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A HIGH-THROUGHPUT SU-8 MICROFLUIDIC MAGNETIC BEAD SEPARATOR

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Abstract: We present a novel microfluidic magnetic bead separator based on SU-8 fabrication technique for high through-put applications. The experimental results show that magnetic beads can be captured at an efficiency of 91% and 54% at flow rates of 1 mL/min and 4 mL/min, respectively. Integration of soft magnetic elements in the chip leads to a slightly higher capturing efficiency and a more uniform distribution of captured beads over the separation chamber than the system without soft magnetic elements.

Keywords: microfluidics, magnetic bead separator, SU-8, high throughput, soft magnetic elements

1. INTRODUCTION

The manipulation and separation of magnetic beads in microfluidic systems is gaining tremendous interests for analytical applications [1]. At MIC, we have previously fabricated several passive magnetic bead separators based on the silicon microfabrication technology [2-3]. In these separators, integrated soft magnetic elements are placed adjacent to the sidewalls of fluidic channel and magnetized by a homogeneous external magnetic field. The magnetic beads are therefore only captured on the two sidewalls of the separation channel. This presents a limitation for applications where a high flow rate and a large amounts of beads are used, *e.g.*, for removal of inhibitors from diluted DNA samples prior to polymerase chain reaction (PCR) amplification.

In this paper, a new microfluidic magnetic bead separator, which can capture and hold a large amount of beads introduced at a high flow rate, is demonstrated. Fig. 1(a) shows a schematic view of the micro bead separator. The system consists of a Pyrex substrate, a Topas lid on the top and an array of permanent magnets under the Pyrex substrate. The bead separation chamber is structured in SU-8 on a 0.5 mm thick Pyrex substrate and has a volume of 10 μL (200 μm deep, 5 mm wide and 10 mm long). An array of integrated permalloy elements is buried just beneath a 5 μm thick SU-8 isolation layer under the separation chamber. The 5 μm thick permalloy elements are perpendicular

to the sample flow and stretching across the whole separation chamber. The Topas lid has holes for liquid access and is coated with PDMS to seal the separation chamber.

As shown in Fig. 1(b), an array (3 $\times$ 5) of permanent magnets is assembled in a checkerboard arrangement and positioned in a chip holder just below the Pyrex substrate to provide long-range capturing forces over the entire 10 mm long separation chamber. The permanent magnets used here are strong Nd-Fe-B magnets with a flux density of about 0.3 T just above a single magnet. The size of each permanent magnet is 2 $\times$ 2 $\times$ 2 mm³. Magnetized by the permanent magnet array, the on-chip permalloy elements greatly enhance the local magnetic field gradient in the separation chamber and thus provide strong short range magnetic capturing and holding forces. A theoretical investigation indicated that this approach leads to a high bead capturing and holding efficiency [4].

Fig. 1: (a) A schematic view of micro bead separator. (b) Checkerboard arrangement of the permanent magnet array.

2. DEVICE FABRICATION

For fabrication on the Pyrex substrate, multi-layer SU-8 patterning and permalloy electroplating processes were used, as outlined in Fig. 2: (a) Definition by lift-off of e-beam evaporated Ti/Pt (10/250 nm) seed layer for electroplating. Pt was chosen because thin film heating elements for on-chip PCR reaction chambers were defined simultaneously on the same mask. (b) Deposition and prebake of 5 μm SU-8 2005 on the front side followed by UV exposure from the back side using the Ti/Pt film as mask to define the electroplating mould. This procedure ensures perfect alignment of the mould and the seed layer. (c) UV exposure from the front side through second mask to cross-link the SU-8 on top of Ti/Pt where electroplating is not desired (e.g., leads for electroplating, Fig. 3). (d) Development of SU-8 after post-exposure bake (PEB) and short O_2 plasma ashing to remove SU-8 residuals. (e) Electroplating of $\approx 5 \mu\text{m}$ thick permalloy ($\text{Ni}_{80}\text{Fe}_{20}$) elements. (f) Deposition of 5 μm thick SU-8 2005 isolation layer followed by flood exposure and PEB. This layer prevents contact between the liquid sample and the permalloy elements during the separation. (g) Definition of chamber walls in 200 μm thick SU-8 2075. Figure 3 shows an image of a processed chip. The lid for the separation chamber was fabricated in 1.6 mm thick Topas with micro milled holes for liquid access and coated with $\approx 300 \mu\text{m}$ cast PDMS. The Pyrex chip and Topas lid were finally assembled in a chip holder with fluidic connections to an external sample injection loop for separation experiments.

Fig. 2: Schematic of fabrication process.

Fig. 3: Image of a Pyrex chip with electroplated permalloy elements and SU-8 fluidic chamber wall. In this chip, the permalloy elements are 400 μm wide and the gaps between them are 400 μm .

3. EXPERIMENTS

Nanomag-D® plain silica 250 nm beads (Micro-mod, Germany) were used in experiments for quantification of the bead capturing efficiency in the micro bead separator. The beads were diluted in DI water to a concentration of $\approx 0.1 \text{ mg/mL}$. Figure 4 illustrates the experimental setup and procedure. Two syringe pumps (Harvard Apparatus, Holliston, MA, USA) were used to pump the sample solution with beads and cleaning buffer (DI water).

Fig. 4: Illustration of setup and procedures for bead capturing experiments. (a) Sample loading. (b) Sample injection and separation.

First, as shown in Fig. 4(a), the bead solution was pumped through a 6-port manual injection valve (Upchurch Scientific, Oak Harbor, WA, USA) into a 1 mL sample loop (Upchurch Scientific) at a flow rate of 1 mL/min. This flow was maintained for 2 minutes to ensure filling of the entire sample loop and all possible dead volumes

in the connection tubing and the injection valve. Simultaneously, a buffer was pumped through the valve to wet and fill the separation chamber (see Fig. 4(a)).

Then, the injection valve was manually turned to the injection position (see Fig. 4(b)) with the flows maintained. Hence, the ≈ 1 mL bead solution isolated in the sample loop was pushed into the separation chamber by the buffer flow.

Direct quantification of the beads captured in the separation chamber is not straightforward. Therefore, the waste solution containing beads escaping the system was collected at the system outlet for quantification. In each separation experiment, 1.5 mL solution was collected in 1.5 mL plastic tube starting when the injection valve was turned into the injection position.

Reference samples were collected at the system inlet (M1) and at the outlet for a chip without permanent magnets and without magnetic elements (M2). To evaluate the magnetic capture efficiency and the effect of the magnetic elements, samples were collected for a chip with permanent magnets but without magnetic elements (M3) and finally for a chip with both permanent magnets and permalloy elements (M4). The permalloy elements were 50 μm wide and placed with 50 μm gaps. Experiments M1-M4 were performed for three different sample injection flow rates, $Q = 1, 2$ and 4 mL/min. The amount of beads retained in the system under the various experimental conditions M2-M4 can be obtained by subtracting the quantity of beads escaping the system (M2-M4) from that injected into the system (M1).

In all collected samples, the beads were captured at the bottom of the tubes by use of a permanent magnet and the supernatant was removed. Then, the beads were fixed at the bottom of the tube by Loctite 420 glue. The amount of beads in each tube was quantified by measurements of hysteresis loops in a LakeShore 7407 vibrating sample magnetometer (VSM). The measured curves of the magnetic moment vs. magnetic field were fitted to an analytical representation of the bead contribution combined with linear background from the sample holder and the tube. The fit resulted in the saturation magnetic moment, which is proportional to the quantity of beads.

4. RESULTS AND DISCUSSION

Figure 5 shows the magnetic moments measured for experiments M1-M4 at flow rates $Q = 1, 2$ and 4 mL/min. These flow rates correspond to average linear flow velocities in the chamber of 1.7, 3.3 and 6.7 cm/s, respectively. Each experiment was repeated 3-5 times. The error bars represent the scattering of the measurements.

Fig. 5: Saturation magnetic moments measured in VSM. Reference sample collected at chip inlet (M1). Samples collected for chip without magnets and elements (M2), chip with magnets but without elements (M3), and chip with magnets and elements (M4). The capture efficiencies relative to the reference M1 are indicated beside the data points for each experiment.

For the reference samples M1 and M2, it is observed that the amount of beads captured depends on the flow rate. Hence, about 10-20% of the injected beads sediment in the fluidic set-up – most likely in the tubes, valves and near the O-ring seals in the chip holder.

For the experiments with permanent magnets and without (M3) and with (M4) permalloy elements a significantly higher fraction of beads were retained in the system. For $Q = 1$ mL/min only about 10% of the beads escaped from the systems. This number increases to about 25% and 45% for $Q = 2$ and 4 mL/min, respectively. These flow rates are large and correspond to average linear velocities of 1.7, 3.3 and 6.7 cm/s. Thus, the systems capture and retain the beads at up to very high flow rates. These quantitative measurements indicate that the studied systems with and without elements yield similar results with a slight advantage of the system with permalloy elements.

Fig. 6: Micrographs before and after bead capture experiments in system without (a)-(d) and with (e)-(h) permalloy elements.

Figure 6 shows micrographs taken before and after beads were injected into systems without (a)-(d) and with (e)-(h) permalloy elements at flow rates $Q = 1, 2$ and 4 mL/min, respectively. It is seen that the beads are successfully captured in both systems but they are distributed differently in the separation chamber. In the system with elements, the beads are concentrated at positions close the permanent magnet edges perpendicular to the flow direction. In the system without elements, the beads are concentrated near the middle of each permanent magnet. At low flow rates ($Q = 1$ mL/min), most beads are captured and pile up near the first column of permanent magnets. Then, at some point, the pile of beads forms a flow restriction and is broken apart by the fluid flow. The beads are then recaptured further down the channel or, in the extreme case, they escape the channel. This tendency is more pronounced at the higher flow rates, where the fluid drag on the bead assemblies is larger. The images in Fig. 6 indicate that the beads are distributed more uniformly in

the system with elements. This will make their surfaces more accessible to the fluid, which will be an advantage for practical applications.

5. CONCLUSION

We have presented, fabricated and demonstrated an efficient magnetic bead separator using a simple fabrication scheme in SU-8. This design relies on an external checkerboard array of permanent magnets providing long range magnetic capturing forces combined with on-chip permalloy elements providing strong short-range magnetic retaining forces. Quantitative characterization by magnetometry indicates that both systems without and with integrated permalloy elements capture beads efficiently up to very high flow rates and that the systems with elements seem to perform marginally better for the studied element geometry. Moreover, the distribution of the captured beads is more uniform in the system with the elements. Both systems could provide high-throughput sample preparation systems for PCR amplification.

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