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Semi-disposable microvalves for use with microfabricated devices or microchips

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Abstract. The design, fabrication and performance characteristics of a semi-disposable CNC (computer numerical control) machined plexiglass microvalve system for use with microfabricated devices or microchips designed for human cell isolation and DNA amplification systems are described. Unlike other silicon chip-based microvalve systems, the CNC machined microvalve system is easy to fabricate, and it does not require a clean-room environment and complicated microfabrication procedures. The non-silicon-based microvalve comprises a disposable CNC machined plexiglass base and a flexible plastic membrane. The microvalve was formed from two discontinuous micro-channel components. The plexiglass used for fabrication does not inhibit biochemical reactions and extensive experimental flow studies were performed to optimize the design of the microvalve assembly so as to allow controlled flow. Different types of plastic membrane and eight different discontinuous micro-channel valve geometries were investigated and an optimum design was chosen based on the experimental results. The final design of the microvalve has minimal dead volume (less than 0.16 μl). We have demonstrated that the CNC machined plexiglass microvalve system can process microliter and sub-microliter sized samples of human whole blood without attendant problems, such as loss of sample on the microvalve system and loss by evaporation.

1. Introduction

The application of microfabrication processes used in the microelectronics industry to bioanalysis has facilitated miniaturization of fluidics and filtration systems (Cheng *et al* 1996a, Wilding *et al* 1994a, b). In particular, the microfabrication of silicon chip-based devices (i.e. microchips) for DNA analyses has been a focus of the past decade (Cheng *et al* 1996b, Shoffner *et al* 1996, Wilding *et al* 1995). Also, micro total analysis systems (μTASs), including microsensors, micropumps and microvalves, for the integration of an analytical reaction involving the steps of sample preparation, biochemical reaction and detection/quantitation have been proposed for medical and biomedical applications (Ohori *et al* 1998, van der Schoot *et al* 1994). However, in order to realize a practical and cost-effective μTAS for biomedical applications, a microvalve system that can handle human whole blood is essential.

Thus far, most microvalve systems have been microfabricated from silicon. The silicon chip-based microvalve systems can be classified into two categories: active microvalves (with an actuator) and passive (check) microvalves (without an actuator) (Shoji and Esashi 1994). The miniaturization of the active microvalve systems is restricted by the size of the actuator. The actuators used for the active microvalve systems include solenoid plunger (Terry *et al* 1979), bimetallic actuator (Jerman 1990), piezoelectric actuator (Shoji *et al* 1991, Esashi 1990, Shoji and Esashi 1988), shape memory alloy (SMA) and bias spring (Shoji *et al* 1988), pneumatic actuator (Ohori *et al* 1998, Sim *et al* 1996), electrostatic actuator (Goll *et al* 1997, Sato and Shikida 1994, Shikida and Sato 1994, Huff *et al* 1993, Ohnstein *et al* 1990), electromagnetic actuator (Yanagisawa *et al* 1993, Bosch *et al* 1993) and thermopneumatic actuator (Goll *et al* 1996, Fahrenberg *et al* 1995, Zdeblick *et al* 1994, Zdeblick and Angell 1987). Recently, silicon chip-based active microvalves have become available commercially, and Redwood MicroSystems (Menlo Park, CA) now offers a silicon valve based on a thermopneumatic operating principle (http://www.redwoodmicro.com). The characteristics of the silicon chip-based active and passive microvalve systems are listed in tables 1 and 2. As expected, the sizes of the passive microvalve systems were generally smaller than the active microvalve systems and the response time of the active microvalve systems ranged from 5 ms to 10 s. Air, nitrogen, helium, water and deionized water were the test mediums for both the passive and active microvalve systems.

Silicon chip-based microvalve systems for medical and biomedical applications are still limited, especially a microvalve system that is suitable for whole blood handling. Overcoming this challenge is a vital step towards developing practical totally integrated microfluidic systems for blood

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Table 1. Silicon chip-based active (with actuator) microvalves. (sccm denotes standard cubic centimeter per minute. psid denotes pound-force per square inch (differential pressure). 1 kgf = 9.806 65 N. ϕ denotes diameter.)

Type	Actuator	Size	Flow range	Response time	Reference
Diaphragm	Solenoid plunger				Terry *et al* 1979
Diaphragm	Bimetallic	ϕ2.5 mm	300 ml min^{-1} (air: 7 kgf cm^{-2})		Jerman 1990
Bulk silicon (normally closed)	Stack type piezoelectric	10 mm × 10 mm × 10 mm	40 ml min^{-1} (N_2: 0.5 kgf cm^{-2})	1 ms	Esashi 1990
Silicone rubber seat	Cantilever type piezoelectric	24 mm × 12 mm × 5 mm	9 ml min^{-1} (H_2O: 0.2 kgf cm^{-2})	1 ms	Shoji and Esashi 1988
Silicone rubber seat	SMA and bias spring	ϕ3 mm × 8 mm		10 s	Shoji *et al* 1998
Silicone rubber seat	Pneumatic	4.2 mm × 8.5 mm	On/off flow ratio $\sim 10^4$ (deionized H_2O: 1 mH_2O and 25 °C)	1 s	Ohori *et al* 1998
Valve plunger	Pneumatic	20 mm	0.5–50 sccm (N_2: 0.26 kgf cm^{-2} and 25–120 °C) Leakage: 0.05 sccm		Sim *et al* 1996
Movable membrane electrode	Electrostatic	ϕ5 mm × 3 mm	0.2 ml s^{-1} (N_2: 110 kPa)		Goll *et al* 1997
S-shaped film element	Electrostatic		10 sccm (air: 60 Pa)		Sato and Shikida 1994
Pressure balance	Electrostatic	1 mm × 1.8 mm × 1.4 mm	160 ml min^{-1} (air: 1.34 kgf cm^{-2})		Huff *et al* 1993
Cantilever	Electrostatic	3.6 mm × 3.6 mm	150 ml min^{-1} (air: 0.25 kgf cm^{-2})		Ohnstein *et al* 1990
Membrane	Electromagnetic and electrostatic	3 mm × 8 mm	3 ml min^{-1} (air: 0.16 kgf cm^{-2} (160 mbar))	0.4 ms	Bosch *et al* 1993
Microheater (normally open)	Thermopneumatic	6 mm × 6 mm × 2 mm (unpackaged)	0.2–3000 sccm (N_2: 20 psid and 25 °C) Leakage: 0.2 sccm	300 ms (10–90% full scale rise time)	Redwood MicroSystems (commercial product)
Microheater (normally closed)	Thermopneumatic	6 mm × 6 mm × 2 mm (unpackaged)	0.1–1500 sccm (N_2: 20 psid and 25 °C) Leakage: 0.1 sccm	1 s (0–100% full scale rise time)	Redwood MicroSystems (commercial product)
Bistable buckled polymer diaphragm	Thermopneumatic	ϕ5 mm × 1 mm	250 μl s^{-1} (N_2: 30 kPa) Leakage < 0.001 μl s^{-1}		Goll *et al* 1996
Microheater (normally open)	Thermopneumatic	ϕ7 mm × 1.9 mm	171 μl s^{-1} (H_2O: 100 kPa)		Fahrenberg *et al* 1995
Microheater	Thermopneumatic	3 mm × 3 mm	60 ml min^{-1} (N_2: 0.35 kgf cm^{-2})	5 ms (calculated)	Zdeblick and Angell 1987

analysis. Prototypes of whole blood gas analysis systems using microvalves driven by SMA actuators (Shoji *et al* 1988) and piezobimorph actuators (Shoji and Esashi 1988) have been developed. Recently, Ohori *et al* (1998) developed a partly-disposable three-way microvalve claimed to be suitable for whole blood handling using pneumatic actuation. However, they presented no data on whole blood handling in their partly-disposable three-way microvalve. Also, the adhesion of the silicon membrane to the substrate must be eliminated before the partly-disposable three-way microvalve can be put into actual use (Ohori *et al* 1998).

We have developed an alternative non-silicon-based semi-disposable microvalve system for use with human whole blood. This microvalve comprises a disposable computer numerical control (CNC) machined plexiglass base and a flexible plastic membrane. The microvalve forms a part of our integrated microchip analysis system (Cheng *et al* 1996b, Shoffner *et al* 1996, Wilding *et al* 1995) for whole blood that integrates sample preparation, biochemical reaction and detection/quantitation steps for DNA analyses.

2. The semi-disposable CNC machined plexiglass microvalve system

The semi-disposable CNC machined plexiglass microvalve system is depicted schematically in figure 1. The microvalve system was constructed from two plexiglass platforms. The microvalve was formed from two discontinuous micro-channel components (figure 1(c)).

Table 2. Silicon chip-based passive (check) (without actuator) microvalves. (1 kgf = 9.806 65 N. ϕ denotes diameter.)

Type	Size	Forward/reverse flow rate ratio	Reverse leakage	Reference
Ring mesa (bulk silicone)	ϕ7 mm			Van Lintel *et al* 1988
Cantilever (bulk silicone)	1 mm × 1 mm	5×10^3 (1.0 mH_2O)	1 μl min^{-1} (0.60 mH_2O)	Tirén *et al* 1989
Cantilever (bulk silicon)		Forward flow rate: 17 μl min^{-1} (H_2O: 1.2 bar)	10 nl min^{-1} (H_2O: 0.1 bar)	Emmer *et al* 1992
Disk (polysilicone)	ϕ1.2 mm	200 (1.0 mH_2O)	5 μl min^{-1} (1.0 mH_2O)	Esashi *et al* 1989
V-shape (bulk silicone)	80 μm × 100 μm	6×10^2 (6.0 mH_2O)		Smith and Hök 1991
Membrane (Ti-polyimide)	ϕ1 mm	2.6×10^3 (He: 0.1 kgf cm^{-2})	360 μl min^{-1} (He: 0.1 kgf cm^{-2})	Schomburg and Scherrer 1992
Float (silicone)	1.2 mm × 1.2 mm	2.1×10^4 (10 mH_2O)	0.26 μl min^{-1} (10 mH_2O)	Shoji *et al* 1992
p+ silicon diaphragm	780 μm × 1580 μm	Forward flow rate: 1.6 ml min^{-1} (H_2O: 4 kPa)	0.05 ml min^{-1} (H_2O: 4 kPa)	Yang *et al* 1996

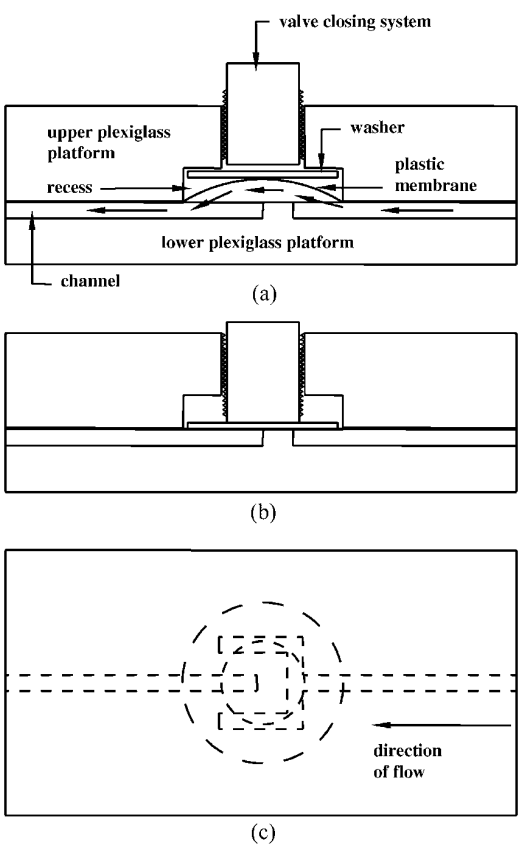

Figure 1. Operating principles of a semi-disposable CNC machined plexiglass microvalve system. (a) valve open, (b) valve closed and (c) bottom view.

The open micro-channel components of the microvalve were first machined on the surface of the lower platform using a CNC machine (Fadal Engineering® Model VMC15XT) with a 250 μm diameter end mill. A spindle speed of 6000 rpm and feed rate of 0.5 in min^{-1} were used in order to produce smooth channel surfaces. Kerosene was used as the coolant during machining. Next, the recess and the valve closing system were machined and assembled in the upper platform. Finally, a flexible plastic membrane with the adhesive side facing the lower platform was placed between the upper and lower platforms. The platforms were then sealed together either by screws or by 'press-and-snap' fittings. The plastic membrane provided sealing for micro-channels and microvalves, and created an airtight microfluidic network from the discontinuous open micro-channels. Also, it operated as a seal/shutoff membrane for the microvalve.

The operating principles of the microvalve system are depicted schematically in figure 1. Pressured flow along the micro-channels causes the flexible plastic membrane to rise into the recess, thus permitting flow across the microvalve (figure 1(a)). The microvalve is closed by positive action on the valve closing system (figure 1(b)). Release of this system allows the microvalve to re-open. We performed extensive experimental flow studies to optimize the design of the valve assembly so as to allow controlled flow. Eight different micro-channel geometries (figure 2) were investigated. Performance characteristics and fluid transfer across the discontinuity of the microvalve were studied for each valve geometry.

The experimental set-up is depicted schematically in figure 3. In the lower plexiglass platform, standard luer fittings for 1 ml syringe were machined for the connections of the microvalve system. A rubberless syringe (NORM-JECT® 1 ml TB Part number A1) filled with fluid sample (either human whole blood or Dulbecco's 1× phosphate buffered saline without calcium chloride and magnesium chloride (PBS)) was inserted into the luer fitting. A syringe pump (Sage Instruments Model 341B) was used to push the piston of the syringe, so as to provide the pressured flow along the microvalve system. A load cell (Sensotec Model 13/2443-06) was placed between the piston and the syringe pump as shown in figure 3 to measure the applied pressure. A video camera or a video camera linked to a microscope was used to record each experiment.

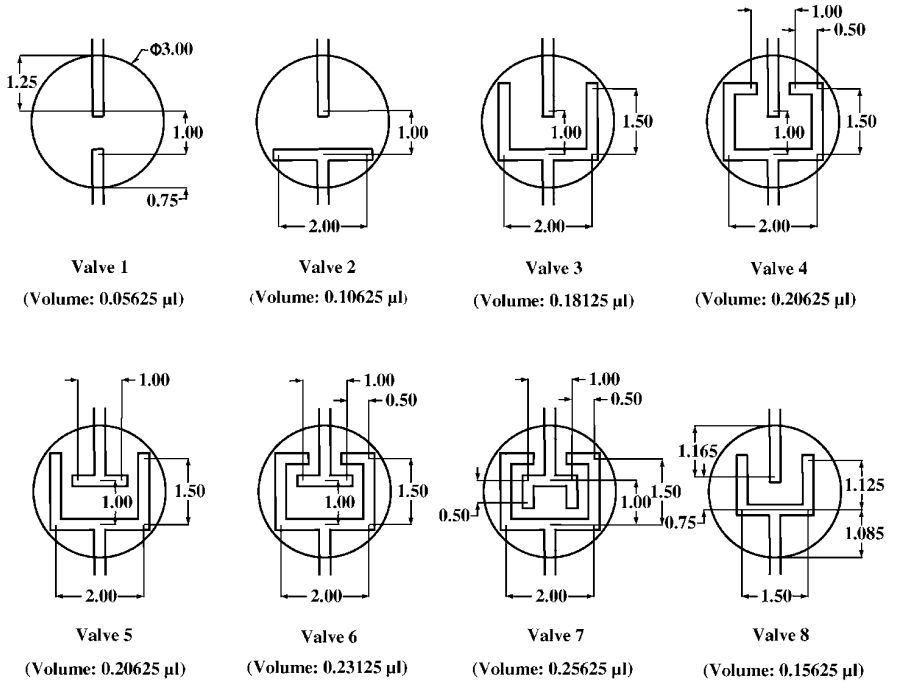

Figure 2. Microvalve geometries. All dimensions (center to center) are in millimeters and each channel is 250 μm (width) $\times$ 100 μm (depth). (ϕ denotes diameter.)

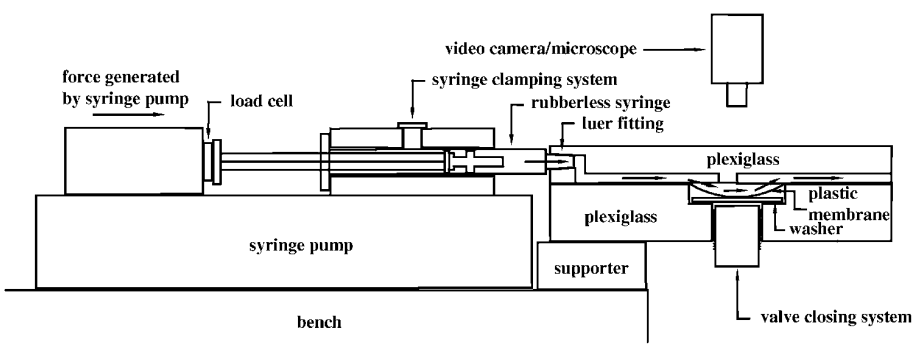

Figure 3. Schematic diagram of the experimental set-up.

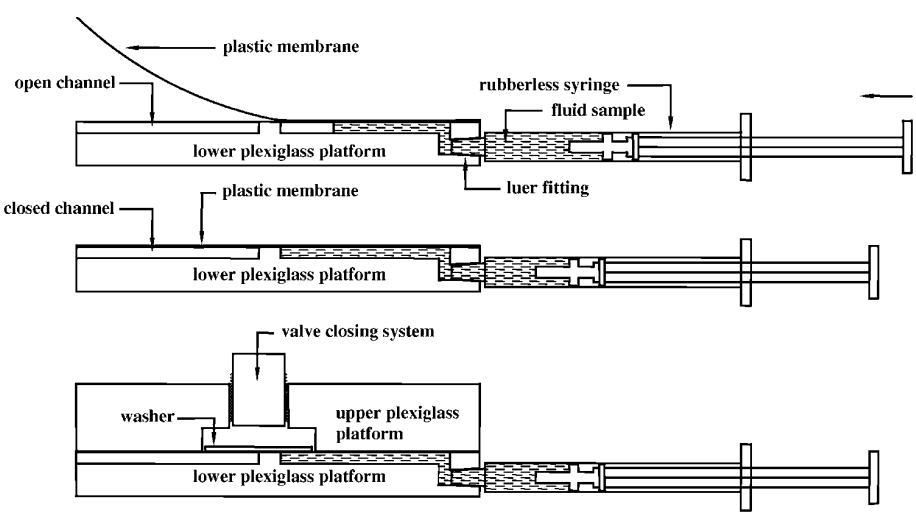

Figure 4. Priming steps for the microvalve system.

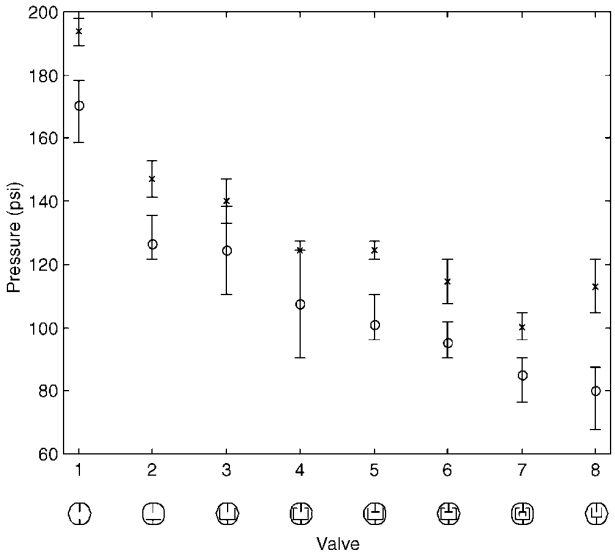

Figure 5. Maximum pressure required to open an unused microvalve using human whole blood. The symbols (○) and (×) correspond, respectively, to microvalve with and without priming with whole blood. The vertical bar is the error limits from three different sets of experiments. The syringe pump setting was 80 μl min^{-1} and the plastic membrane used was 3M Tape number 471 (Lot No 3 3^{97}) (3M, St. Paul, MN).

During each experiment, the micro-channel and the luer fitting were pre-primed with either human whole blood or PBS. The series of priming steps for the microvalve system are depicted schematically in figure 4. This was performed by first inserting the filled syringe into the luer fitting in the lower platform. The flexible plastic membrane was then placed on the surface of the lower platform to only cover half of the microvalve. Next, the fluid sample was injected into the micro-channel. Once the micro-channel was filled with the fluid sample, the plastic membrane was completely placed on the surface of the lower platform. Finally, the upper and the lower platforms were sealed together either by screws or by 'press-and-snap' fittings.

We should emphasize that the above priming steps are not necessary in actual use of the microvalve system since a solution such as PBS would first be used to prime the microvalve system in order to remove air before the sample, i.e. human whole blood, was injected. In this case, pressured air would be the first fluid media to open the valve, then the priming solution and finally, the whole blood.

3. Experimental results and discussion

Figure 5 depicts the maximum pressure required to open an unused microvalve using human whole blood. The symbols (○) and (×) correspond, respectively, to microvalves with and without priming with whole blood. The results illustrate that regardless of the microvalve geometries, less pressure was required to open the microvalve when it was primed with whole blood. This is mainly due to the fact that protein contained in whole blood removed the plastic membrane's adhesive material while priming. Also, the bonding of this adhesive material might be damaged during priming (figure 4) which is reflected in the relatively large magnitude of error in the data (figure 5).

In addition, figure 5 illustrates that valve 7 (see also figure 2) required the lowest pressure for whole blood to transfer across the discontinuous micro-channel components. During experiments, we have consistently observed that pressured flow along the micro-channels first caused the plastic membrane at the lower corners of the micro-channel to rise into the recess (figure 6). Therefore, it is expected that valve 7 would require less pressure to open the microvalve.

For illustration purposes, the actuation sequence of a microvalve (valve 7) during an experimental valve actuation are depicted in figure 6. The microvalve was first primed with human whole blood (figure 6(a)). When pressured flow was introduced, the plastic membrane at the lower corners started to lift up (figure 6(b)). As the pressure increased along the micro-channels, the raised membrane areas 'grew' towards the center of the microvalve (figures 6(c)–6(e)). Eventually, the raised membrane areas connected the discontinuous micro-channel components allowing whole blood to transfer across them (figure 6(f)).

Next, we studied the effect of different plastic membranes on the performance of the microvalve. An unused microvalve was forced to open using a priming solution (PBS). The maximum pressure was recorded and the microvalve was closed by positive action on the valve closing system (figure 1(b)). With the microvalve in the closed position, no leakage was observed in the microvalve even though the applied pressure was more than two times the maximum valve opening pressure. Then, the valve closing system was released and the maximum pressure required to re-open the microvalve was recorded. The open and close of the microvalve were continuous for several cycles, i.e. the opening and closing of the microvalve were repeated for several times. We denoted p_1, p_2, ... and p_n as the maximum pressure required to open the microvalve in the first, second, ... and nth instances. With the valve closing system activated and applied pressure of greater than 300 psi, no leakage was observed in the microvalve for all experiments.

The maximum pressures required to open a microvalve for two different plastic membranes using PBS are depicted in figures 7–10. The symbols (×), (○) and (*) correspond, respectively, to first (p_1: valve had never been opened), second (p_2: valve had been opened once and closed once), and third (p_3: valve had been opened twice and closed twice) valve openings. With a 3M Tape number 480 as the plastic membrane (purchased from Frank W Winne & Son, Philadelphia, PA), p_1 (×) was always greater than p_2 (○) and p_3 (*) (figures 7 and 8), i.e. once the microvalve had been opened, less pressure was required to re-open it. Also, p_2 and p_3 were less sensitive to the microvalve geometries.

When a 3M Tape number 471 (purchased from Frank W Winne & Son, Philadelphia, PA) was used as the plastic membrane, p_1 (×) was always greater than p_2 (○) and p_3 (*) only for valves 1, 2, 4 and 8 (figures 9 and 10). This is surprising as one may expect that p_1 should always be greater than p_2 and p_3, as is the case for 3M Tape number 480 (figures 7 and 8), regardless of the microvalve geometries. We speculated that the bonding of the adhesive material for

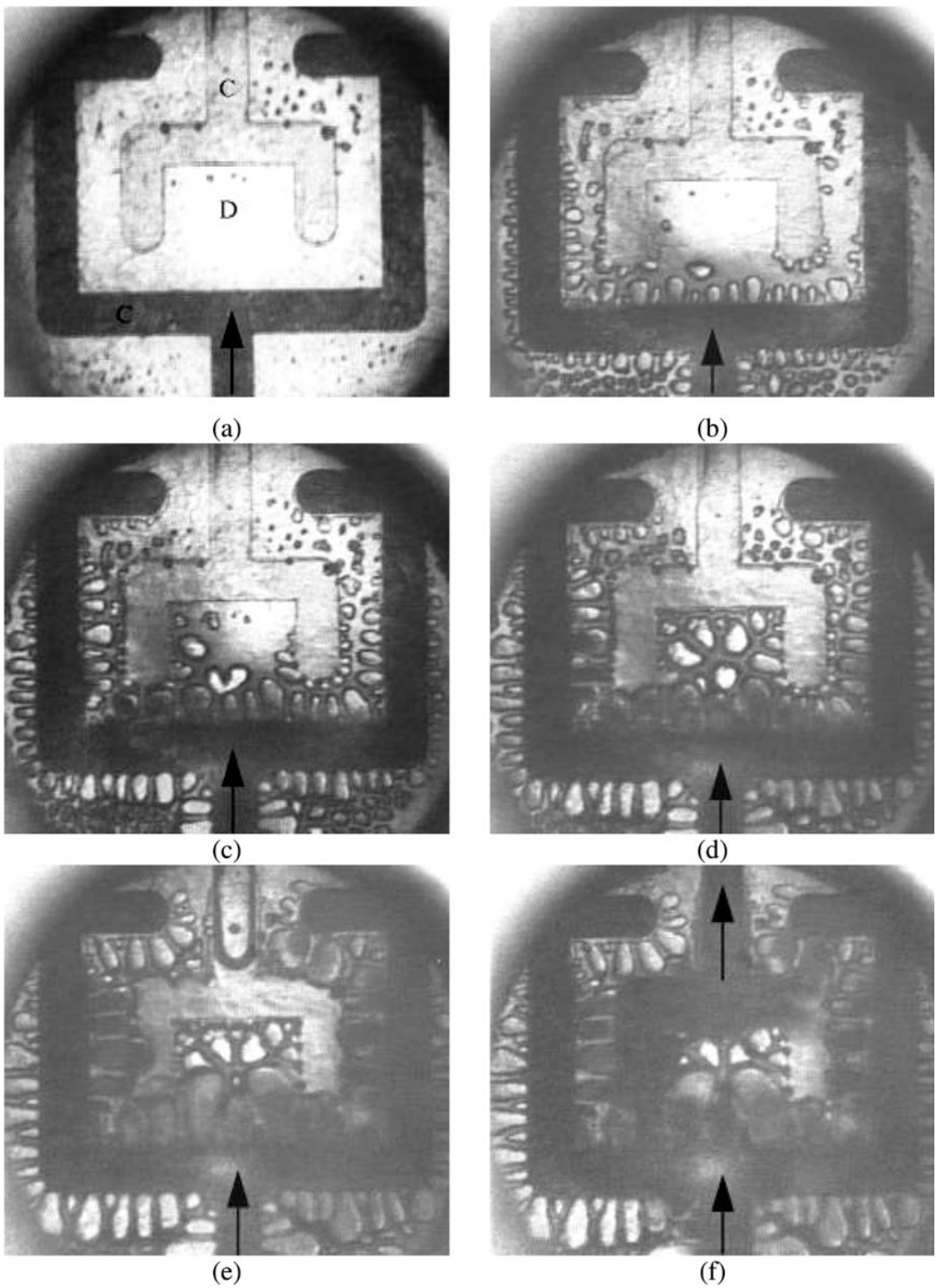

Figure 6. Actuation sequence of a microvalve (valve 7) during an experimental valve actuation. The microvalve was primed with human whole blood. Syringe pump flow rate setting was 80 μl min^{-1}. C is the micro-channel and D is the discontinuity of the micro-channel. An arrow indicates the direction of flow. The plastic membrane used was 3M Tape number 471 (Lot No 3 3^{97}) (3M, St. Paul, MN). Magnification: 28 times.

the 3M Tape number 471 is much stronger and more difficult to 'wash away' than the 3M Tape number 480. Indeed, only residuals of the adhesive material for the 3M Tape number 480 were found on the lower plexiglass platform after the plastic membrane was removed. In the actual use of the microvalve system, the plastic membrane's adhesive material would first be 'washed away' by the priming solution such as PBS before the specimen is injected, and hence, the contamination of the specimen with the adhesive material would be negligible. We are currently investigating the possibility of using other types of 3M tapes that have no adhesive material for the plastic membrane.

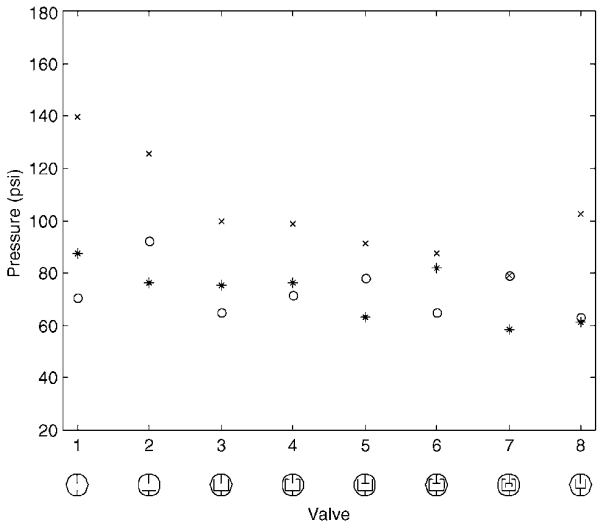

Figure 7. Maximum pressure required to open a microvalve using a priming solution (PBS). The symbols (×), (○) and (*) correspond, respectively, to first (p_1: valve had never been opened), second (p_2: valve had been opened once and closed once) and third (p_3: valve had been opened twice and closed twice) valve openings. The micro-channel was primed with PBS. The syringe pump flow rate setting was 80 μl min^{-1} and the plastic membrane used was 3M Tape number 480 (D.C. Part No 021200-05151).

The above results contributed to the design of the microvalve system as they determined the pressure required for valve closing, the 'optimal' plastic membrane and most importantly, the 'optimal' microvalve geometry. The experimental results indicate that the valve closing system must be able to withstand at least 200 psi in order to avoid leakage. In this study, the valve closing system consists of a linear actuator and is capable of withstanding more than 300 psi. For the final design of the microvalve system, the linear actuator will be driven by a micromotor with a response time of less than 1 s. Also, the valve closing system will be fully computerized for accurate and fast control of flow. This is currently under investigation and a prototype has been tested.

After extensive experimental studies, the 'optimal' plastic membrane chosen for the microvalve system was 3M Tape number 480 since its performance is more consistent than other plastic membranes we tested. Finally, in order to choose the 'optimal' microvalve geometry, we considered the following criteria: the amount of fluid sample required inside the microvalve, the maximum pressure required in opening the microvalve, the complexity of the microvalve geometry and the sealing of the microvalve. Although valve 7 requires the least pressure to open, it has the largest volume. Also, its geometry is the most complicated. As a result, we chose valve 8 as the 'optimal' microvalve geometry for our microvalve system. Valve 8 is simple, has a small volume (less than 0.16 μl), is easy to close and its performance is comparable with the other microvalve geometries.

Since the width of the micro-channel depended on the size of the milling tools used, the width of the micro-channel is limited. The smallest diameter of the end mill available commercially is 125 μm, hence, the smallest micro-channel width one can machine by using the CNC machine is 125 μm.

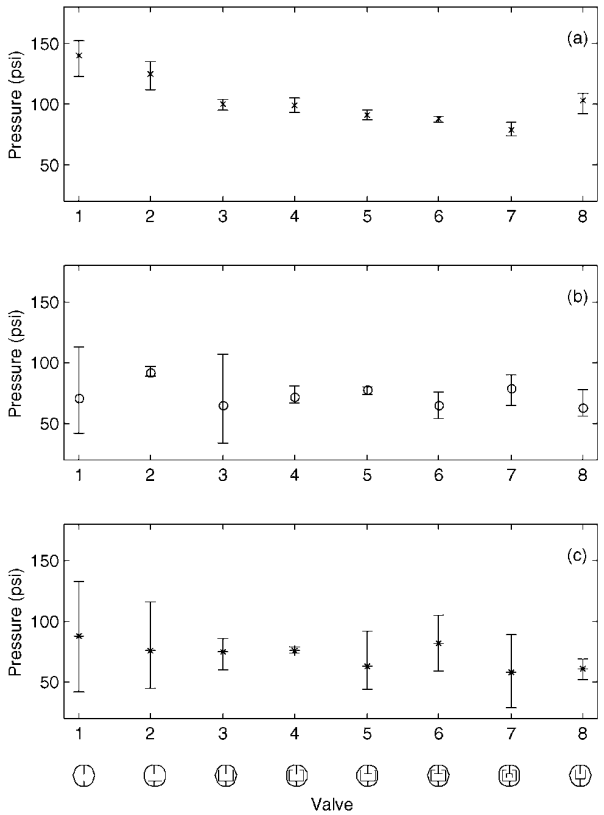

Figure 8. Maximum pressure required to open a microvalve using a priming solution (PBS). The symbols (×), (○) and (*) correspond, respectively, to first (p_1), second (p_2) and third (p_3) valve openings. The micro-channel was primed with PBS. The vertical bar is the error bound from three different sets of experiments. The syringe pump setting was 80 μl min^{-1} and the plastic membrane used was 3M Tape number 480 (D.C. Part No 021200-05151).

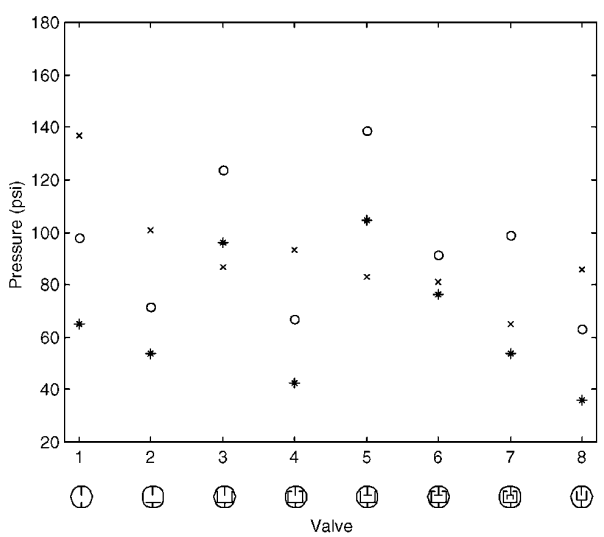

Figure 9. Maximum pressure required to open a microvalve using a priming solution (PBS). The symbols (×), (○) and (*) correspond, respectively, to first (p_1), second (p_2) and third (p_3) valve openings. The micro-channel was primed with PBS. The syringe pump setting was 80 μl min^{-1} and the plastic membrane used was 3M Tape number 471 (D.C. Part No 021200-07228).

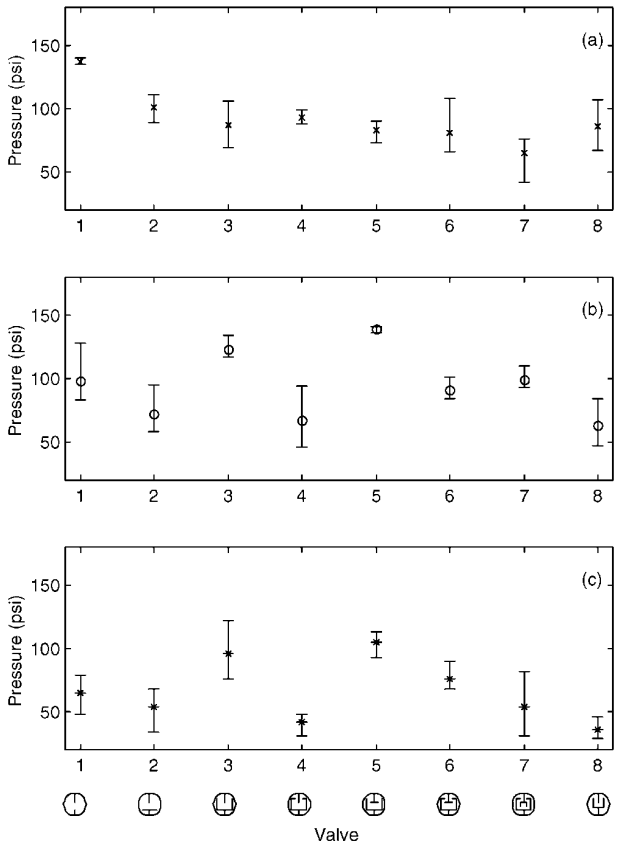

Figure 10. Maximum pressure required to open a microvalve using a priming solution (PBS). The symbols (×), (○) and (*) correspond, respectively, to first (p_1), second (p_2) and third (p_3) valve openings. The micro-channel was primed with PBS. The vertical bar is the error bound from three different sets of experiments. The syringe pump setting was 80 μl min^{-1} and the plastic membrane used was 3M Tape number 471 (D.C. Part No 021200-07228).

However, there is no limitation on the depth of the micro-channel. If one desires, a micro-channel a few micrometers in depth can be machined using the CNC machine. For example, with a channel dimension of 125 μm (width) $\times$ 10 μm (depth), one can dispense 1.25 nl mm^{-1} of fluid sample. The effect of the channel dimensions on the performance of the microvalve has not been investigated in this study.

4. Conclusions

We have demonstrated that the semi-disposable CNC machined plexiglass microvalve system can process microliter and sub-microliter sized samples of whole blood without attendant problems, such as loss of sample on the microvalve system and loss by evaporation. The advantage of the CNC machined plexiglass microvalve is that it is easy to manufacture and it provides an alternative for the conventional silicon chip-based microvalve systems. Currently, we are employing the CNC machined plexiglass microvalve in a totally integrated microfluidics system for analytical reactions involving sample preparation (for example, microfabricated human cell isolation), biochemical reaction (for example, polymerase chain reaction) and detection/quantitation steps (for example, hybridization) for DNA analyses. The results will be presented in a future publication.

Acknowledgments

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