Magnetic Microbeads Trapping using Microfluidic and Permanent Magnet System

N.Z. Zaini
School of Mechanical Engineering, Faculty of Engineering, University Teknologi Malaysia

N.B Kamaruzaman
School of Mechanical Engineering, Faculty of Engineering, University Teknologi Malaysia

U. Abidin
School of Mechanical Engineering, Faculty of Engineering, University Teknologi Malaysia

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Magnetic Microbeads Trapping using Microfluidic and Permanent Magnet System

N.Z. Zaini[1], N.B Kamaruzaman[1], U. Abidin[1,*]

[1]School of Mechanical Engineering, Faculty of Engineering, University Teknologi Malaysia, Malaysia

*Author to whom correspondence should be addressed:
E-mail: ummi@utm.my

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Abstract: In Lab-on-Chip (LoC) magnetic system, magnetic microbeads are used in selective binding and separation of targeted biological cells under influence of a magnetic field. Enhancing magnetic trapping efficiency is vital for further biological analyses. In this study, trapping efficiency of 4.5 µm diameter magnetic microbeads under permanent magnet configurations and varying microfluidic flow rates has been investigated. In the experimental studies conducted, neodymium iron boron (NdFeB) permanents magnets and polydimethylsiloxane microfluidics with trapping chamber design were used as a LoC magnetic system. At 5 µl/min microfluidics flow, trapping efficiency of single magnet configuration was 92.06 %. Improved trapping efficiency of 95.24 % was observed with double magnet configuration. On the other hand, the trapping efficiency at greater microfluidics flow rate of 20 µl/min were only 20.63 % and 15.87 % for single and double magnet configuration respectively. Trapping efficiency is greater for double permanent magnets configuration and at the slowest microfluidics flow rate.

Keywords: Lab-on-chip (LoC); magnetic system; microfluidic; trapping efficiency

1. Introduction and background

Recent novel Coronovirus (Covid-19) pandemic outbreak has a tremendous impact to the society all over the world. New norms have been practicing everywhere and new diagnostic kits and vaccine research development have been accelerated. In addition, statistical tools and methods have also been conducted for prediction of the virus spread[1)]. Early detection of chronic and pandemics diseases are vital in order to minimize the treatment procedures and cost. Development of Lab-on-chip (LoC) devices as single diagnostics chip is currently an advancement in healthcare industry due to its low in cost, ease of operation, fast reaction, limited sample and reagent needed. LoC features resemble ideal Point of Care Testing (POCT) diagnostics kit by World Health Organization (WHO). In addition, low resources requirement is an important factor to be considered in LoC development. This strategy will have a tremendous impact for poor nations, resource-constrained area and remote location application[2)]. Promoting less energy usage is also beneficial as part of environmental friendly society encouragement and sustainability in developed countries[3)4)].

LoC is a sub field of microfluidics which has a range application not just in medical industry. Microfluidics field is also applied in cooling system where better heat transfer was observed[5)]. LoC system in primarily fabricated using a standard polydimethylsiloxane soft lithography from SU-8 master mold[6)]. Other than the standard method, fabrication techniques employing conventional machining capability[7)] for master mold and innovative adaptive manufacturing using 3D printer are still in progress[8)9)].

Magnetic microfluidic as part of LoC system has the ability to trap and separate biological cells using combination of microfluidic channel and magnetic system. Cell sorting method using magnetic field is called magnetophoresis (MAP) and is categorized as active method due to external force field is required[10)]. To date, the magnet system used is either permanent magnet or electromagnet to capture targeted biological cells using labelled magnetic beads. Small- or micro-scaled electromagnet system is commonly integrated with microfluidic channel. However, several issues like microfabrication complexity and cost, external power source requirement and Joule heating effect are the disadvantages using electromagnet. In comparison with electromagnet system, permanent magnet system of high magnetic field required no external power source, simple and easy to set up[11)]. In addition, no Joule heating effect is present and therefore no issue on denaturation of the cells is expected.

In microfluidics application, small neodymium iron

boron (NdFeB) magnets are usually used due to its ability in generating high magnetic flux density[11]. Permanent magnet was used in continuous separation of magnetic beads with two and multiple outlets demonstrated by Pamme[12]. In many of microchannel designs, a straight channel and T-shaped design are commonly been used[12][13]. This design is associated with continuous separation of the magnetic bead where the magnetic beads are guided to the outlet directly. As Pamme employed single permanent magnet system, Kashan et al. used two vertical side-by-side arrangement permanent magnet in his study. To increase the magnetic field gradient, permalloy wire was integrated in the experimental setup[13]. Zeng et al. employed offset permanent magnet configuration and be able to separate 3 μm and 10 μm magnetic microbeads in continuous microchannel flow[14]. In another research, Bahadorimehr et al. conducted a qualitative study of magnetic nanoparticle trapping efficiency in microfluidic device using single rectangular-shaped permanent magnet[15]. NdFeB magnet of 3 mm x 3 mm and thickness of 1 mm magnet was placed under the fluid chamber. Significant number of trapped magnetic nanoparticles were observed in a rectangular-shaped trapping chamber. This type microfluidic system is regarded as batch type separation where the permanent magnet system is to be disintegrated for release of the magnetic beads. A review paper by Shuang et al.[16] has listed single and multiple permanent magnet configurations in separation of magnetic microbeads with diameter ranging from 3 μm to 10 μm. Greatest trapping efficiency with higher than 90 % was achieved at the slowest microfluidic flow.

Although NdFeB permanent magnet has been used in trapping magnetic microbeads in microchannel flow, comparison on the trapping efficiency between the setup of single and double permanent magnets used with trapping chamber has not been investigated. In this study, the trapping efficiency of microbeads with single and double setup of permanent magnet were studied. The single magnet configuration experiment was setup by placing it below the trapping chamber. On the other hand, experiment on double magnet configuration was conducted with the magnet placed below and upper sides of the trapping chamber. In addition, effect of microchannel flow rate with the trapping efficiency was determined and discussed further in the results and discussion section.

2. Method and experimental setup

2.1 Design and fabrication

In this work, the design of the microfluidic channel or microchannel was based on previous work by Ayuni et al.[17]. The microchannel has one inlet and one outlet, 300 μm in width and 100 μm in thickness. The total length of the microchannel is 14.0 mm. A chamber of 750 μm was designed at the middle of the straight channel. The trapping chamber was introduced in lowering down the microchannel flow rate. At lower flow rate, hydrodynamic force on a magnetic microbead will become less and greater trapping efficiency is expected. The microchannel SU-8 master mold was fabricated by Australian National Fabrication Facility (ANFF) using photolithography technique.

In this study, polydimethylsiloxane (PDMS) microchannel was fabricated using replica molding from SU-8 master mold. The first step in the replica molding of PDMS was mixing Slygard 184 kit (Downconing Corporation, USA), silicon elastomer and its base. The silicon elastomer was mixed with the curing agent with ratio 10 to 1[18]. The mixture was stirred and then proceed with degassing process to eliminate the bubbles. The mixture was stirred by overhead stirrer at 450 rpm for 20 minutes[17]. The next step was PDMS pouring on the SU-8 mold. Prior to that, the SU-8 mold was cleaned with liquid isopropanol (IPA) to remove dust and impurities that could affect the quality of PDMS device. The SU-8 master mold was placed inside furnace at 50℃ for 10 minutes to ensure the mold surface was fully dried. Upon pouring, the PDMS were cured inside a furnace for 1 hour at 65℃. After the PDMS was cured, the thin layer of PDMS with the microchannel design was peeled from the SU8 mold using tweezer. It was done carefully to prevent from making scratches on the surface of mold and to avoid the PDMS from tearing.

The base of PDMS was fabricated by using the same method above except that the PDMS was poured on a planar surface without any pattern and then was spin for 20 seconds at 120 rpm. The spinning of the PDMS base was conducted to ensure approximate 100 μm PDMS layer thickness will be obtained. A thin PDMS layer base is required in minimizing the magnetic field loss during the magnetic bead trapping experiment.

2.2 Device preparation

Prior to device testing, the PDMS microchannel and its base undergo bonding to create a tight seal in order for the fluid to flow. In this work, bonding of PDMS microchannel with PDMS was done using oxygen plasma process. Both the PDMS microchannel and its base layer were exposed in oxygen plasma chamber for 12 seconds at 150 W[17]. The oxygen plasma is used for surface treatment of the PDMS layer surface and later facilitate the layers bonding. Moreover, hydrophobic PDMS microchannel surface is converted to hydrophilic surface by oxygen plasma treatment. This hydrophilic surface is needed to facilitate the liquid flow smoothly through the microchannel. After the bonding process, a leakage test was done by injecting color-dyed deionized (DI) water into the PDMS microchannel. If no leakage is observe, the PDMS microchannel is ready to be used for the microbeads trapping experiment.

2.3 Measurement of magnetic field

The permanent magnet used in this work is a round NdFeB magnet N35 4.0 x 2.0 mm with magnetization axial and zinc plated. The magnetic field of the permanent magnet was measured in order to determine its strength. The measurement was conducted using digital gauss meter (Model DGM-102). The digital gauss meter probe was placed on top of the permanent magnet center and the magnetic field reading was recorded. The reading of magnetic strength of the magnet was 3021.25 Gauss which was equal to 0.302125 Tesla.

2.4 Experimental testing

This section presented the experimental setup for the magnetic microbeads trapping in microfluidic flow. Prior to the experiment, DI water and microbeads were mixed and agitated before been injected into the microchannel. The amount of 2 µl of polystyrene magnetic microbeads were mixed with 5 ml of DI water. The dilution factor after mixing microbeads and DI water was 2501. The concentration of the solution was 2.5% w/v with volume of 10 ml. The estimation from the calculation of microbeads in that solution was for every 1 ml, the amount of microbeads was $4.99x10^8$ particles. The size of microbeads used in this project were average 4.5 µm with catalogue number of PMS-40-10 (Spherotech Inc. USA). The 4.5 µm is a paramagnetic-typed microbeads which is easily detachable from magnet. Moreover, the 4.5 µm magnetic microbeads is within the range used in standard conventional cell separation technique.

A dual syringe pump with model of NE 4000 (KdScientific) was used to manipulate the flow rate at 5, 10, 15, and 20 µl/min. A 10 ml B-D syringe was attached to the pump and the syringe tip was connected to the 2 mm tube at the inlet of microchannel. An end of 2 mm tube was linked to the outlet and the other end was placed into 10 ml bottle were collected the samples for each flow rates. The magnet was placed at the bottom part of the trapping chamber for first configuration and for second configuration, the magnets were placed at the bottom and upper part of trapping chamber in attraction mode. The experimental setup for this study was shown in Figure 1.

Microchannel was cleaned with DI water after experimental process for each flow rates were done. Residual magnetic microbeads that was trapped at the trapping chamber during each flow rates in the microchannel were eliminated. In order to clean the fluid chamber, magnet was removed from the system first before injecting it with pure DI water. This DI water would ensure that there was no microbeads left in the system that would affect the result for analysis of trapping efficiency.

After the process of collecting the samples at the outlet were completed for both configurations, 2 µl of the sample for each flow rates were taken to be captured for microscopic image. The sample was located on the surface of microscope slide after the slide was cleaned by IPA. In order to get a clear image of microbeads in the sample, cover slip was placed on top the sample. The magnification of the microscope for this project was 200x. The images are important as it were required for microbeads counting in trapping efficiency calculation.

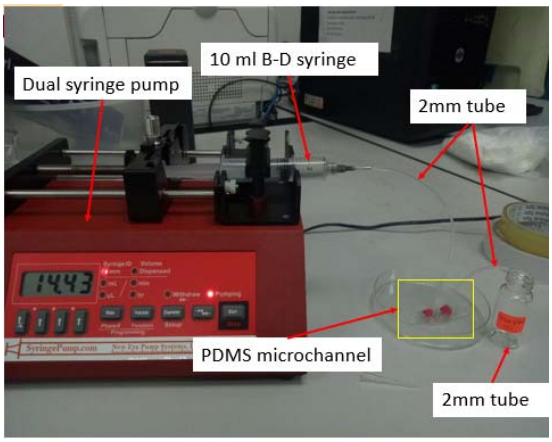


Fig. 1: The experimental setup in investigating the separation efficiency at different flowrates using the fabricated PDMS microfluidic device.

2.5 Image Processing

Image processing phase was essential in this study to analyze and manipulate the digitized image in order to get the total count of the microbeads at the outlet. The image processing software that was used for the counting of microbeads was ImageJ and it was freely downloaded. This software provided the user with the platform to conduct scientific image analysis especially for microscopic analysis. A large number of images were taken during the experiments using optical microscope at magnification of 200x. These microscopic images were then analyzed by ImageJ to determine the number of microbeads at the outlet.

2.6 Magnetic Microbeads Trapping Efficiency

A nominal size of 4.5 µm microbeads were magnetic trapping efficiency experiment. In order to analyze the trapping efficiency, the number of microbeads at the inlet were counted first. The trapping efficiency of beads were calculated using the Eq. 1 below[19].

$$Trapping\ efficiency, \% = (Total\ number\ of\ trapped\ microbeads)/(Total\ number\ of\ injected\ microbeads)\ x\ 100\% \quad (1)$$

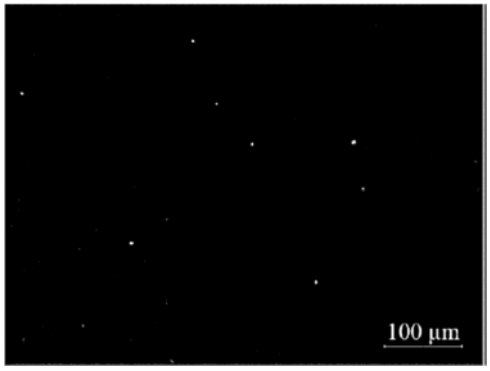
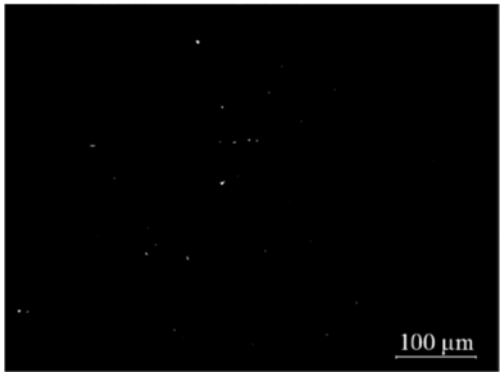
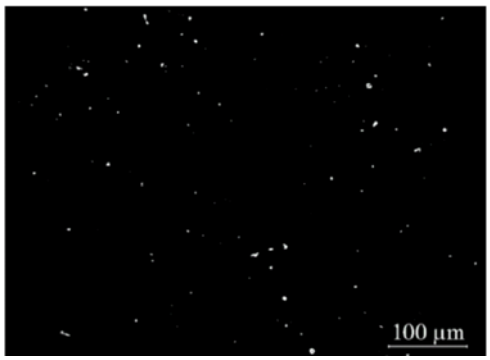
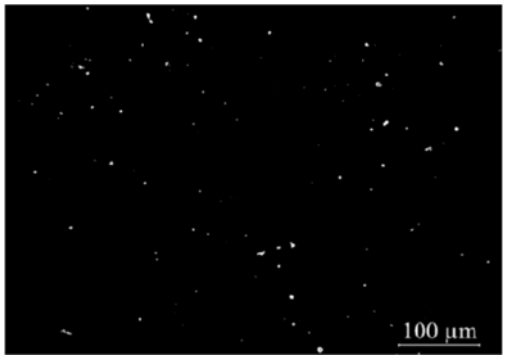
3. Results and Discussion

The magnetic beads trapping at different configuration of magnets and different flow rates were determined and quantified. As what has been mentioned in the methodology, the single configuration NdFeB permanent

magnet was placed at the bottom part of the trapping chamber. On the other hand, double magnet configuration was established on upper and bottom parts of the trapping chamber.

Table 1 shows ImageJ results of the magnetic microbeads counting at the outlet of the microchannel. The white dots representing the 4.5 μm magnetic microbeads used in this work. It was observed that at lower flow rate in the microchannel, lower number of microbeads were observed for configuration of single and double NdFeB permanent magnet. This indicates that more magnetic microbeads were trapped in the trapping chamber and resulted in higher trapping efficiency. However, at higher flow rate, the number of magnetic microbeads in the microchannel outlet is also greater. The magnetic microbeads flowing at higher flow rate escaped from the trapping chamber and flowed to the microchannel outlet. This effect is due to magnetic force from the permanent magnet was not able to capture the microbeads due to high drag force experienced. The explanation of this will effect will be elaborated further in this section.

Table 1. ImageJ images used for microbeads counting at flow rate of 5 μl/min and 20 μl/min for (a) single and (b) double magnet.

Flow rate	**(a) Single magnet**	**(b) Double magnet**
5μl/min		
20 μl/min		

The results of both single double magnet configuration shows that the trapping efficiency decreases with increasing flow rates from 5 μl/min to 20 μl/min. The outcome of the study is plotted in Fig. 2. At slowest flow rate of 5 μl/min, the trapping efficiency of the magnetic microbeads were the highest which are 92.06 % and 95.24 % for single and double magnet setup respectively. Generally, the trapping efficiency decreases at increased flow rate. At flow rate of 20 μl/min, trapping efficiency of single magnet configuration is 15.87 % while for double magnet, the trapping efficiency is 20.63 %. A clear comparison of the magnetic microbeads trapping is presented in Table 2.

There is no distinct differences in the magnetic microbeads trapping efficiency for the single and double configuration of the NdFeB permanent magnet. The trapping efficiency differences of approximately 3 % to 5 % were observed for this magnet configurations. In the work by Gassner et al.[20], single magnet configuration resulted in microbeads accumulation at only one side of the channel. However, with two magnet configuration, central plug formation from the fluid loaded with magnetic microbeads was observed. This central plug magnetic microbeads behavior is due to different poles used for the double permanent magnet configuration. This plug flow observation was demonstrated from the microscopic visualization of the work of Gassner et al.[20].

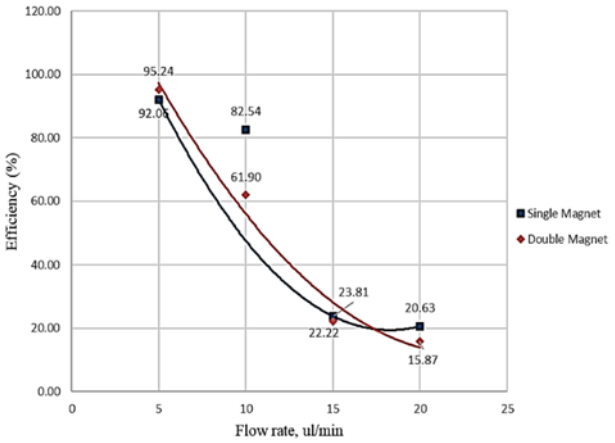


Fig. 2: Graph of magnetic microbeads trapping efficiency versus flow rates.

Table 2. Trapping efficiency comparison for different magnet configurations.

Magnet configurations	**Trapping Efficiency (%)**	
	5 µL/min	**20 µL/min**
Single	92.06	15.87
Double	95.24	20.63

The behavior of plug flow is more favorable as to minimize the tendency of the magnetic beads to adhere on the PDMS channel surface. In addition, plug flow is expected in lowering down the shearing effect between the microbeads and PDMS microchannel. This effect is demonstrated from Fig. 2 graph trend, where double magnet configuration resulted in slightly higher trapping efficiency in comparison with single magnet configuration.

A slight different in the single and double magnet configuration is also due to different thicknesses of PDMS materials at the bottom and upper part of the microchannel. An estimation of ~100 µm PDMS layer was used as the bottom microchannel layer. This thickness layer is determined from the spinning of the uncured PDMS and planarization method[21]. However, the thickness of PDMS on the upper microchannel was not be able to be controlled during the fabrication process. Magnetic field decreases with increased distance from the permanent magnet source. Therefore, less significant effect of placing NdFeB magnet on the upper layer for double magnet configuration is resulted.

From the results of the experiment, in order for magnetic microbeads trapping action to be highly efficient, the flow should be in order of 5 µL/min and less. The relationship between flow rate and drag force is as shown in Fig. 3. The proportional relationship of hydrodynamics drag force, F_{drag} on a sphere flowing in a laminar flow is evaluated by Stoke's law of Eq. 2.

$$F_{drag} = 6\pi\eta r_m \Delta v \qquad (2)$$

In the drag force equation, η is the fluid dynamic viscosity, r_m is the magnetic microbead radius and Δv is the relative velocity between the fluid and the magnetic microbead. As the drag force increases at higher flow rate, magnetic field from the permanent magnet loses its capability to trap the magnetic microbeads. At this condition, the drag force already exceeded the magnetic force, $F_{drag} > F_{magnetic}$. The study of Ramadan et al., Fucrand et al. and Abidin et al. demonstrated the same trapping efficiency trend with the flow rate[22)23)24)].

At higher flow rate where the hydrodynamics drag force is greater, the constant magnetic force generated by the permanent magnet is not sufficient and unable to capture or trap the magnetic microbeads. Therefore, lower trapping efficiency is expected. In this study, only the magnitude of the magnetic field can be measured using Gaussmeter. The magnetic field obtained was 0.3 Tesla. The magnetic force value could not be obtained using theoretical equation as magnetic field gradient measurement was not conducted. Theoretically, magnetic force is the measure of the magnetic field and its gradient as in Eq. 3. The magnetic force, $F_{magnetic}$ on the magnetic microbeads of volume, $V = (4/3)\,\pi r_m^3$ (r_m is the magnetic microbeads radius), $\Delta\chi$, is the difference in magnetic susceptibility, μ_o is magnetic constant of $4\pi \times 10^{-7}$, B and $\nabla \cdot B$, are strength and gradient of the magnetic flux density respectively.

$$F_{magnetic} = \frac{V\Delta\chi}{\mu_o}(B \cdot \nabla)B \qquad (3)$$

In this study, in order to achieve trapping efficiency greater than 90 % at higher flow rate, the magnetic force magnitude should be higher than 20 pN. This statement agrees well with the previous research by Yu et al.[25].

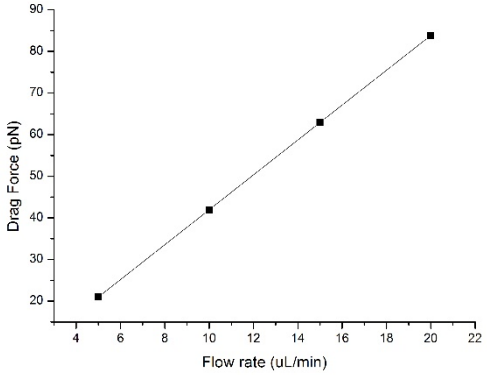


Fig. 3: Relationship between flow rate and drag force for 4.5 µm microbead flowing in the microchannel.

3. Conclusions

In conclusion, low cost and easy setup magnetic microbeads trapping was proven using the active technique of permanent magnets of single and double configuration. The efficient trapping of 4.5 µm smooth

magnetic microbeads at 5 µl/min were 92.06 % and 95.24 % with single and double magnet configuration respectively. At lower flow rate, the magnetic force exceeded drag force and resulted in higher trapping efficiency. Trapping efficiency of the permanent magnet with two different configurations show insignificant results. This result is expected due to the magnetic microbeads plug flow behavior and thicker upper PDMS microchannel layer used. This study has contributed a new insight in magnetic microbeads trapping using a design of a microchannel with trapping chamber. Furthermore, permanent magnet of single and double configuration be able in demonstrating greater than 90 % trapping efficiency of 4.5 µm diameter magnetic microbeads. Further works on using different diameter magnetic microbeads and live biological cells will be conducted in the future.

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Nomenclature

LoC	Lab-on-Chip (–)
POCT	Point of Care Testing (–)
WHO	World Health Organization (–)
MAP	magnetophoresis (–)
NdFeB	neodymium iron boron (–)
ANFF	Australian National Fabrication Facility(–)
PDMS	polydimethylsiloxane(–)
F_{drag}	drag force (N)
$F_{magnetic}$	magnetic force (N)
DI	deionized (–)
IPA	isopropanol
B	magnetic flux density
r	radius (m)
V	volume (m^3)

Greek symbols

μ_o	magnetic constant (H m^{-1})
η	dynamic viscosity (Pa s)
ν	relative velocity (m s^{-1})
χ	magnetic susceptibility (–)

Subscripts

m	magnetic microbead
o	constant

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