Development of novel passive check valves for the microfluidic CD platform

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ABSTRACT

Microfluidic CD platforms are utilized to perform different biological processes and chemical analyses. In general, a microfluidic CD implements the centrifugal force that is created by the spinning of the platform to pump liquid through the microfluidic network of chambers and channels. Over the last few decades, a wide range of active and passive valving methods were proposed and tested on various microfluidic platforms. Most of the presented valves are too complex to design and involve lengthy fabrication processes. In this paper, easy to fabricate air and liquid check valves for centrifugal microfluidic platforms are presented: a Terminal Check Valve (TCV) and a Bridge Check Valve (BCV). To understand the characteristic of the proposed valves, theoretical and experimental studies are conducted. Moreover, to test the effectiveness of these valves, liquid swapping is demonstrated by integrating TCV and BCV chips with thermo-pneumatic (TP) pumping on a CD. The valves are shown to accurately control flow direction which makes them an excellent choice for a variety of complex microfluidic processes. The experimental and theoretical results also indicate that these valves require low pressure for actuation. Furthermore, the theoretical results confirm the ability to adjust the required actuation pressure by changing the valve chip size. Finally, as a proof of concept for implementing the check valves on a biological application, an enzyme linked immunosorbent assays (ELISA) is performed. The result shows that the TCV and BCV valving chips enhance the operating range of the processes that can be performed on the microfluidic CD.

1. Introduction

Since the introduction of the miniaturized total analysis system by Manz et al. [1], the miniaturization of commercial bio-analytical systems became the focus of many researchers in this field. As a result of these efforts, several microfluidic biomedical and chemical processes were successfully performed on two main types of microfluidic platforms: the Lab-on-Chip (LOC) and the Lab-on-Disc (LOD)/microfluidic compact disc (CD) [1–3]. Although both platforms aim to reduce the amount of liquid and time consumed in any process, the LOC is a stationary platform mostly dependent on external forces for liquid flow, while the microfluidic CD platform relies on the centrifugal force (which is derived from the spinning of the disc) to pump liquid on the platform. In addition to not needing any external pumping source, the microfluidic CD platform also has the benefit of utilizing capillary valves for fluid flow sequencing [3]. Some examples of the implementation of the microfluidic CD platform for biomedical processes include enzyme linked immunosorbent assays (ELISA) [4,5], plasma and particles separation [6–8], and real time polymerase chain reaction (PCR) [9,10].

Liquid flow control on both microfluidic platforms present a serious challenge for the researchers in this field. In the last few decades, the field of micro-valves has been heavily investigated and various types of valves have been presented. According to Madou et al. and Oh et al. [3,11], most of the developed micro-valves belong to one of two main categories: active valves or passive valves. An active valve can be defined as a valve that requires an external force to actuate (open or close). Examples of active valves that have been

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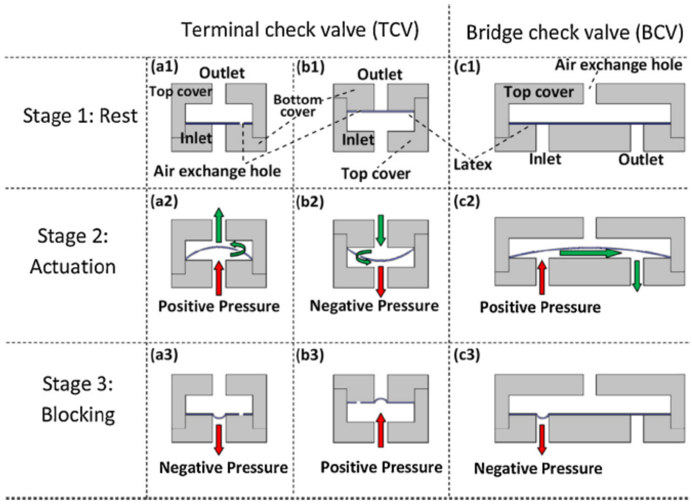

Fig. 1. Check valve operation principle. (a1, b1, and c1) TCV and BCV valve at rest, (a2) TCV valve activated by applying positive pressure at the inlet, (b2) TCV valve activated by implementing negative pressure at the inlet, (c2) BCV valve activated by applying positive pressure at the inlet, (a3) TCV valve blocking air-flow due to the negative pressure at the inlet, (b3) TCV valve blocking air-flow by implementing positive pressure at the inlet, (c3) BCV valve blocking air/liquid flow as negative pressure is applied at the inlet.

proposed and tested in different applications are ice valves [9], wax valves [12–15], pneumatic valves [16], hydrogel valves [17], electro-mechanical valves [18,19] and active check valves [20,21]. On the other hand, a passive valve only utilizes centrifugal and capillary forces to control liquid flow without the need of an external force to actuate it. Examples include hydrophobic and hydrophilic valves [22], siphon valves [23], flap valves [24], and passive check valves [25–30].

In recent years, active and passive check valves have drawn the attention of many researchers in the field of LOC. Kim et al. [20] and Bozhi et al. [21] proposed two active check valves that respectively utilize hydrogel and paraffin wax. Both researchers reported high reliability in their check valves with low leakage volume. However, complexity in the fabrication of the valves and the need for external actuation are the main drawbacks of the proposed valves. In contrast, passive check valves (mostly a variation of flap valves) have shown the ability to work without external actuators for improved portability option [25–30]. However, some flap valves require high-end and precise fabrication methods. Moreover, internally installed simple flap valves suffer from issue such as leakage when the flow reversed.

This paper presents two passive check valves that are simple to fabricate and implement on the microfluidic CD platform: a terminal check valve (TCV) that restricts air flow in one direction between the microfluidic process and the surrounding environment; and a bridge check valve (BCV) that allows one way flow of air and liquid between two points in the microfluidic process. Both valves are designed as modular chips that can be installed at any location on the disc. The valves can be implemented to perform various microfluidic processes such as flow switching, continuous pumping, platform vacuuming and chamber isolation. In this paper, the TCV and BCV valves are coupled together with thermo-pneumatic pumping (TPP) in a demonstration of liquid swapping. The utilization of the valves in this process extends the ability of the TPP method to control the direction of push/pull pumping of liquid to and from a chamber (i.e. pushing of liquid out from a source chamber/pulling of liquid into a destination chamber). This solve the limitation the pumping method that presented by Abi-Samara et al. [31] and Thio et al. [32]. Finally, as a demonstration of the valves' application in biological processes, a microfluidic CD design for enzyme linked immunosorbent assays (ELISA) is presented.

2. Check valve

Check valves have the ability to restrict fluid flow (liquid or gas) in only one direction. These valves are implemented in various forms such as cantilever, membrane, and spherical ball valves, and can be constructed from a wide range of materials such as silicone, metal, PDMS, photo-deformable polymer, copper foil, etc. [27,29,33,34]. However, as most check valves require a complex design process and lengthy fabrication method, implementing them on a multi-stepped process is difficult and can be costly. In this work, we present two simple and easy to fabricate check valves that are modular and easy to implement on any process on a microfluidic CD.

2.1. TCV and BCV

The principle of operation of the TCV and BCV are illustrated in Fig. 1. Both valves consist of a latex film sandwiched between rigid top and bottom covers. One crucial element of the valves is the air exchange hole: for the TCV chip the hole is cut through the latex film, while for the BCV the hole is cut through the top cover (see Fig. 1(a1, b1, and c1)). The air exchange hole allows the check valve to operate in one of two modes: *flow* and *blocking* mode.

Fig. 1(a1–a3) illustrates the operation of the TCV. When positive air pressure is applied to the inlet of the TCV, the latex is deflected upwards towards the open space between the top and bottom covers. Air can then travel through the space created by the deflection, and then via the air exchange hole to escape through the outlet (see Fig. 1(a2)). However, when a negative pressure is applied on the inlet of the TCV valve, the latex film is pulled slightly into the inlet, thus forming an air tight seal, and air flow through the valve is restricted (see Fig. 1(a3)). In this configuration, the TCV chip can be installed on the CD with the inlet facing the CD surface (over a channel opening) to allow only one way air flow from within the

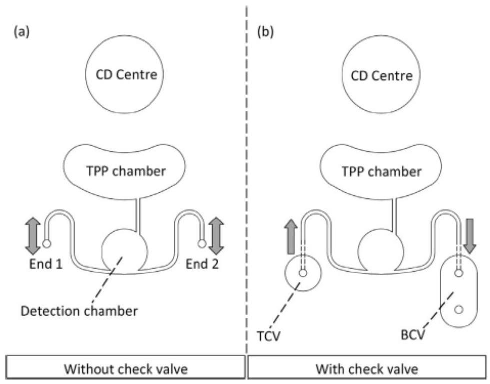

Fig. 2. Thermo-pneumatic pumping (a) without check valve where the direction of air/liquid from End 1 and End 2 is incontrollable (b) with the proposed TCV check valve and BCV check valve installed on End 1 and End 2 respectively.

CD to the surrounding environment. By flipping the TCV chip over, and having the top cover placed on the CD surface, it will then allow only one way air flow from the surrounding environment into the CD (see Fig. 1(b1–b3)).

Fig. 1(c1–c3) demonstrates the principle of operation for the bridge valve. As both the inlet and outlets are in the bottom cover in this case, it is the bottom cover that must be placed on the CD surface. Similar to the TCV chip, when the CD is at rest, the latex film is flat against the bottom cover (see Fig. 1(c1)). When a positive pressure is applied on the inlet of the BCV valve, the latex film is deflected upwards, and air/liquid is allowed to flow through the space under the latex to the outlet (see Fig. 1(c2)). However, when a negative pressure is applied on the inlet of the BCV valve, the latex forms a tight seal over the inlet, preventing any backward flow of air/liquid (see Fig. 1(c3)). Note that for the BCV valve, the inlet and outlet positions are interchangeable, and the valve only allows liquid to flow if there is positive pressure on either the inlet or outlet, but blocks fluid flow if there is negative pressure applied instead (i.e. you can push fluid through the valve, but not pull liquid through it).

By implementing this directional flow control on TPP, the capability of this pumping method can be significantly improved. Fig. 2 presents a microfluidic CD design where a detection chamber is connected to a TPP chamber. TPP is a well-established pumping method in the microfluidic CD field that employs heat to pump liquid towards the CD centre. However, when the detection chamber is connected to two terminals (see Fig. 2(a)), liquid can only be pumped concurrently from both terminals End 1 and End 2 (or pumped concurrently to both End 1 and End 2). This is an impractical process as there is no way to control the liquid volume pumped, and the flow of liquid to only a particular terminal. By installing a TCV valve on terminal End 1, and a BCV valve on terminal End 2, the direction of liquid/air flow is restricted to be on way: from terminal End 1 towards the detection chamber, and subsequently towards terminal End 2 (see Fig. 2(b)). This enhancement greatly extends the ability to perform multi-stepped complex process on the microfluidic CD.

2.2. Design and fabrication method

The check valves presented are simple and easy to fabricate. Each valve consists of three layers: two polymethyl methacrylate (PMMA) layers and one latex layer (see Fig. 3). For both valves, the top layer is fabricated using 4 mm PMMA while the bottom layer is

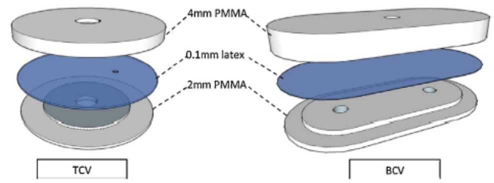

Fig. 3. TCV and BCV check valves layers: top 4 mm PMMA layer, bottom 2 mm PMMA layer, and middle 0.1 mm latex layer.

made of 2 mm PMMA. The PMMA layers are machined using a computer numerical control (CNC) machine. A commercially available latex sheet is utilized to fabricate the middle layer of the developed check valve. A special latex fabrication tool is developed for a consistent preparation of the latex layer. When the two PMMA layers are precisely machined, the fit is tight and a good seal is established using the latex layer. Moreover, the middle latex layer plays as a gasket between the two PMMA layers to insure no liquid/air leakage. This tight fit will also clamp the latex from all sides while leaving the middle area free to allow for valve activation and deactivation. For detailed design and fabrication steps of the developed check valves, please refer to the "Supplementary material" document available at the link provided at the end of this article. Moreover, a fabrication method for mass-production of the proposed check valve is presented in the same document.

2.3. Check valve application on a microfluidic CD for "liquid swapping"

To evaluate the effectiveness of the TCV and BCV chips on a microfluidic CD platform, a microfluidic CD design that performs liquid swapping was fabricated and tested. In Fig. 4(a) we show a microfluidic CD design consisting of three chambers (chamber A, chamber B and the waste chamber), and with connecting micro channels with widths and depths given by 0.7 mm and 0.5 mm respectively. A TCV chip was installed in conjunction with chamber B, and a BCV chip was installed in the channel between chamber A and the waste chamber. The TCV chip is configured to only allow air flow from the outside of the CD into chamber B (and not from chamber B to the outside), while the BCV chip only allows the liquid to flow from chamber A to the waste chamber. For controlled one-way liquid pumping, a TPP chamber is placed near the CD centre and connected directly to chamber A to allow for push/pull pumping. For TPP chamber heating, a customized industrial hot-air gun is fixed 1 cm on top of radial track of the TPP chamber. A 1 cm diameter focusing nozzle installed on the hot-air gun focuses the heat and prevents heating other parts of the CD. The CD surface temperature during spinning is measured using a digital infrared (IR) thermometer. Push pumping creates positive pressure in chamber A during heating of the TPP chamber, while pull pumping creates negative pressure in the chamber during cooling of the TPP chamber. Further details of push/pull pumping can be found in Thio et al. [32]. Although the purpose of the CD design shown in Fig. 4 is to demonstrate the effectiveness of the check valves, the design can be easily modified to incorporate check valves in a wide variety of complex biomedical diagnostic assays.

The experiment starts with the filling of chamber A with 45 μl of red coloured deionized (DI) water, and the filling of chamber B with the same amount of blue coloured DI water (see Fig. 4(a)). Two different coloured DI water are implemented in this test to make the liquid swapping process more visible. First, the loaded microfluidic CD is spun up to 300 rpm, and the heat source is powered on to activate push pumping. The positive pressure created this way pushes on the liquid in chamber A, and the liquid flows

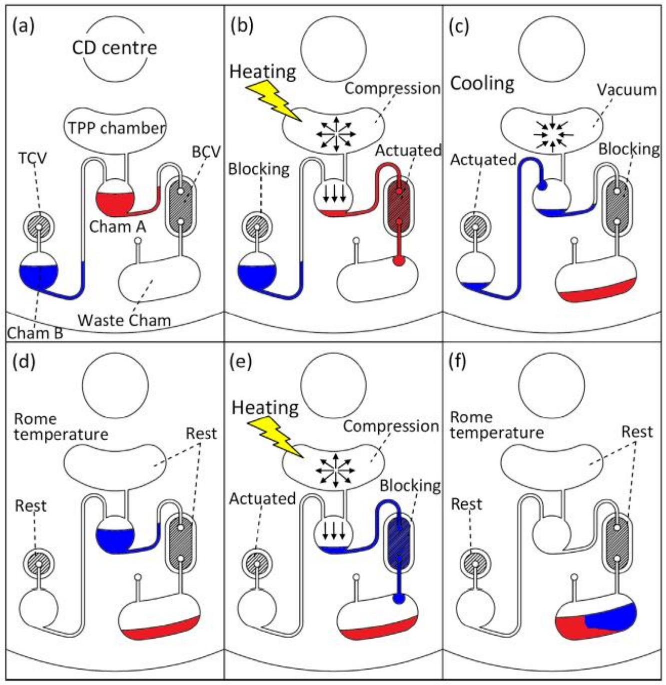

Fig. 4. Liquid swapping sequence, (a) liquid status before start the process, (b) heating the TPP chamber where the TCV valve is blocked while the BCV chip is activated, (c) cooling the TPP chamber actuates pull pumping where the TCV valve is activated and the BCV chip is blocking reverse airflow from the waste chamber, (d) liquid position after the cooling process stops, (e) heating the TPP chamber pushes the liquid from chamber A towards the waste chamber, (f) final liquid status.

through the BCV chip towards the waste chamber (see Fig. 4(b)). The heat source is then turned off, and pull pumping is activated. The negative pressure generated pulls the liquid from chamber B into chamber A (Fig. 4(c and d)). The heat source is then turned on again to repeat pushing the liquid from chamber A to the waste chamber (Fig. 4(e and f)).

3. Results and discussions

The results and discussion section is split into two sections. The first section evaluates the design parameters of the check valves theoretically. Moreover, this section discusses the pressure required to activate the check valves, and the achievable flow rate of the check valves. The second section presents the implementation of the check valves in a liquid swapping demonstration.

3.1. Check valve analytical model

In this section, the operation of the developed TCV and BCV chips are evaluated both theoretically and experimentally. The theoretical study is conducted to confirm that very little pressure is needed to actuate the chips (to allow air/liquid flow) and that this required pressure is negligible, and does not affect the burst frequencies of liquids on the microfluidic CD. Subsequently, experimental work is conducted to investigate the actuation points of the two check valves, and the flow rate of air/liquid under different pressure.

To evaluate the operation of valves on the microfluidic CD, the centrifugal pressure resulting from the spinning of the CD must first be evaluated. The centrifugal pressure acting on a volume of liquid, $P_{centrifugal}$ can be calculated using the following equation [35]:

$$P_{centrifugal} = \rho\omega^2\Delta r\bar{r} \quad (1)$$

where ρ is the liquid density, ω is the CD spin speed in radians per second (rad/s), Δr is the difference between the top and bottom liquid levels at rest with respect to the CD centre, and $\bar{r}$ is the average distance of the liquid from the centre of the CD. The pressure on a spinning CD varies in the range of kilo- to megapascals depending on the spinning speed, liquid density and the relative position of the liquid from the CD centre. To experimentally determine both the activation pressure, and achievable flow rate, channels of dimensions 150 mm length by 1 mm width and 1 mm depth are fabricated in a vertically standing PMMA plastic. The TCV or BCV valve is installed at the bottom end of the channel, and the channel is then loaded with liquid of different heights (to achieve a range of pressure) to test the operation of the valve. By positioning the channels vertically, the resulting pressure can be calculated as follows:

$$P_{static\,fluid} = \rho g h \quad (2)$$

where ρ is the liquid density, g is the acceleration of gravity, and h is liquid height. In our experiment, the height of the liquid in the channel was varied from 24 mm to 58 mm (with an incremental step of 2 mm) to give a range of pressure from 220 Pa to 580 Pa (for more information about the developed flow rate test platform, please refer to the supplementary material). Fig. 5 shows the experimental flow results for the TCV and BCV valve under different pressures. It is observed that both valves are actuated under the same pressure which is 220 Pa. However, it can be seen that the flow rate of TCV

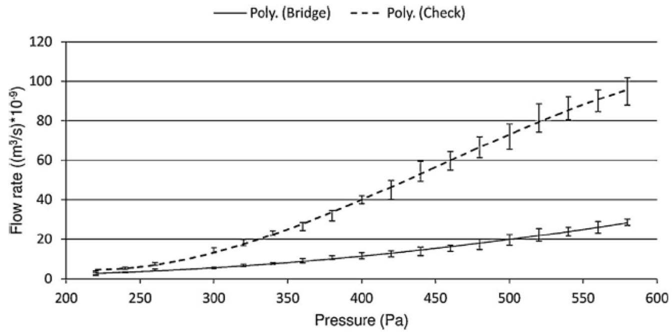

Fig. 5. TCV and BCV flow rate at different pressure.

valve is much higher compared to the BCV valve especially under high pressure. This is because the longer pathway between within the BCV (from the inlet to the outlet of the valve) which is constantly constricted by the deflected latex film (i.e., this decreases the flow rate). It is also observed that at the actuation pressure, liquid flow rate is intermittent as the latex deflection fluctuates.

On a typical microfluidic CD with a liquid column of 5 mm height, the check valve actuation pressure of 220 Pa can be achieve with a spin speed as low as 270–480 rpm for relative liquid distance of 17–67 mm from the CD centre (refer to Eq. (1)). Microfluidic CDs are typically designed to operate at frequencies of 300 rpm and above, (up to thousands of rpm). This range of operation allows for the easy integration and actuation of the check valves in microfluidic processes on the CD. In other words, the developed valves can be implemented for controlling fluid flow direction during both passive pumping of liquid (which depends only on the centrifugal pressure), and active pumping of liquid (for example using TPP).

Once the actuation pressure is experimentally determined above (as 220 Pa), the deflection of the latex film in the TCV chip can be calculated using the following equation [29]:

$$u = \frac{3pa^4}{16t^3E}(1 - \nu^2) \qquad (3)$$

where u is the deflection of the latex layer, p is the pressure applied across the latex layer, a is the radius of the TCV chip, ν is Poisson's ratio, E is Young's modulus, and t is the thickness of the latex layer. The same equation can be applied to approximate the deflection for the BCV chip as the maximum deflection is limited by the smallest dimension of the chip (where the smallest dimension of the BCV chip is identical to the TCV chip). However, there is some variation in the amount of deflection between the TCV and BCV chips dues to the difference in path length and the air/fluid flow direction within the two chips.

Using Eq. (3), the effect of the pressure on the deflection of the latex layer is shown in Fig. 6, while the effect of the chip size on the deflection of the latex is shown in Fig. 7.

The result in Fig. 6 shows that the deflection of the latex film increases linearly with the increase of the pressure applied on the chip. Also, the results indicate that latex film deflection is approximately 100 μm at the valve activation pressure (for air and liquid to flow at a minimum pressure of 220 Pa). On the other hand, the result in Fig. 7 shows that at the actuation pressure of 220 Pa, the maximum latex film deflection theoretically increases exponentially with increasing chip diameter. It can be seen that increasing the chip diameter by 2 mm approximately increases the deflection threefold. This indicates that a larger chip is easier to operate under low pressure. However, the exponential increase in latex deflection is true as long it does not exceed the elasticity limit of the latex

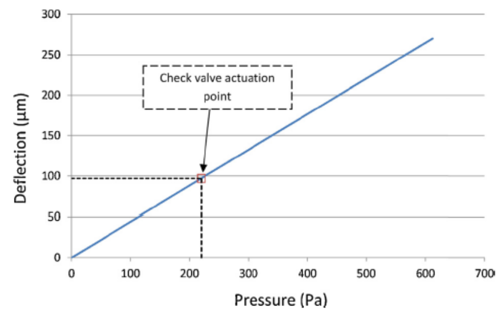

Fig. 6. Latex deflection for different pressure during valve activation.

film. To protect the latex film from overstretching, the spacer area is limited to a height of 1 mm in our chips.

3.2. Liquid swapping results

The steps of the experimental demonstration mentioned in the methodology section are shown in Fig. 8 while actual images recorded are shown in Fig. 9. The process starts with the loading of both chambers A and B each with 45 μl of differently coloured DI water (see Fig. 9(a)). After loading the chambers, the venting holes on both chambers are sealed with a special thermal transparent tape. The holes are sealed to trap the air inside the microfluidic system to allow the TPP to work [32]. At the same time, the TCV and BCV chips are installed in designated positions on the bottom surface of the microfluidic CD using PSA material. Then, the microfluidic CD is mounted on the spin test system to start the spinning process. The experimental step for the microfluidic process can be broken

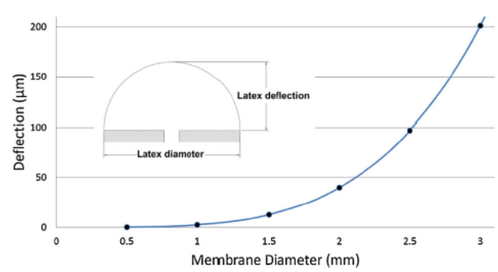

Fig. 7. Latex deflection for different valve diameter.

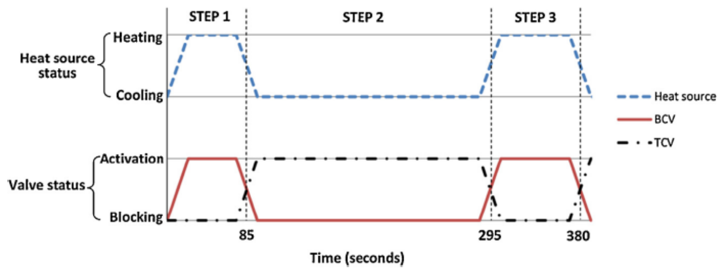

Fig. 8. Experimental steps: (Step 1) heating source is turned ON, BCV valve is activated, and TCV valve is in blocking mode: liquid is pumped from chamber A to the waste chamber, (Step 2) heating source is turned OFF, BCV valve is in blocking mode, and TCV valve is activated: liquid pulled from chamber B into chamber A, (Step 3) heating source is turned ON, BCV valve is activated, TCV valve is in blocking mode: liquid pumped from chamber A to the waste chamber. The experiment performed at 300 rpm.

into three steps (see Fig. 8): Step 1: first heating process (push the liquid from chamber A to waste chamber), Step 2: cooling process (sucks the liquid from chamber B into chamber A), Step 3: second heating process (to push the liquid from chamber A into the waste chamber). The three steps are discussed as follows.

3.2.1. *Step 1: first heating process*

This step starts with the spin up of the CD to 300 rpm (pretested spinning speed for optimum push/pull pumping performance [32]) and the focusing of the heat source on the TPP air chamber. Next, the heat source is set to 150 °C and turned ON (see Fig. 8). The heating process gradually raises the temperature in the TPP air chamber from room temperature (25 °C) to reach a temperature sufficient for the air to start expanding significantly. This air expansion exerts pressure on the liquid in chamber A and B. However, the blue liquid from chamber B cannot be pushed from the adjoining channel because of the TCV chip preventing any air from escaping from chamber B. Therefore, the pressure generated by the TPP air expansion will only force the red liquid in chamber A to move towards the waste chamber through the BCV chip. It is observed that the red liquid from chamber A is completely transferred to the waste chamber in 85 s when the temperature reaches 64 °C (Fig. 9(b and

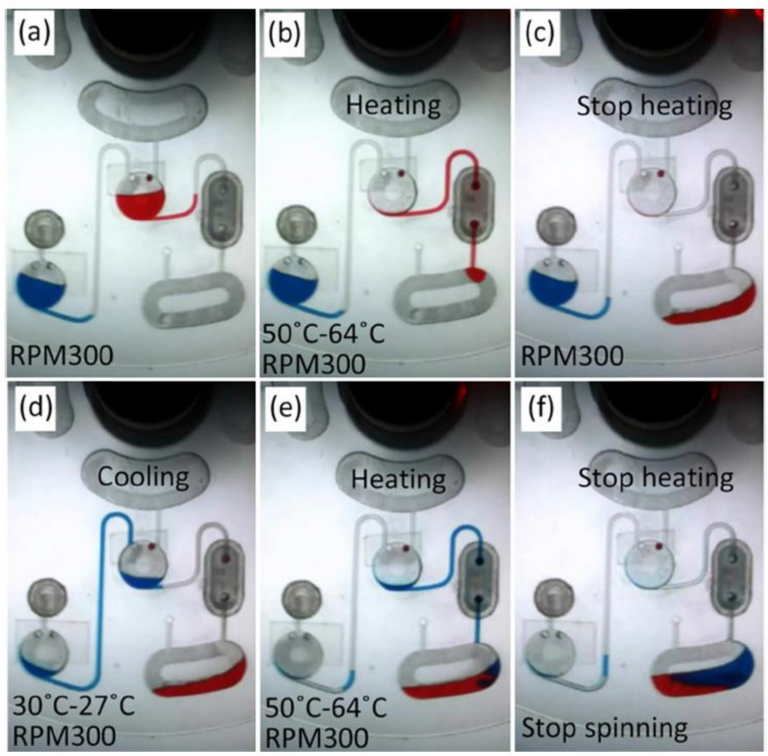

Fig. 9. Experimental results, (a) liquid status before the start of the heating process, (b) heating the TPP chamber pushes the red DI liquid towards the waste chamber, (c) the heating process is stopped, (d) cooling the TPP chamber pulls the blue DI liquid from chamber B into chamber A, (e) heating the TPP chamber pushes the blue liquid from chamber A into the waste chamber, (f) final liquid status after completion of the experiment.

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