A Fully Integrated Micromachined Magnetic Particle Manipulator and Separator

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ABSTRACT

A micromachined magnetic particle manipulator which can be used to influence magnetic particles suspended in liquid solutions has been realized on a silicon wafer. One important application for these devices is the separation of magnetic particles from dilute fluid suspensions. Previously, macro-scale versions of such devices have been realized using permanent magnets. In the device presented here, integrated inductive components have been used in place of permanent magnets, which yields several advantages in design flexibility, compactness, electrical control, and integration feasibility (thus enabling mass production). To show the feasibility of the device, magnetic fluid containing superparamagnetic particles of 0.8 - 1.3 μm in diameter suspended in a buffer solution is flowed through a 100 μm wide channel arranged between the poles of an integrated electromagnet quadrupole. An initial movement of magnetic particles is observed when the DC current in the coils reaches 100 mA. At 500 mA of DC current, approximately 0.03 Tesla of magnetic flux density is achieved at the gap between the quadrupoles, and the particles rapidly move toward the quadrupoles, separate from the buffer solution, and clump on the poles. The magnetic particles clumped on the poles are also easily released when the DC current is removed, achieving the primary purpose of a separator. This prototype device illustrates the high potential of integrated micromagnetics in chemical and biological applications where the manipulation of small amounts of reagent are important.

INTRODUCTION

Purification techniques which are widely used in conventional chemistry such as distillation and crystallization become more difficult to apply as the quantity of material to be purified becomes small. In addition, biological purifications requiring separations of biological cells or cell fragments from suspensions can be difficult due to the fragility and ease of aggregation of these materials. However, magnetic separation techniques [1-2] provide unique advantages that have been exploited to solve these problems, since the primary role of the biological molecules in many cases is essentially coincidental to the magnetic properties of magnetic particles. The most important strength of magnetic separation techniques is that they provide probably the most rapid and convenient method in separating appropriate particles from diluted suspensions.

In conventional magnetic particle separators as shown in Figure 1, magnetic particles which are suspended in a fluid are subjected to spatially nonuniform magnetic fields (0.01-0.2 Tesla) produced by an array of arbitrarily positioned, rectangular, rare-earth permanent magnets. In practical separators, in order to achieve a magnetic field gradient which is sufficient to separate the particles, quadrupole or multipole permanent magnet arrangements [3-4] are adopted and ferromagnetic wires are also introduced to generate the required magnetic gradient in an otherwise uniform magnetic field. When the magnetic particles are subjected to the field, magnetic forces are generated on the particles. The particles then migrate and coalesce into the magnetic poles or the ferromagnetic wires. Figure 2 shows a separator system [4] which generates the magnetic gradient internally in a microtitre well as well as a permanent magnet-pair. The device consists of a non-magnetic T-shaped frame which holds removable ferromagnetic wires, a pair of permanent magnets, and a microtitre well to contain a suspension. In a typical magnetic particle separation experiment, suspension with a specific ferrofluid reagent is pipetted into microtitre wells. Cells specifically labeled with

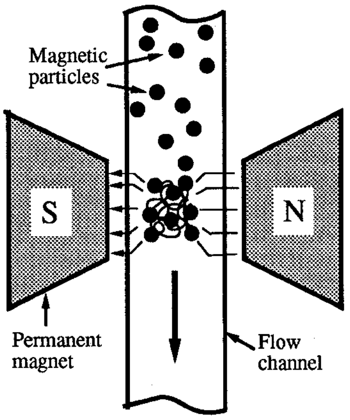
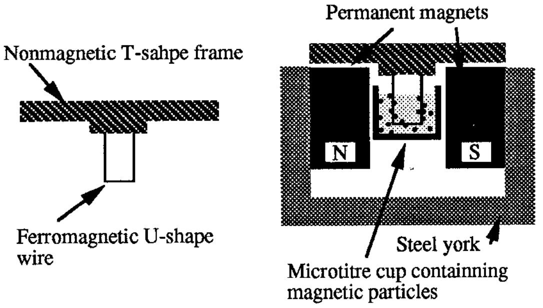


Figure 1. Schematic diagram of a conventional magnetic separator with permanent magnets.



(a) (b)

Figure 2. Practical separator system which generates the magnetic gradient internally in a microtitre well as well as a permanent magnet-pair: (a) T-shaped frame; (b) high gradient magnetic separator.

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the ferrofluid reagents or magnetic particles are pulled onto the wires and thus immobilized within minutes. The wells can then be lowered and subsequent wash steps can be performed on the immobilized cells (still in field) using fresh buffer.

As described above, the conventional separators require hybrid-type components such as T-shape loop holders, wires, permanent magnets, and yoke frames to construct the separators, which consequently increases the device cost. In addition, these separators usually involve somewhat complicated as well as time-consuming separation steps. A micromachined version of the separator, with potentially lower cost and relative ease of handling of small quantities of material, would therefore be a useful device in achieving these separations.

Planar integrated magnetic microactuators [5-7] which have been realized recently using planar integrated inductive components [7-8] exhibit magnetic fields in air gaps (0.2 Tesla) large enough to separate magnetic particles from fluid suspensions. In this study, a integrated inductive component with completely insulated and integrated coils [8] has been used in place of permanent magnets, which yields several advantages in design flexibility, compactness, electrical control, and integration feasibility (thus enabling mass production). The major advantages of this micromachined separator come from simplification of separation steps, ease of device handling, and low product cost, compared with the conventional hybrid separators, and illustrates the high potential of integrated micromagnetics in chemical and biological applications where the manipulation of small amounts of reagent are important.

PRINCIPLE OF MAGNETIC SEPARATIONS

There are generally two types of magnetic separations. First, the material to be separated is intrinsically magnetic, which is usually used for biological particles such as red blood cells [9] or magnetic bacteria [10]. Second, by the attachment of a magnetically responsive entity, one or more components to be separated have been rendered magnetic. This latter technique is useful for otherwise nonmagnetic chemical and biological systems. In such systems, magnetic separations generally are performed through conferring magnetism upon a non-magnetic molecule (e.g., the molecule is absorbed or attached to a magnetically responsive particle). The magnetic particles used in the separation are normally very small ferromagnetic materials (0.1-1.3 μm in diameter); these particles are small enough that they may be unable to support magnetic domains. Such particles are classed as superparamagnetic materials which have high magnetic susceptibilities and saturation magnetization but a very weak magnetic hysteresis [11]. Such particles become magnetic dipoles when placed in a magnetic field but lose their magnetism when the field is turned off. Hence, individual particles can be readily removed or resuspended after exposure in a magnetic field since no permanent magnetic dipoles can be sustained in these particles.

The force on a particle [1] which can be generated magnetically is described as

$$F_x = V \chi_v \vec{H} \frac{\partial \vec{H}}{\partial x}, \qquad (1)$$

where F_x is the force on the particle in direction x, V is the volume of the particle, χ_v is its magnetic susceptibility per unit volume, $\vec{H}$ is the strength of the magnetic field, and $\frac{\partial \vec{H}}{\partial x}$ is the magnetic field gradient. In Equation 1, the shape of particle is assumed to be spherical and interactions between magnetic particles are not considered. As indicated in Equation 1, the force on a particle is proportional to V, χ_v, $\vec{H}$, and $\frac{\partial \vec{H}}{\partial x}$. In order to achieve a high attraction force on the particles, $\vec{H}$ and $\frac{\partial \vec{H}}{\partial x}$ are controllable parameters by optimizing the geometry of separators in design.

MAGNETIC PARTICLE SEPARATOR DESIGN

To realize a separator on a silicon wafer in a planar integrated shape, all the functions of the hybrid components used in the conventional separator should be integrated together on the substrate. Thin film electromagnets with integrated coils have been used in place of the permanent magnets and a flow channel to guide the magnetic fluid suspension has been introduced in place of the vessel containing the fluid. The integrated device concept is shown in Figure 3, where two integrated inductive components are placed between the flow channel which is used to guide magnetic fluid. In this separator, suspended magnetic particles are subjected to the magnetic fields (generated by the integrated inductive components) and field gradients (generated from the component pole geometries) and thus forced to move from the suspension to the surface of electromagnetic poles while the magnetic field is on in accordance with Equation 1. The collected particles on the surface of the poles can be released by removing the current excitation of the electromagnets.

As indicated in Equation 1, the magnetic field strength $\vec{H}$ and the magnetic field gradient $\frac{\partial \vec{H}}{\partial x}$ are the only controllable factors in designing the separator to achieve a high force on the particles. From both factors, the achievable magnetic field strength $\vec{H}$ depends on the performance of the inductive component which is limited by the allowable size and planar fabrication processes. This device discussed here is designed to be implemented in an area of 2 mm x 3 mm. The achievable magnetic field strength is also strongly affected by the width of the flow channel, which is analogous to an air gap in magnetic circuits. From the point view of reluctance in the magnetic circuit, a narrower width of the channel would be preferred but it should have an appropriate width since the flow rate of a viscous magnetic fluid will be limited as the channel width

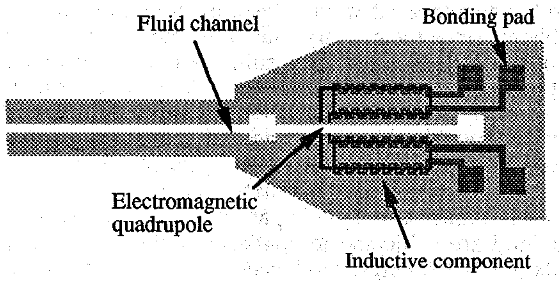
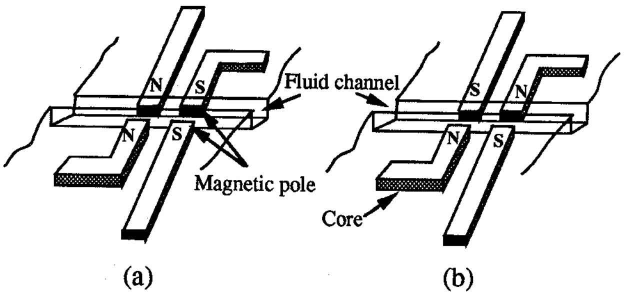


Figure 3. Schematic diagram of a micromachined magnetic particle separator using integrated inductive components.

is reduced [12-13]. Thus, in this device, the width of the flow channel is designed to be 100 um, which can allow an appropriate flow rate for the magnetic fluid to be used in this study, while a magnetic flux density of 0.03 Tesla can be achieved in the air gap by flowing 500 mA of DC current through the coil conductors.

In contrast to the conventional separator, the magnetic core in this device has a shape of a bar and the electromagnet poles located at the end of the core are almost similar to the tip of a needle in shape. Thus, a high magnetic field gradient will be generated at the tip of the poles. In this small pole geometry, in order to achieve a high magnetic field gradient in the air gap, appropriate positioning and allocation of the poles is a dominant design consideration. An electromagnet quadrupole is adopted using two inductive components which are placed at both sides of the channel, and thus two combinations of quadrupoles can be produced flexibly by switching DC excitation polarities at the coils as shown in Figure 4. In order to achieve high magnetic field gradient at the tip of the poles, magnetic flux leakages should be prevented between cores which are placed in proximity to each other, ensuring that as much of the flux as possible is concentrated at the tip of the poles. For this purpose, a magnetic shield layer as shown in Figure 5 is introduced, which reduces the flux leakage at the cores and maximizes the flux at the pole tips.



(a) (b)

Figure 4. Two different quadrupoles which are generated by using different DC excitations in coils: (a) N-N-S-S pole combination; (b) N-S-N-S pole combination.

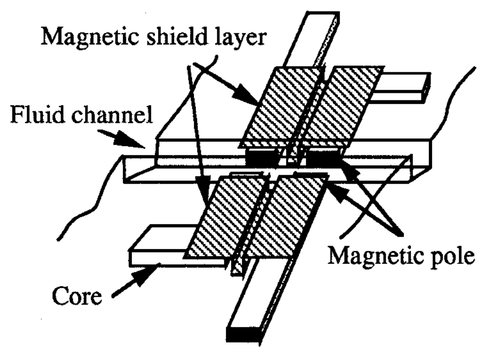


Figure 5. Schematic diagram of quadrupole with a magnetic shield layer.

FABRICATION

A meander-type integrated inductive component [7-8] was fabricated using a polyimide multilevel metal interconnection technique [14], in which an electroplated high permeability Ni(81%)-Fe(19%) permalloy was used as the magnetic material. A brief fabrication process of this separator is shown in Figure 6. The process started with 2-inch <100> silicon wafers as a substrate, onto which 0.3 μm of PECVD silicon nitride was deposited. Onto this substrate, titanium (1000 Å) / copper (2000 Å) / chromium (700 Å) layers were deposited using electron-beam evaporation to form both a seed layer for electroplating and a bottom layer for the flow channel. Polyimide (Dupont PI-2611) was then spun on the wafer in multiple coats to build electroplating molds for the bottom magnetic core. After the deposition of all coats, the polyimide was cured at 300 °C for 1 hour in nitrogen, yielding an after-cure thickness of 40 μm. Holes which contained bottom magnetic cores were etched in this polyimide using a 100 % O_2 plasma etch and an aluminum hard mask until the titanium/copper/chrome seed layer was exposed. The electroplating molds were then filled with Ni(81%)-Fe(19%) permalloy using standard electroplating techniques [15-16]. To build a magnetic shield layer, a shield trench was made around at the quadrupole region using the same dry-etch process described earlier. A DC-sputtered titanium (500 Å) layer was deposited and then patterned over the region which requires the magnetic shield. In order to insulate the bottom magnetic core and the shield layer from the conductor coil, polyimide was spin-coated (as above) and hard-cured at 300 °C for 1 hour. To construct a thick planar meander conductor coil, copper was plated on a chromium (500 Å) / copper (2000 Å) / chromium (700 Å) seed layer through a thick photoresist mold, in which a 70 μm wide copper plating mold was formed in 8 μm thick positive photoresist. The copper conductors were plated through the defined molds using standard electroplating techniques [14]. Upon completion of the electroplating, the photoresist was removed with acetone, and the copper seed layer was etched in a sulfuric-acid-based copper etching solution.

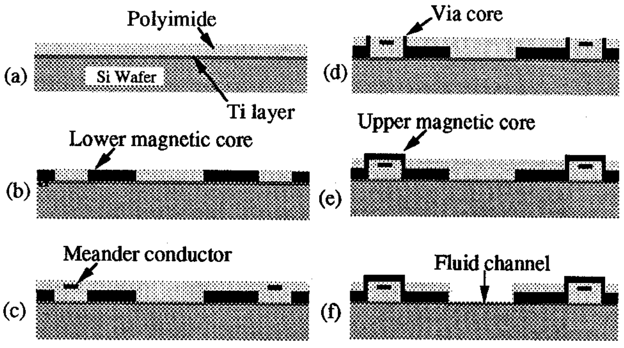


Figure 6. Fabrication steps of the micromachined separator: (a) polyimide deposition; (b) plating lower core and magnetic shield layer deposition; (c) conductor deposition; (d) plating magnetic vias (e) plating upper core; (f) dry etching fluid channel.

One coat of polyimide approximately 10 μm in thickness was deposited for conductor insulation and cured as described above. Via holes were dry-etched through the polyimide layer between the meander conductors using 100% oxygen plasma and an aluminum hard mask. The vias were filled with nickel-iron permalloy using the electroplating bath and conditions described previously. After completing the via electroplating, top magnetic cores were processed on the same level using the same process used for conductor plating with thick positive photoresist. Upon completion of the top core electroplating, the photoresist and seed layer were removed. The final thickness of the device relative to the substrate was approximately 90 μm.

Finally, fluid flow channel and bonding pads were opened in the polyimide layers by using the via etch process sequence described above. To remove the copper / chrome layer located on the bottom of the channel, the structure was dry etched to the bottom achieving 90 μm of channel depth, and the copper/chrome layer was then selectively wet etched. A bright titanium layer, which can be served as a mirror to verify or to monitor separation process, is thereby exposed on the bottom of the channel. Figures 7 and 8 show a photomicrograph and a scanning electron micrograph of the fabricated magnetic particle separator respectively, which has a size of 2 mm x 3 mm.

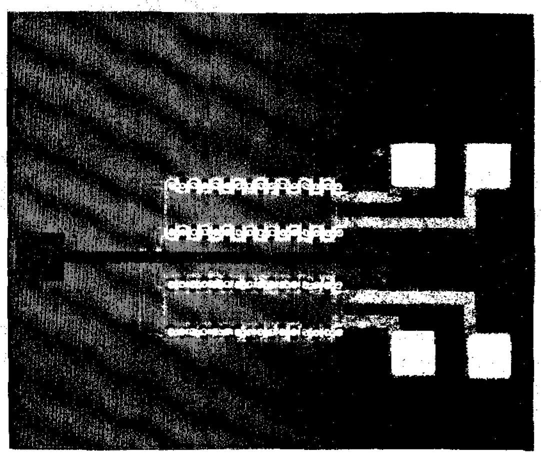
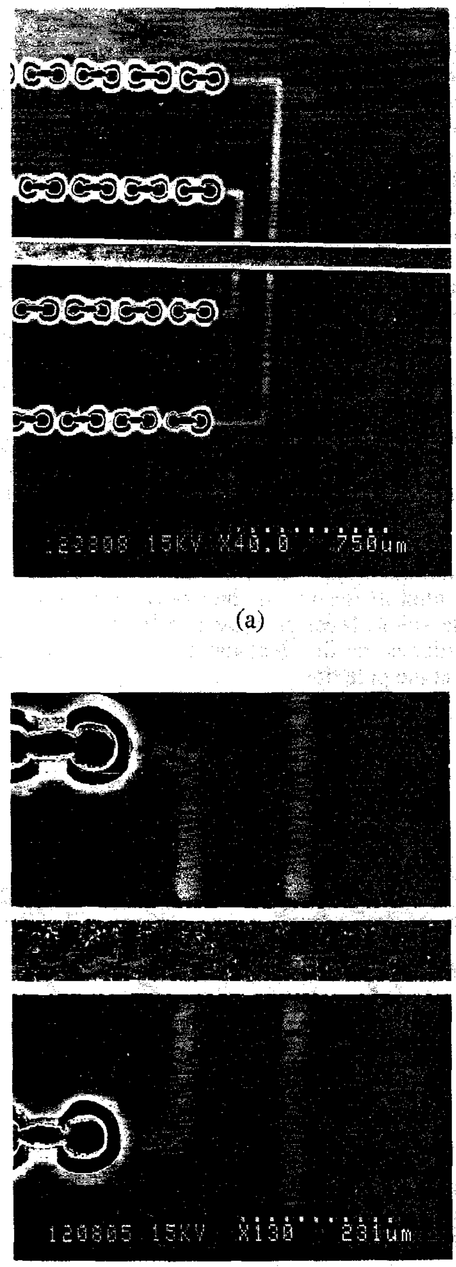


Figure 7. Photomicrograph of the fabricated magnetic particle separator.



(a)

(b)

Figure 8. Scanning electron micrograph of the micromachined particle separator: (a) overview; (b) quadrupole area.

EXPERIMENTAL RESULTS AND DISCUSSION

The magnetic particles used in this experiment are commercially available superparamagnetic particles (Estapor carboxylate-modified superparamagnetic particles, Bangs Laboratories, Inc.) which are supplied as a aqueous dispersion with 60 % solid content of magnetite. This magnetic particle consists of a ferrite crystal (Fe_2O_3, magnetite) with median diameters of 0.8 μm -1.3 μm. The magnetic particle density is 2.2 g/ml. The particles are surrounded by the usual polystyrene and carboxylic acid modified shell to isolate iron from the surface, so that they can be used for adsorption as well as covalent attachment.

Separation tests can be performed either by flowing a suspension through the channel or by dipping the quadruple of the separator into the suspension. It was mentioned above that the major advantages of this separator come from a simplicity of separation steps and a ease of device handling as compared with the conventional hybrid separator in Figure 2. As described in Figure 9, the conventional separator requires at least five test steps; however, the

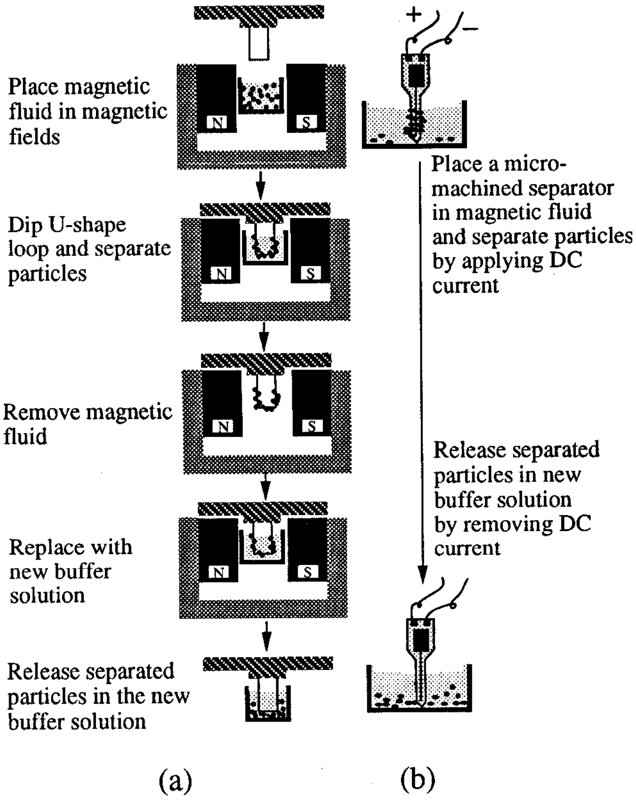


Figure 9. Separation steps: (a) conventional separator; (b) micromachined separator.

micromachined separator just requires two simple steps to achieve the separation.

In this study, the magnetic fluid is placed in a syringe for handling convenience. To begin the experiment, several drops of fluid are applied to the reservoir resulting in fluid flow through the channel. With no current applied to the coils (i.e., without a magnetic field), no significant sedimentation or attachment of dispersed particles on the poles occurs even over a time span of several hours. An initial movement of magnetic particles is observed through a microscope when the DC current in coils reaches 100 mA. To achieve a magnetic flux density of 0.03 Tesla at the air gap, it is estimated that the applied coil current should be at least 500 mA. When 0.8 V of DC voltage is applied to each inductor, resulting in a current flow of 500 mA, the particles move rapidly toward the quadrupole, separate from the buffer solution, and clumped on the poles. Upon removal of the current, the particles are immediately redispersed or removed from the poles without clumping.

As shown in Figure 4, two different combinations of electromagnet quadrupole can be produced by changing the polarities of the DC excitation in the coils. The effect of the magnetic polarity on the separation was qualitatively assessed by applying 500 mA of DC current to each inductor for 10 seconds for both magnetic polarities. The results of this experiment are shown in Figure 10, where the separated particles on the poles of polarity N-N-S-S and N-S-N-S quadrupole (clockwise in series) are shown. From Figure 10, it is qualitatively observed that the magnetic particles are attracted more strongly from the N-N-S-S pole combination than the N-S-N-S combination, which may be due to a stronger magnetic field gradient attained from the N-N-S-S pole combination because of differing magnetic flux paths.

The inductance of a inductor usually varies as the reluctance of the magnetic path is varied. As particles are clumped on the poles, the reluctance in the air gap between poles will vary, resulting in a change in the inductance of the drive component. If this inductance variation as a function of separation time and current can be detected, the amount of separated particles may be approximately evaluated from the inductor geometry and the magnetic properties of the particles. This in-situ evaluation of particle separation efficiency is currently under development.

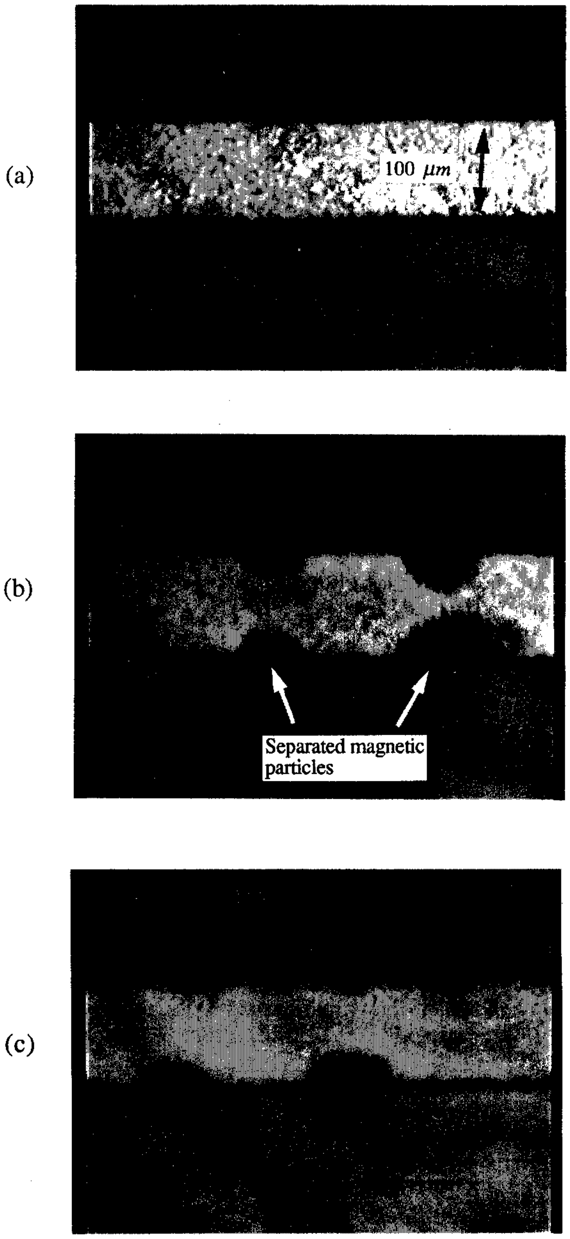


Figure 10. Magnetic particles which are collected on the edges of magnetic electrodes: (a) before applying current; (b) 10 seconds after applying current at N-N-S-S quadrupoles ; (c) 10 seconds after applying current at N-S-N-S quadrupoles. The magnetic particle size is approximately 0.8 -1.3 μm and the width of channel is 100 μm.

CONCLUSIONS

A micromachined magnetic particle manipulator which can be used to influence magnetic particles suspended in liquid solutions has been realized on a silicon wafer. A meander-type integrated inductor with fully integrated and insulated coils has been used as a basic component for the manipulator electromagnet. One potential application of this manipulator is magnetic particle separation from solution. When 500 mA of current with a drive voltage less than 1 (V) is applied to each inductor, very fast particle separation is observed. The magnetic particles clumped on the surface of electromagnet poles can be released and resuspended easily by removing the applied current. This separator can be repeatedly used for different separations after washing using acetone- and methanol-based cleaning steps. This prototype device illustrates the high potential of integrated micromagnetics in chemical and biological applications where the manipulation of small amounts of reagent are important.

ACKNOWLEDGEMENT

This work was supported in part by the National Science Foundation under grant ECS-9117074. Microfabrication was carried out at the Microelectronics Research Center (MiRC) of the Georgia Institute of Technology. Valuable technical discussions with Professor Shyam Sumerermarili of Princeton University and Dr. William Trimmer of Belle Meade Research are gratefully acknowledged. The authors would also like to acknowledge DuPont and OCG Microelectronic Materials for their donations of polyimide and Lake Shore Cryotronics, Inc. for their assistance in measurements of the magnetic properties of permalloy thin films.

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