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FABRICATION AND TESTING OF POLYDIMETHYLSILOXANE (PDMS) MICROCHANNEL FOR LAB-ON-CHIP (LOC) MAGNETICALLY-LABELLED BIOLOGICAL CELLS SEPARATION

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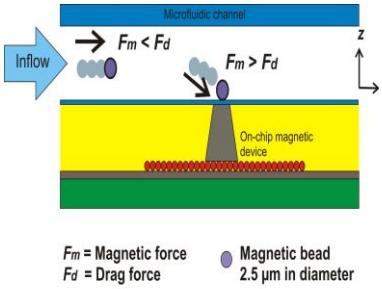
Graphical abstract



Abstract

Microfluidics channel of micron- to millimeter in dimension has been widely used for fluid handling in transporting, mixing and separating biological cells in Lab-on-Chip (LoC) applications. In this research, fabrication and testing of Polydimethylsiloxane (PDMS) microfluidic channel for Lab-on-chip magnetically-labelled biological cells separation is presented. The microchannel is designed with one inlet and outlet. A reservoir or chamber is proposed as an extra component of the microchannel design for ease of trapping the intended biological cells in LoC magnetic separator system. The PDMS microchannel of circular-shaped chamber geometry has been successfully fabricated using replica molding technique from SU-8 negative photoresist mold. An agglomerate-free microbeads flowing has been observed using the fabricated PDMS microchannel. Trapping of microbeads in the trapping chamber with 2.0 A current supply in the continuous microfluidics flow > 100 µL/min has also been demonstrated. In conclusion, a separation of biological cells labelled with magnetic microbeads is expected to be realized using the fabricated PDMS microchannel.

Keywords: Microfluidics channel; Lab-on-Chip (LoC); polydimethylsiloxane (PDMS); biological cells; microbeads

Abstrak

Saliran bendalir mikro berdimensi mikro hingga millimeter telah digunakan secara meluas dalam pengendalian bendalir bagi penghantaran, pembauran dan pengasingan sel-sel biologi Makmal-atas-Cip (LoC). Dalam kajian ini, pembuatan dan pengujian saliran mikrofluidik PDMS telah dibentangkan. Saliran mikro ini direkabentuk dengan sebuah salur masukan dan keluaran. Sebuah kebuk pemerangkapan telah dicadangkan sebagai komponen tambahan bagi pemerangkapan sel-sel biologi dalam sistem pemisahan bermagnet LoC. Saliran mikro PDMS dengan kebuk pemerangkapan berbentuk bulatan telah berjaya difabrikasi daripada acuan rintang foto negatif SU-8 menggunakan teknik acuan replika. Aliran bebas aglomerasi manik-manik magnet telah diperhatikan dalam saliran mikro PDMS tersebut. Pemerangkapan manik-manik magnet dalam aliran bendalir mikro > 100 µL/min telah berjaya ditunjukkan dengan bekalan arus 2.0 A. Kesimpulannya, pemerangkapan sel-sel biologi yang dilabel dengan manik-manik magnet dijangka akan dapat direalisasi menggunakan saliran mikro PDMS yang telah difabrikasi ini.

Kata kunci: Saliran bendalir mikro; Makmal-atas-Cip (LoC), *polydimethylsiloxane* (PDMS); sel-sel biologi: manik-manik magnet

1.0 INTRODUCTION

Blood contains numerous biological cells which provide important information on human health conditions. The intended biological cell of interest is required to be separated from blood heterogeneous cells population for applications including clinical diagnostics, therapeutics and cell biology fundamental studies [1]. Biological cells can be separated depending on its physical properties i.e. density and size or cell affinity i.e. adhesives, magnetic or electrical properties [1].

Magnetic activated cell sorting (MACS) exploited magnetic forces to isolate or separate certain biological cells population which have been labelled with functionalized magnetic beads. The advantages of using MACS are easy and simple contactless process which results in no damage to the biological cells. Furthermore, the large surface-to-volume ratio and commercially available biofunctionalized magnetic beads of different sizes are also some of MACS advantages [2].

Lab-on-chip (LoC) magnetic device integrates magnetic Microelectromechanical System (MEMS) and microfluidics channel in order to separate the intended biological cells of interest. The biological cells are preliminarily tagged with magnetic nanoparticles or microbeads based on its affinity characteristics towards the beads surface coating. The advantages of the LoC magnetic are compactness and portability, fast reaction time, low sample and reagent volume, ability of manipulating the magnetic field and low power requirement.

Microchannel made of polymer materials has been extensively used in separating biological cells in LoC magnetic applications. To date, several polymer materials including polydimethylsiloxane (PDMS), polyurethanemethylacrylate (PUMA), and polymethylmethacrylate (PMMA) have been used in microchannel fabrication. PDMS microchannel is fabricated using micromolding or replica molding technique have been widely employed [3]. Selection of PDMS as microchannel material is primarily due to its biocompatibility and ease of fabrication using replica molding technique. Furthermore, PDMS optical transparency make any optical detection integration feasible [4].

The ability of the biological cells labelled with magnetic beads to be trapped and then further separated is depending on the interaction of magnetic force generated by the magnet system and drag force from the hydrodynamic microfluidics flow. Trapping is enabled in microfluidics continuous flow whenever magnetic force is greater in comparison to the drag force experience by the magnetic beads.

In this work, fabrication and testing of the PDMS microchannel are presented. The fabrication of the PDMS microchannel using replica molding technique and its fluidic interconnect are discussed. Then, the microfluidics channel and the magnet system are integrated and test on trapping the magnetic microbeads. Furthermore, problems related to the microbeads using fabricated PDMS microchannel will also be discussed.

2.0 METHODOLOGY

2.1 Magnetic System Design Principle

Whenever a spherical-shaped magnetic microbeads is placed in a continuous microfluidics flow and under the influence of magnetic field, four major forces exist i.e. gravity, buoyancy, magnetic and hydrodynamics drag. Magnetic and drag forces are the main forces influencing the small size and volume magnetic microbeads.

In trapping biological cells labelled with magnetic microbeads within a microchannel fluid volume, an inhomogeneous high magnetic field and its gradient are required. The concept and design of the LoC magnetic device used in this work has been presented in previous papers. In magnetic separation, the magnetic force developed on a magnetic bead of volume, $V = (4/3)\pi r^3$, with different magnetic susceptibility, $\Delta\chi$ (χ_p for particle and χ_m for the fluid buffer medium) and the strength and gradient of the magnetic flux density, B can be theoretically calculated as equation

$$\vec{F}_m = \frac{V\Delta\chi}{\mu_0}(\vec{B}\cdot\vec{\nabla})\vec{B} = \frac{V\Delta\chi}{2\mu_0}\vec{\nabla}(\vec{B}\cdot\vec{B}) \quad (1)$$

In the direction of flow, the x-component of the force on the magnetic particles can be written as

$$F_{m,x} = \frac{V\Delta\chi}{\mu_0}\left(B_x\frac{\partial}{\partial x} + B_y\frac{\partial}{\partial y} + B_z\frac{\partial}{\partial z}\right)B_x \quad (2)$$

A magnetic particle of radius, R experiences hydrodynamics drag force in the microfluidics channel flow of x-direction. According to Stoke`s Theorem, the drag force, F_d is

$$\vec{F}_d = 6\pi\eta R\left(v_p - v_{medium}\right) \quad (3)$$

where v_p is the particles velocity, v_{medium} is the fluid velocity and η is the fluid viscosity.

In order to successfully trap the magnetic particles in the continuous microfluidics channel flow, the magnetic force must be greater in comparison to the

drag force experience by the magnetic particle as illustrated in Figure 1.

$$\vec{F}_m > \vec{F}_d \quad (5)$$

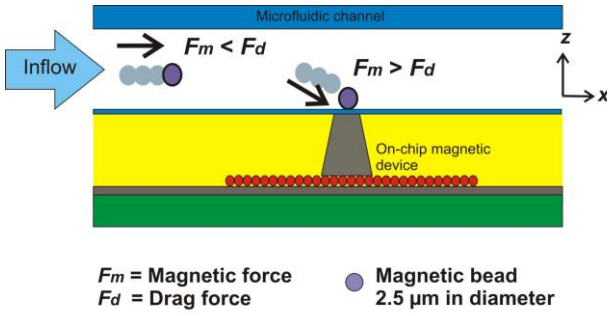


Figure 1 Schematic of the magnetic microbeads trapping in the continuous microchannel flow

2.2 Microchannel Fabrication

In this study, the PDMS microchannel was fabricated using polymer micromachining. The main processes involved were thick resist photolithography using negative photoresist SU-8 and replica molding technique using PDMS polymer. The replica molding technique duplicates the 3D shape, morphology and structure of the SU-8 mold [5].

2.2.1 SU-8 Mold

SU-8 photoresist is a negative photoresist developed by IBM company, US. The SU-8 photoresist consisted of basic epoxy resin EPON SU-8 which has been formulated by Shell company [6]–[8]. SU-8 photoresist contains gamma butyrolactone; 22-60%, mixture of triarylsulfonium/hexafluoroantimonate, propylene carbonate; 1-5%, and epoxy resin (CAS: 28906-96-9); 35-75% [9].

In this work, negative photoresist SU-8 2075 from Micro Chem, US was used. SU-8 2075 has kinematic viscosity of 0.022 m^2/s with density of 1236 kg/m^3 [10]. The SU-8 2000 series is intended to be used for thick, thermally and chemically stable structure using micro machining process. Other characteristics of the SU-8 2000 series are the ability to produce high aspect ratio structure, film thickness of 0.5 µm to < 200 µm can be achieved with one time spin, shorter film drying, better spreading on surface and possibility of vertical sidewalls structure. The SU-8 negative photoresist is used for UV exposure of wavelength 350 to 400 nm [10].

Prior to the photolithography process, a silicon substrate was first cleaned with a standard silicon cleaning process. Silicon substrate dehydration process at 200 degree Celsius for 10 minutes was performed on an aluminum topped hotplate to ensure SU-8 processing reliability. The selection of spin speed for the desired SU-8 mold thickness is available from the manufacturer's datasheet. In this work the recommended spin speed for 110 µm thickness SU-8 mold is 2000 revolution per minute (rpm) for 30 second (MicroChem Spin Speed vs. Thickness for SU-8 3000 resists at 23 °C Japan and Asia). Then, a pre-heat treatment at 65 and 95 degree Celsius was performed to the liquid SU-8 prior to photolithography process.

In photolithography process using negative SU-8 photoresist, a transparent window will permit the UV light through it and changes its chemical structures. The changed chemical structures will cure the SU-8 negative photoresist. The uncured SU-8 will be stripped off during the development process. In this work, UV light mask aligner machine (Karl Suss, Germany) with light intensity 2.6 W/cm^2 was used. The pattern transfer from the mask to the photoresist is using i-line UV light of wavelength 365 nm. Proximity photolithography process of minimal distance between the pattern mask and substrate was conducted using the mask aligner. Photoresist development is a process of transforming the latent image produced by the UV light exposure to a visible pattern using liquid developer. After the photolithography process, a post-heat treatment process was performed at the temperature of 65 and 95 degree Celsius. Rinsing of the silicon chip with the SU-8 mold was then conducted with IPA until all the undeveloped SU-8 film is cleaned. The SU-8 mold is then dried with nitrogen gas gun. Hard baking process on a hotplate was performed for 1 hour at temperature of 150 °C.

2.2.2 PDMS Microchannel

PDMS is a biocompatible polymer materials for biomedical applications. In this work PDMS replica molding technique from cured SU-8 mold has been employed to fabricate microchannel with trapping chamber. The Sylgard 184 Silicone Kit (Dow Corning, USA) contained PDMS oligomer and crosslinking pre-polymer agent. The PDMS oligomer and crosslinking agent was mixed in a ratio of 10:1 in weight ratio. The mixture is then thoroughly mix with disposable plastic pipette tip for two minutes until mixture is milky due to air bubbles. To remove the air bubbles from the mixture a degassing process was performed. The mixture was degassed under vacuum condition in preen plasma machine for 30 minutes or until free bubbles mixture is obtained. After the degassing process, the PDMS mixture is ready to be poured on the SU-8 mold for replica molding.

In this work, spin coating of the uncured liquid PDMS was performed prior to the thermal curing process. This process is to ensure that the approximate thickness of the microchannel layer can be determined. The relationship of the cured PDMS layer thickness with respect to the spin coating speed is as shown in Figure 2. The result shows consistency on the cured PDMS layer thickness from five measurements conducted. This extra step was performed due to the microchannel thickness layer which is the distance between the magnetic fluid and the magnetic field source is an important parameter affecting the trapping capability of the magnet system. Then, the uncured PDMS which has

been spin-coated onto the SU-8 mold was baked in an oven at 65 degree Celsius for 1 hour for curing or crosslinking the polymer. Finally, peeling process was performed on the way to detach the PDMS microchannel pattern layer from the SU-8 mold.

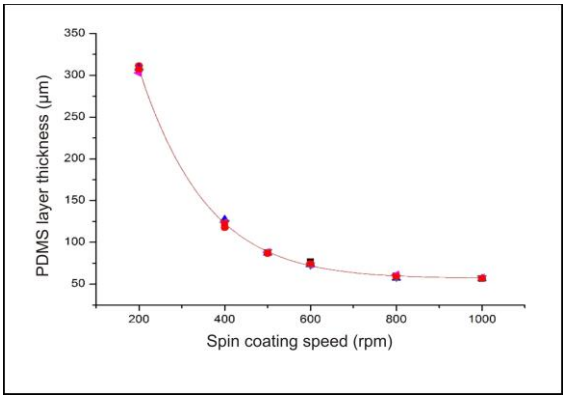


Figure 2 Cured PDMS layer thickness with respect to the spin coating speed

2.2.3 PDMS Fluidics Interconnect

Fluidics interconnect integrates the inlet and outlet tubing with the microchannel system. In this work, polytetrafluoroethylene (PTFE) plastic tubing (1/32 inch inner diameter, 1/16 inch outer diameter) from Coleparmer was used as the inlet and outlet tubing. The fabrication of the tubing layer starts with the pouring of the liquid PDMS into a petri dish which contains the PTFE tubing. The PTFE tubing was positioned vertically with the distance according to the inlet and outlet connection of the PDMS microchannel. Then, the liquid PDMS was cured in the 65 degree Celsius oven for 2 hours. The PDMS and PTFE tubing layer will be able to be peeled from the petri dish upon curing completion. The tubing layer was then bonded with the PDMS microchannel using hand held corona discharge as shown in the schematic as in Figure 2.

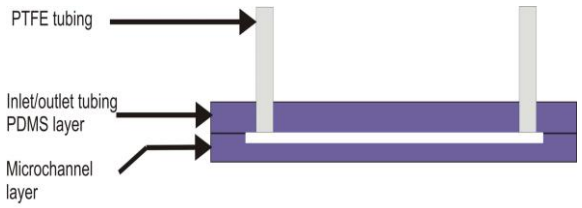


Figure 3 Schematic of the PTFE inlet and outlet tubing fluidics interconnect and the microchannel

2.3 Experimental Set-up

Testing using the fabricated microchannel and LOC magnet system has been conducted. The testing set-up comprises of a syringe to supply the liquid into the microchannel, an optical microscope (Olympus, Germany) with image analysis software (Analysis) to observe the magnetic beads flowing and trapping, a programmable power supply to supply electric current to the electromagnet system and a stop watch to measure the time taken for the experiment. The set-up of the testing is as shown in Figure 4.

SPHERO™ polystyrene smooth surface magnetic microparticles or microbeads (Spherotech, USA) of nominal diameter 2.0 to 2.9 µm are used for the testing. These magnetic microbeads are 2.5 % weight-to-volume (w/v) concentration in a 10 mL packaging. According to the manufacturer, the magnetic microbeads were prepared by coating a layer of magnetite and polystyrene onto uniform sized (monodispersed) polystyrene core particles [11]. The smooth surface of the magnetic microbeads was obtained by coating a thick layer polymer in order to encapsulate the iron oxide coating [11]. The advantages of using smooth surface magnetic microbeads are no iron oxide surface is exposed and suitable for application where exposed iron oxide can cause undesirable interferences to the surrounding media or other particles. The magnetic microbeads are paramagnetic where it will be easily detached from the suspension when removed from the magnetic field source. In addition, the magnetic microbeads will not retain any detectable magnetism even after being used repeatedly under strong magnetic field exposure. The magnetic microbeads are suitable to be used in biomedical application like cell separation, DNA probe assays and affinity purification [11]. In this work, a 2 µL sample of the magnetic microbeads was diluted in 5 mL deionized (DI) water. The characteristics of the magnetic beads in the DI suspension are observed using an optical microscope with 200x and 500x magnification lens. Monodispersed spherical shaped magnetic microbeads of 2.0 to 2.9 µm are observed as shown in Figure 5(a) and 5(b).

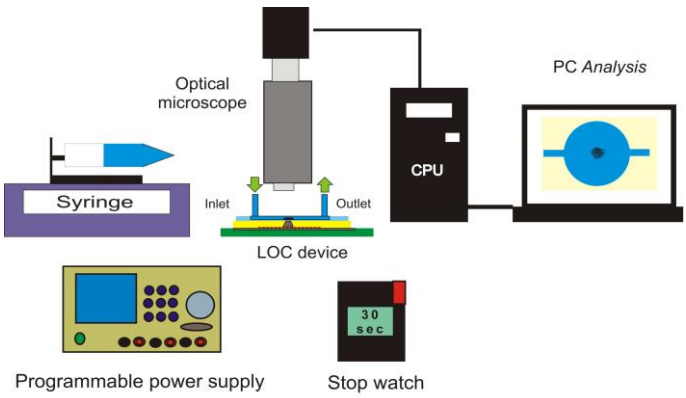
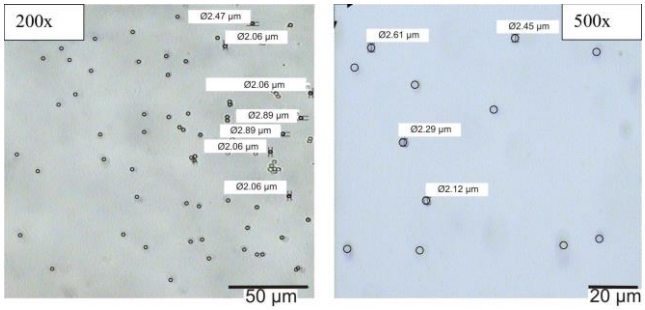


Figure 4 Schematic of the experimental setup for magnetic microbeads flow testing in the microchannel



(a) (b)

Figure 5 Enhanced images of monodispersed spherical shaped magnetic microbeads of diameter 2.0 to 2.9 µm in DI water under optical microscope magnification of (a) 200x (b) 500x

3.0 RESULTS AND DISCUSSION

The SU-8 mold fabricated onto the silicon wafer has a well-defined pattern and adhered strongly on the silicon substrate as shown in Figure 6. An SU-8 material is an epoxy based photoresist of two steps cross-linking process. Upon UV exposure, a strong acid forms and then become a catalyst for thermally driven epoxy cross linking during the post exposure baking phase. The microchannel mold height of 100 µm and microchannel chamber of diameter of 2.437 mm were obtained as seen from the Scanning Electron Microscopy (SEM) results as shown in Figure 7a and 7b. From the manufacturer datasheet, at a spin speed of 2000 rpm, a 110 µm structure height should be achieved. The reason of this discrepancy is due to the instability of the spin coating machine which fluctuated to higher than 2000 rpm during the spin coating process. Slightly non- vertical sidewalls were also observed for this SU-8 structure. From the technical datasheet, the manufacturer's recommended on using long pass filter during UV exposure in order to obtained vertical sidewalls structure. The filter is use to eliminate UV exposure below 350 nm [10]. However no filter is used in this work during the UV exposure. Filter usage is recommended in future work in maintaining

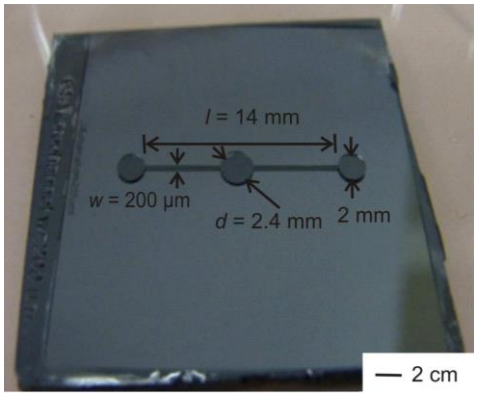
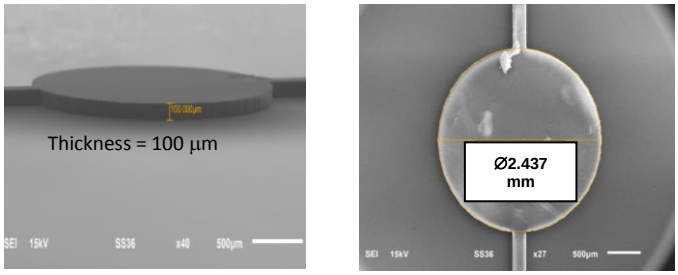


Figure 6 The SU-8 mold on the silicon substrate



(a) (b)

Figure 7 SEM of the SU-8 mold on the silicon substrate with (a) thickness 100 µm (b) 2.4 mm in diameter

SU-8 structure formation consistency during the lithography process.

The PDMS microchannel replicates the SU-8 mold pattern by replica molding technique. The cured PDMS layer is clear and optically transparent. The thickness of the PDMS layer to the magnetic field source is the crucial factor in determining the magnetic capturing ability. The distance of the magnetic beads and the magnetic field source must be minimized. Therefore, a spin-coating of the PDMS layer according to Figure 2 was performed to determine the thickness of the PDMS layer. In this work, PDMS thickness layer ranging from 123 µm to 140 µm have been determined between the microchannel chamber and the magnetic field source. An attempt to obtain a much thinner distance is not performed due to the thin PDMS layer is hard to be peeled-off from the mold and will be easily damaged.

To complete the microchannel as LoC magnetic device, a cured PDMS layer with inlet and outlet tubing was bonded to the pattern layer. The bonding was performed by treating the PDMS surface with corona discharge. The corona discharge used in this work is a handheld typed of model BD20-AC (Enercon, USA). The output voltage generated by the corona discharge is 15 kV. To treat the PDMS surface for bonding, the corona discharge's tip was placed at a distance of 0.5 cm from the PDMS surface and the treatment was performed for 30 s. The corona discharge generated high voltage from its tip and ionizes the surrounding air in order to create the localized plasma or corona [12]. In this surface activation process, –O-Si(CH3)2- in PDMS will change to silanol, -OH. Therefore, the hydrophobic surface of the PDMS is changed to a hydrophilic surface for ease of microfluidics flow in PDMS microchannel [13]. The complete PDMS microchannel and LoC magnetic device which is ready for testing is as shown in Figure 8.

In the functional testing, the microchannel with a trapping chamber of 2.4 mm in diameter and thickness layer of 140 µm is used. The magnetic core tip from the magnetic device is positioned at the trapping chamber area.

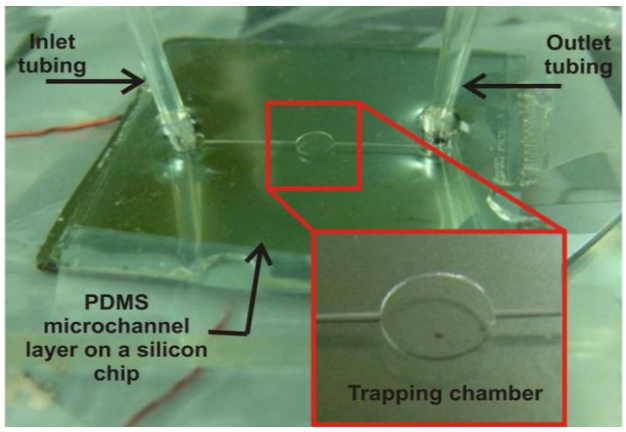


Figure 8 The integrated components of LoC magnetic separator

The important step prior to the testing is degassing or removing the trapped air inside the small volume microchannel structure. The degassing step was done by injecting the DI water slowly into the microchannel. The degassing process is completed when there is no flow blockage is observed and until the flow can easily flowing out from the outlet tubing.

The flowing of the magnetic microbeads suspension is observed as shown in Figure 9. A good scattering and agglomeration-free magnetic microbeads flowing in the continuous microfluidics flow of channel width 200 μm is observed. Due to manual syringe used in the test, the exact volume flow rate is not able to be computed. The volume flow rate is approximated at > 100 μL/min corresponding to syringe plunger movement with respect to time.

In the testing, a direct current of I_{DC} = 2.0 A is supplied to the electromagnetic system. After duration of 3 minutes, a trapping of magnetic beads is observed and at duration of 5 minutes more magnetic microbeads have been captured as shown in Figure 10(a) and (b). Another testing is performed to determine the effect of capturing magnetic beads at the straight microchannel flow. From the testing, no magnetic microbeads capturing is observed even after 5 minutes duration time which is shown in Figure 11(a) and (b). This is expected due to the higher fluid velocity of the smaller width straight microchannel flow in comparison to the much slower fluid velocity of bigger area microchannel chamber.

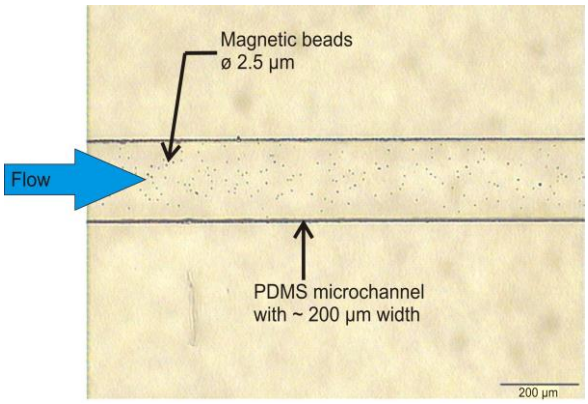
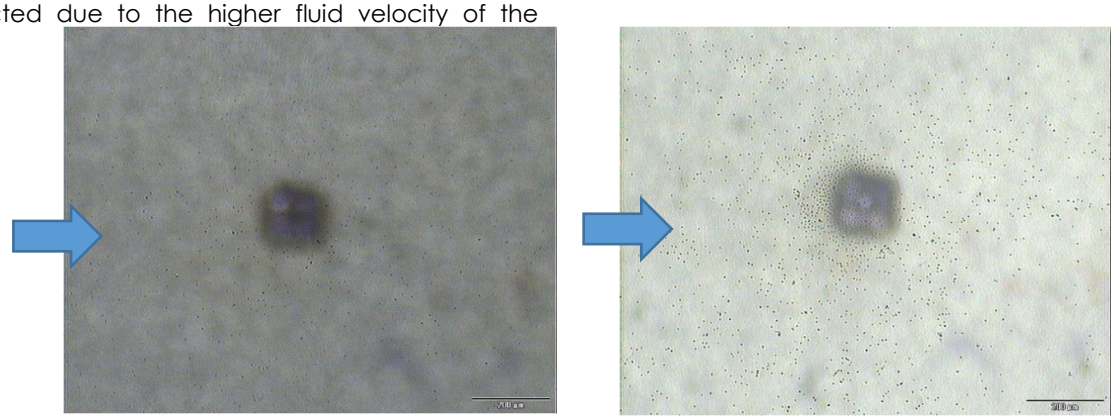


Figure 9 Agglomerate-free 2.5 μm diameter magnetic microbeads flowing in the microchannel

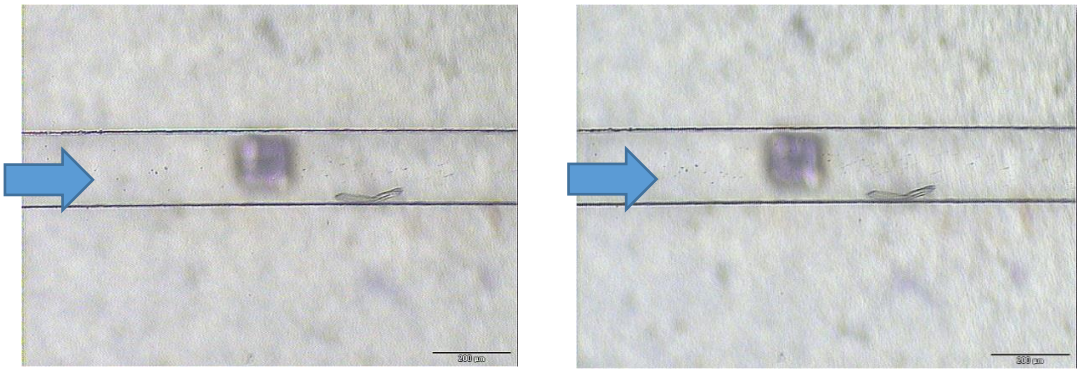
In this case, the magnetic force is not able to overcome the drag force experiences by the magnetic microbeads. Therefore, no microbeads trapping are observed at the straight microchannel area. In this testing, microchannel with a trapping chamber design has shown its capability in magnetic microbeads trapping.

Some problems associated with the microchannel of 2.4 mm trapping chamber diameter design have been observed. One of the important problems is the possibility of trapped air or bubbles formation at the low pressure area during the testing as shown in Figure 12. This problem has caused magnetic microbeads suspension backflow and the testing need to be halted. In order to remove the trapped air, a much higher volume flow rate of liquid must be injected to the microchannel. This procedure has to be carefully done as to prevent any delamination of the PDMS layer at higher volume flow rate (Elveflow 2015). For that reason, a microchannel with smaller trapping chamber is proposed to be designed and fabricated in the future. Moreover, smaller microchannel chamber dimension is expected to increase the trapping efficiency due to smaller capturing area of the magnetic field source. The comparison between microbeads capturing effect using different dimension of microchannel chamber design are as illustrated in Figure 13 (a) and (b).



(a) (b)

Figure 10 Trapping of the magnetic microbeads at the microchannel chamber of 2.4 mm diameter after (a) 3 minutes (b) 5 minutes



(a) (b)

Figure 11 Trapping of the magnetic microbeads was not observed at straight channel of 200 μm width after (a) 3 minutes (b) 5 minutes

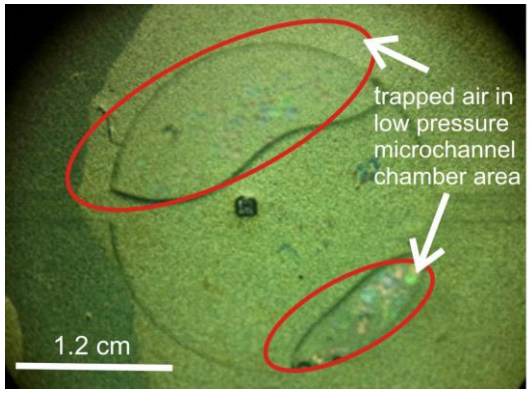


Figure 12 Trapped air was observed in low pressure microchannel chamber area

4.0 CONCLUSION

In this work, PDMS microchannel and its tubing layer has been successfully fabricated. Corona discharge effect has bonded the PDMS layers irreversibly and formed a liquid tight structure between the microchannel and fluidic interconnect layer. Testing of 2.5 μm magnetic microbeads and DI water mixture has demonstrated agglomeration-free magnetic microbeads flowing in the microchannel. Furthermore, trapping of the microbeads under 2.0 A direct current supply in the continuous microfluidics flow has been demonstrated using the PDMS microchannel with trapping chamber at volume flow rate > 100 μL/min after 5 minutes time duration. For further work, a smaller dimension microchannel chamber is proposed to be used with much lower fluid volume flow rate. This recommendations are to ensure better magnetic microbeads trapping efficiency. In conclusion, a trapping of biological particles labelled with magnetic microbeads are expected to be realized using the fabricated PDMS microchannel with integrated magnet system.

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