams. The resulting flows are joined combinatorially, producing four different mixed concentrations at the downstream reservoirs. To characterize the gradient generator, and referring to Fig. 3, an acid solution consisting of 0.1 M HCl was injected from inlet A, and a base solution consisting of 0.1 M NaOH mixed with 0.01 mg/mL fluorescein was injected from inlet B. Programmable syringe pumps were used to inject each solution into the chip through needle ports. The four PDMS valves control the generation of variable acid ( $A_1$ ,  $A_2$ ) and base ( $B_1$ ,  $B_2$ ) flows. A series of vertical through-channels milled into the middle layer of the chip were used to couple the multilayer microchannels and route solutions between the inlets and mixing channels. Desired mixing concentrations were generated by adjusting the proportional valve angles to yield specific acid/base flow rates in each channel, with the resulting mixtures collected at the output reservoirs. Experiments were performed by setting the valve positions and injecting the acid and base solutions through the needle interfaces at 5  $\mu\text{L}/\text{min}$  for 10 min. Fluorescence intensities were monitored near the end of each mixing channel using a CCD camera installed on a fluorescence microscope.

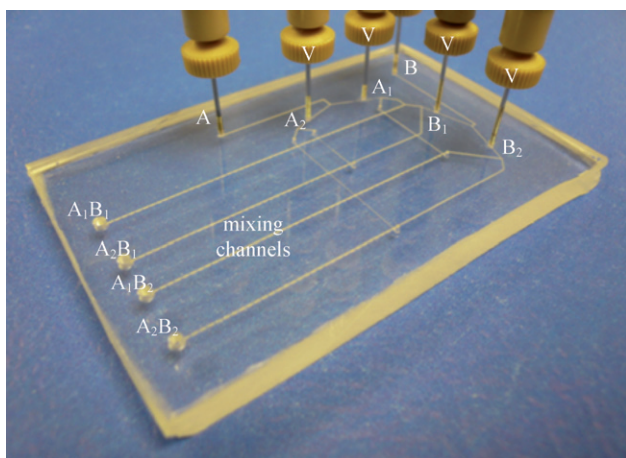
## Results and discussion

### Valve fabrication

The use of threaded needles as manual actuators for thermo-plastic-integrated PDMS valves was motivated by our recent



**Fig. 2** (a) Photograph of a fabricated PDMS valve. A 1 mm thick PDMS piston aligned above a flow channel is actuated by a threaded needle to occlude flow in the microchannel. (b) SEM image of a polished threaded needle tip. (c) SEM image of a PDMS valve surface revealing the clean COP/PDMS interface. The fabrication process yields a smooth valve seat with no voids between the thermoplastic COP substrate and PDMS valve surface.



**Fig. 3** Image of a 3-layer chemical gradient reactor. An acid solution is injected from inlet A, and a base solution mixed with fluorescein is injected from inlet B. Four needle valve actuators (V) control the generation of variable acid ( $A_1$ ,  $A_2$ ) and base ( $B_1$ ,  $B_2$ ) flows. Vertical through-channels link the multilayer microchannels used to route solutions between the inlets and mixing channels. Specific mixing concentrations are generated in each channel and collected at the output reservoirs ( $A_xB_y$ ) through control of the proportional valves.

demonstration that needles used for high-pressure world-to-chip fluid interfacing<sup>25</sup> could maintain high pressure seals following many tens of repeated insertion and removal cycles. Unlike silicon, glass, or elastomer materials, an important advantage of thermoplastics for microfluidic applications is their excellent machinability. While previous screw-type PDMS valves require epoxy<sup>21,22</sup> or an external frame<sup>23</sup> to mate screws to the microfluidic chip, the current approach avoids these additional fabrication steps by machining the mating threads directly into the thermoplastic substrate. Using 710  $\mu\text{m}$  diameter stainless steel needles, valve displacement volume is minimized while providing a rigid and mechanically robust interface for valve actuation.

Several steps in the fabrication process were found to be crucial to producing reliable valves. Plastic deformation of the microfluidic substrate is unavoidable during the tapping process used for valve port threading, typically resulting in several tens of microns of out-of-plane surface deformation around the circumference of the hole. The resulting surface topography produced non-uniform pressure distributions during chip bonding, leading to poor bond quality. Heating the cover chip containing the threaded holes under moderate temperature and pressure prior to bonding was found to be necessary to eliminate surface swelling caused by tapping.

Polishing the needle end seated against the bottom thermoplastic substrate during PEG injection was critical for achieving a smooth and void-free valve seat. Unpolished needles were found to produce significant roughness of the solidified PEG, due to both pattern transfer from the rough needle end as well as the tendency for bubbles to become trapped on the rough surface. The resulting PDMS surfaces exhibited voids which increase the valve dead volume, as well as protrusions which can shear from the valve during operation and clog the downstream microchannel.

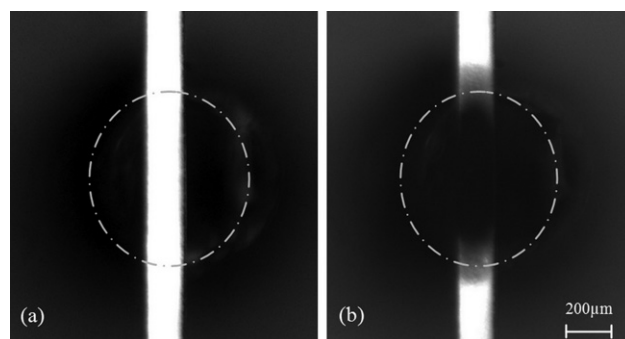
A clean and unobstructed needle capped by a capillary fitting was partially threaded into the valve port to define the elastomer

height during curing. Although miniature machine screws could theoretically serve the same purpose while eliminating the need to custom-fabricate the threaded needles, the use of a hollow needle critical in achieving a well-formed PDMS plug with a flat valve seat. When threading the needle, excess PDMS prepolymer is expelled through the needle bore, ensuring that the PDMS is not forced into the microfluidic flow channel while also providing an egress for trapped air bubbles. Using this approach, together with needle tip polishing, smooth and flat valve seats that are co-planar with the COP substrate were consistently achieved, as shown previously in Fig. 2(c).

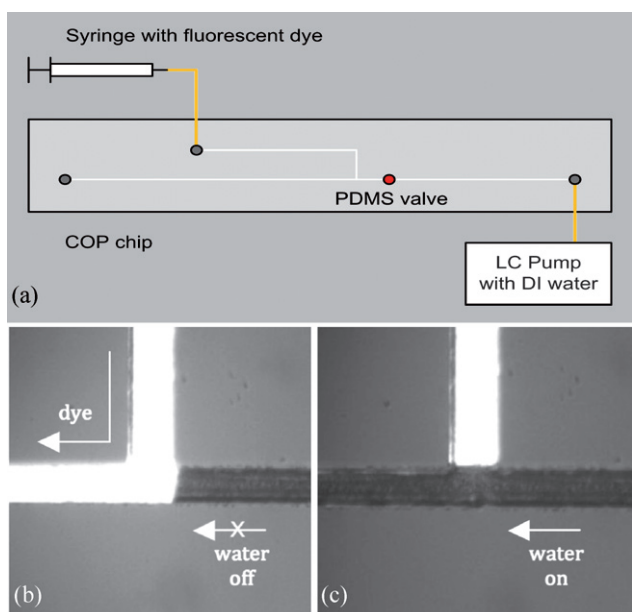
The effective dead volume of the threaded needle PDMS valve was estimated by observing the displacement of fluorescein solution while closing the valve. Fluorescein was injected through the channel with the valve set at its open position (Fig. 4a). In all tests, the dye was confined within the channel, with no leakage beneath the PDMS piston observed beyond the channel width. From the fluorescent image after turning the threaded needle until the flow was blocked (Fig. 4b), the occluded channel volume was estimated to be 6.5 nL for the particular channel geometry used in this work.

### Proportional flow control and pressure resistance

Using a chip containing a single valve, the relationship between valve position, defined by the needle rotation angle, and flow rate was examined. The chips consisted of a T-junction, with fluorescein injected past the junction using a syringe pump, and fluorescent microbeads injected past the junction using either an LC pump or a constant pressure source (see Experimental section). The PDMS valve was located between the microbead inlet and the T-junction, allowing flow of the beads to be modulated with the valve. Measurements of bead flow were performed using three different chips, with an average of 10 repeated operation cycles using each chip. A schematic diagram of the chip design is shown in Fig. 5(a), and images of the T-junction with the valve in the off and on positions are shown in Figs. 5(b) and 5(c). Defining 0° as the position at which the valve first closes for a small input pressure of 0.1 MPa, with negative angles reflecting an open valve and positive angles representing additional compression of the PDMS valve, measurements of flow rate at different valve positions are shown in Fig. 6. The flow



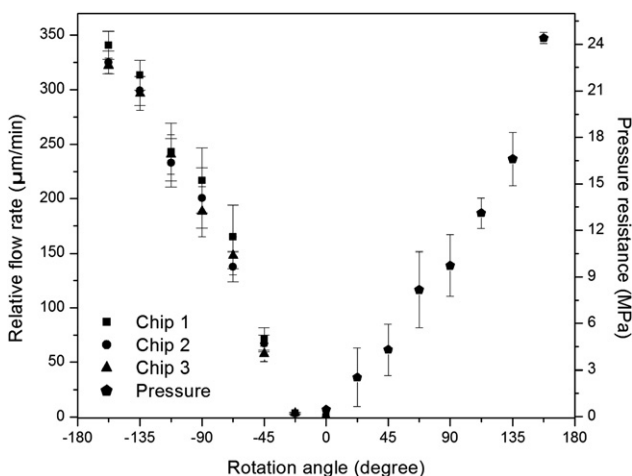
**Fig. 4** Images of a fluorescein-filled microchannel with the PDMS valve in its (a) open and (b) closed positions. Note that no dye is observed to leak beneath the valve seat in the open position, and the dye is fully expelled from beneath the valve in the closed position.



**Fig. 5** (a) Schematic diagram of the system configuration for characterization of the thermoplastic-integrated PDMS valves, and fluorescent images of the channel intersection with the valve in the (b) closed position blocking water flow from the LC pump and (c) open position allowing water to displace dye in the downstream channel.

rate exhibits a nearly linear dependence on valve rotation angle, with good reproducibility between the different chips.

Also shown in Fig. 6 is the relationship between positive valve angles and pressure resistance measured using the same 3 chips. In the initial closed position, the maximum pressure resistance for the valves was measured at 0.4 MPa. Gradually increasing the rotation angle resulted in a linear increase in maximum pressure before valve leakage was observed. The maximum pressure of 24.4 MPa was achieved for a rotation angle of approximately



**Fig. 6** Experimental measurements revealing relationships between valve rotation angle and flow rate for negative (open valve) angles, and between valve rotation angle and pressure resistance for positive (closed valve) angles. Three chips were tested to evaluate valve repeatability, and an average of ten tests was performed using each chip for flow rate measurements.

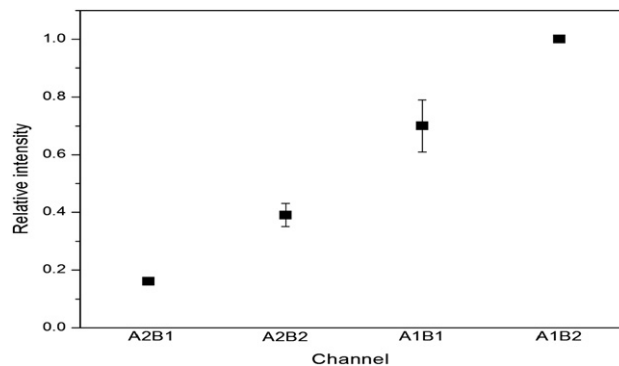
158°. However, it should be noted that for a valve rotation angle of 113°, small portions of PDMS were occasionally observed to shear off the valve body when the maximum back pressure of about 13 MPa was reached. Thus while the valves can operate at pressures above 24 MPa for single-use applications, a lower pressure limit of 13 MPa is more suitable when repeated valve cycles are required. However, below 13 MPa the repeatability and robustness of the valves were found to be excellent, with valves actuated more than one hundred times over a period of a month at the 13 MPa pressure limit without failure.

The channel aspect ratio is an important factor affecting the functionality of regulation and valving. In this work, the microchannels beneath the valve seats were approximately 130 µm wide and 70 µm deep. Valves fabricated using deeper channels were found to result in lower pressure limits due to shear forces producing debris from the PDMS at lower valve rotation angles. More shallow channels, on the other hand, constrained the valve rotation angle range without significantly improving pressure resistance.

### Chemical gradient reactor

Because the quantum yield of fluorescein is highly dependent on pH, it is useful as a pH indicator dye. While its fluorescence is relatively stable under basic conditions, the quantum yield of fluorescein drops dramatically over the range of *ca.* pH 9 to 4.<sup>26</sup> This pH dependence provides a simple optical method for estimating solution pH. Using the chemical gradient reactor chip (Fig. 3) containing acid/base inlets and four on-chip PDMS valves to adjust the flow rates of the combinatorial mixing stage, a series of six mixing tests were performed using two different chips to evaluate the ability of the thermoplastic-integrated PDMS valves to provide repeatable proportional control in the system. For each test, valve positions were selected to adjust the relative flow rates of the acid and base inlets to produce a linear gradient in fluorescence intensities across the distal ends of each mixing channel, corresponding to a pH gradient across the resulting mixtures.

The normalized fluorescence intensity measured in each channel is shown in Fig. 7. The results demonstrate that the



**Fig. 7** Normalized measurements of fluorescence intensity in the four-channel chemical gradient reactor chip, with multiple PDMS valves enabling proportional flow control. Increasing intensity reflects a higher pH value due to the pH dependence of fluorescein quantum yield. Channel designations correspond to matching labels in Fig. 3.

valves offer an effective method for achieving on-chip proportional flow control in this multi-valve system.

## Conclusion

The threaded needle PDMS valves offer a simple solution for realizing proportional valves in thermoplastic microfluidic systems. In addition to providing mechanically-robust and repeatable valving, the thermoplastic-integrated valves are well suited for high pressure chips due to the threaded actuator interface, offering a novel low-cost solution for flow control in applications such as high performance liquid chromatography. The hybrid material approach takes advantage of the benefits provided by traditional elastomeric PDMS microfluidic valves, but integrated into discrete regions of thermoplastic chips, allowing the overall physiochemical properties of the system to be dictated by the thermoplastic rather than the PDMS. The valves introduce low dead volumes and are compatible with operating pressure over 24 MPa for single-use applications, and up to 13 MPa for repeated use. Manual valve operation is amenable to chip prototyping, while automation operation may be achieved using off-chip rotary actuators.

The maximum pressure resistance of the valves demonstrated in this work is presently limited by the PDMS material properties. However, because the threaded needles generate high compressive forces on the elastomeric valve plugs, a wide range of elastomers with higher elastic moduli and shear strengths than PDMS may be suitable for use as the elastomeric valve material without sacrificing valve function. The use of fluoroelastomers, for example, may provide higher pressure resistance while also offering excellent solvent compatibility.

## Acknowledgements

This work was supported by the National Institutes of Health (R01 GM072512), and the National Science Council, Taiwan (NSC 96-2811-E-002-054).

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