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Simultaneous magnetic particles washing and concentration in a microfluidic channel

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Abstract

Purification of magnetic microparticles was demonstrated, with a purification efficiency of (72±14) % at a flow rate of 3 µl/min, in a microfluidic chip using a rotational magnetic system under continuous flow conditions. The rotation of a periodically arranged magnetic assembly close to a fluidic channel carrying magnetic particles suspension allows the trapping and releasing of particles in periodical manner, leaving other particles to be discarded in the waste. Each trapping and releasing event resembles one washing cycle in a conventional biological assay.

Keyword: magnetic separation, purification, washing, microfluidic

1. Introduction

The use of functionalized magnetic nano/micro particles as solid phase carriers for bio-analytical targets has received increasing interest [1-2], since they can be coated with a selected ligand against the target of interest and they can be remotely manipulated thanks to their superparamagnetic properties.

In a typical immunomagnetic assay, the functionalized magnetic particles are mixed with the sample to capture the target analyte. Then the beads-analyte complex is separated from the solution using a magnet and subsequently washed in a buffer solution.

Microfluidic-based magnetic separation has been demonstrated utilizing external permanent magnets [3-4], integrated magnetic posts [5-6] or integrated micro-electromagnets [7-8]. However, these devices and/or processes still have a major drawback: the capture of the magnetic particles is occurring only at the walls of reservoirs in a static trapping mode. In consequence, a relatively large single aggregate is formed with a considerable presence of impurities due to the physical trapping of unwanted particulates within the cluster. Current devices, such as those cited above, do not provide any means for washing the analyte obtained during the extraction process. Therefore, it is necessary to carry out subsequent washing steps before the analyte can be analyzed further to eliminate false positive results. To do so, the sample is typically transferred into another vessel and washed in a new buffer solution. Carrying out subsequent washing steps enhances the risk that quantities of analyte may be lost during transfers between different containers. In the case of a low concentration of analyte in the starting sample, washing steps may cause a sharp decrease of the analyte concentration such that it may become undetectable. In this paper we report a miniaturized and continuous flow magnetic separation system for sample washing and concentration in a close-loop protocol that minimizes the human interference, sample loss and cross-contamination efects.

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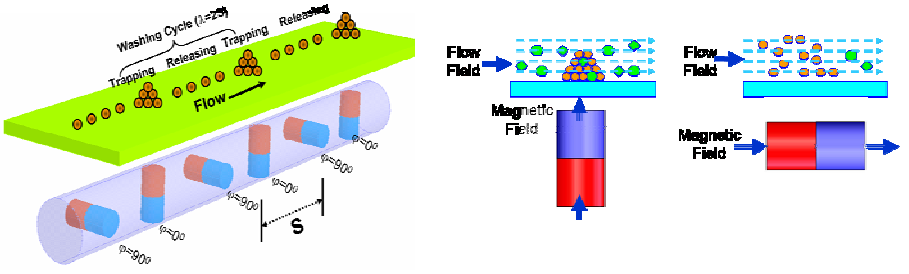
2. Simultaneous trapping and releasing mechanism

The present purification approach is based on the concept of simultaneous trapping and releasing of a magnetic particle suspension under continuous flow conditions. The trapping and releasing is achieved by employing a set of permanent magnets (magnetic assembly) rotating under a fluidic channel carrying the magnetic particle suspension, as shown in Fig. 1a. The magnetic assembly is constructed from a number of permanent magnets that are embedded in a non-magnetic cylindrical carrier (magnet carrier) in a periodical arrangement such that each magnet is perpendicular to the next one. When the magnetic assembly rotates, the magnetic force on a magnetic particle would be modulated accordingly (Fig. 1b and c). When the magnet pole is pointing at the fluidic channel surface the magnetic particles are attracted and trapped in a steep magnetic potential well. The magnetic force decreases steadily when the magnet assembly rotates. At a rotation angle of 90^0 the magnetic force becomes very weak, hence magnetic particles demagnetize, disperse and flow downstream. The continuous rotation of the magnet assembly transforms into a continuous series of trapping and releasing events. The simultanuous flow of buffer allows continuous washing of the magnetic particle suspension. If the magnet assembly is made of N magnets, at a given time, there will be N/2 active trapping zones that are frequently activated. Therefore, magnetic particles would be trapped at these zones for a residence time of $t = 1/f$, where f is the frequency of the magnet assembly rotation.



(a) (b) (c)

***Figure 1**: (a) Schematic view of the simultaneous trapping and releasing mechanism. Magnetic particles are trapped in the channel when the magnet points at the channel (b) and released when the magnet rotates 90° i.e. the pole is perpendicular to the channel surface (c).*

: Magnetic particle

: Impurities

Each cycle of trapping and releasing of particles represents a washing event similar to the washing process of biological samples using a pipette. The transition time between the trapping and releasing events allows the particles to be detached from each other and consequently allows releasing any impurity that may have been trapped previously. To further purify the sample, the washing cycle is repeated along the fluidic channel for several cycles.

Fig. 2 shows the simulated magnetic force due to the rotation of the magnetic system for three magnets in series. The peaks show the locations where the magnet pole points at the channel ($\varphi=0^o$) and magnetic particles are subjected to a strong magnetic force (F_{mag}). The flat portion of the curves shows the location where the pole is pointing away from the channel ($\varphi=90^o$) and the magnetic force is not strong enough to trap the particles, hence particles are released and flow downstream with the carrying fluid. The magnetic force required to trap a particle of volume V is given by: $F_{mag} = \frac{V\chi}{2\mu_0}\nabla B^2$, where χ is the magnetic susceptibility of the particle, μ_o is the permeability of space and B is the magnetic flux density produced by the magnet. In addition to the magnetic force, a magnetic particle of radius R experiences mainly a hydrodynamic drag force: $F_d = 6\pi\eta R\left(v_p - v_{medium}\right)$, where η, v_p, v_{medium}, are the medium viscosity, particle velocity and medium velocity, respectively. Under conditions typical for the trapping of a magnetic bead $\eta \cong 10^{-3}$ Nsm^{-2}, $R = 10^{-6}$ m, and $v \approx 10^{-4}$ m/s, resulting in a typical drag force $F_d \approx 1.88\times10^{-12}$ N.

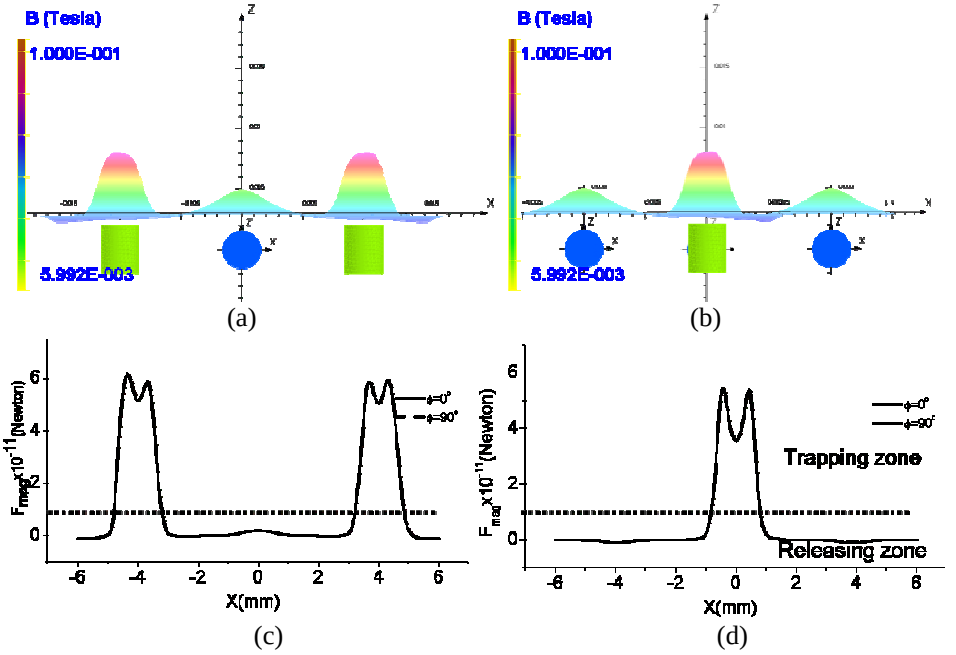


Figure 2: *Simulated magnetic flux density (a) and (b) and force (c) and (d) for a three-magnet configuration with each having a 90° orientation angle with the previous/next one. The magnet with an orientation angle of φ=0°generate a magnetic force within the range of force required to trap the magnetic particles inside the channel, while the magnet with an orientation angle of φ=90° ° generates a very weak magnetic force that is not sufficient to trap the particles.*

3. Experimental methods

Fig.3 shows a schematic view and image of the fabricated magnetic separation system, where 24 neodymium-iron-boron (*NdFeB*) magnets with diameter of 2 mm and 4 mm length are embedded in a cylindrical Teflon rod (magnet carrier) with a diameter of 4 mm and length of 150 mm. The magnets have been arranged in the magnet carrier with each magnet's long axis perpendicular to the next one and with a spacing between each two adjacent magnets of 10 mm. Each magnet carrier carries 8 magnets in an alternative polar orientation and 3 magnet carriers are arranged along a meander-shaped microfluidic channel made of polydimethylsiloxane (PDMS) using the soft lithography technique. The diameter of the channel is 200 μm with a total length of 120 mm. Therefore, sample traveling through the meander channel passes through 12 washing events.

The magnet carriers are inserted beneath the fluidic channel resulting in a total separation distance between the magnets and the inner surface of the fluidic channel (at φ=0° mode) of 1.5 mm, which ensures sufficient magnetic force on the magnetic particle suspension. The magnet carriers are joined together at one end by a set of gears and actuated by a stepper motor of which the rotation frequency and angle can be adjusted. It should be noted that the magnet assembly can selectively comprise a variable number of magnet carriers and that the number of washing cycles is determined by the number of magnets in the magnetic assembly. The purification efficiency (PE) was measured by counting the number magnetic particles and non-magnetic particles *Q* (acting as impurities) both before and after the sample processing in the chip and comparing the two counts according to the following formula: $PE(\%) = \left(1 - \frac{Q_2 - q}{Q_1}\right) \times 100\%$. Where, Q_1 is the number of the non-magnetic particles in the sample before the injection into the chip, Q_2 is the number of non-magnetic particles in the waste sample and *q* is the number of non-magnetic particles lost in the system during the sample flow which measured independently.

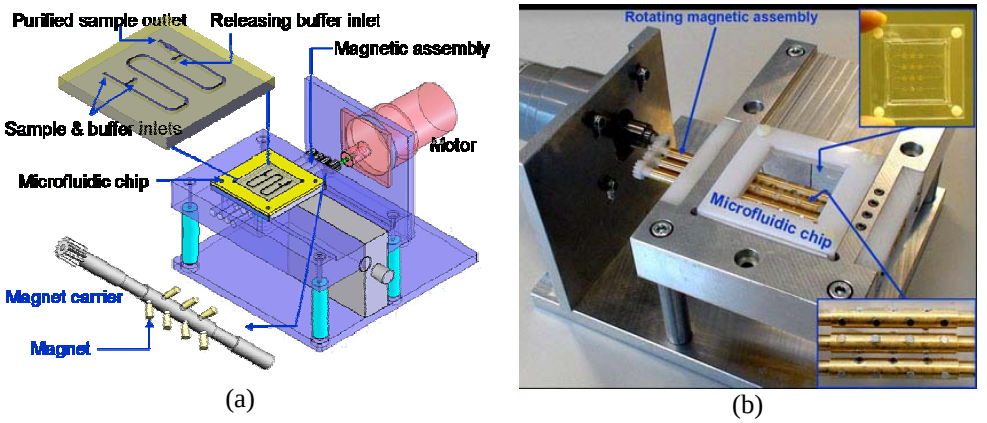


Figure 3: *(a) Assembly view of the magnetic separation system with the chip and magnet carrier shown in the insets (top and bottom); (b) an image of the system. The magnet-assembly rotates by employing a stepper motor. The fluidic channel within the chip is aligned along the magnetic assembly.*

4. Results and Discussion

Fig. 4 shows the purification efficiency obtained through the system with a maximum of (72.60±14) % at a flow rate of 3 µl/min. To investigate the effect of trapping and releasing events (washing cycles) on the purification efficiency the same experiments have been conducted by using various numbers of magnets within the magnetic assembly by including 1, 2 or 3 magnet carriers within the magnetic assembly and by re-introducing the sample into the system for a second run. For example, when one magnet carrier is used, the sample would go through 4 washing cycles and when the sample passes through the system twice using 3 magnet carriers, each time a total number of 24 washing cycles can be achieved. Fig. 5 shows that the purification efficiency simply increases with the number of washing cycles.

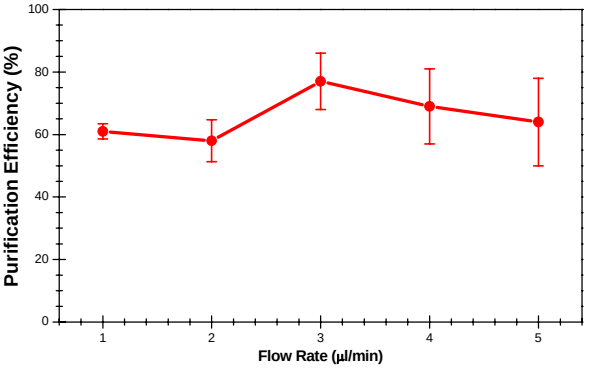


Figure 4: Purification efficiency of the system measured for different flow rates.

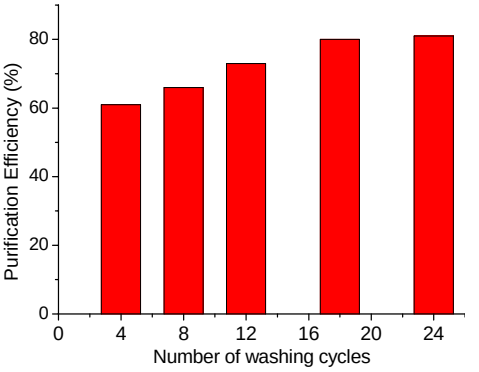


Figure 5: The purification efficiency increases with the number of washing cycles.

5. Conclusions

Purification of magnetic microparticles was demonstrated, with a purification efficiency of (72±14) % at a flow rate of 3 µl/min. In general, the methodology and results obtained from this work demonstrates the feasibility of implementing sample purification in a close-loop protocol that minimizes the human interference, sample loss and cross-contamination. It represents a step forward towards a fully automated sample preparation system.

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