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On-chip bio-analyte detection utilizing the velocity of magnetic microparticles in a fluid

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A biosensing principle utilizing the motion of suspended magnetic microparticles in a microfluidic system is presented. The system utilizes the innovative concept of the velocity dependence of magnetic microparticles (MPs) due to their volumetric change when analyte is attached to their surface via antibody–antigen binding. When the magnetic microparticles are attracted by a magnetic field within a microfluidic channel their velocity depends on the presence of analyte. Specifically, their velocity decreases drastically when the magnetic microparticles are covered by (nonmagnetic) analyte (LMPs) due to the increased drag force in the opposite direction to that of the magnetic force. Experiments were carried out as a proof of concept. A promising 52% decrease in the velocity of the LMPs in comparison to that of the MPs was measured when both of them were accelerated inside a microfluidic channel using an external permanent magnet. The presented biosensing methodology offers a compact and integrated solution for a new kind of on-chip analysis with potentially high sensitivity and shorter acquisition time than conventional laboratory based systems. © *2011 American Institute of Physics*. [doi:10.1063/1.3556952]

I. INTRODUCTION

In recent years there is a fast growing demand in biomedical diagnostics for integrated, portable solutions, which can operate outside a laboratory environment. This is due to the need for point-of-care devices, cost reduction, shorter acquisition time, minimization of human intervention, and requirement for smaller sample amounts.[1–3] The impressive advances in microtechnology and biotechnology enable the integration of a variety of analytical functions on a single chip. Analytical microfluidic systems can be fabricated at low costs, are easily disposable, and generally provide quick and reliable measurements from small volumes of fluids. Additionally, many research groups worldwide have reported on bioanalytical methods utilizing magnetic microparticles.[4–8] The merits of these microparticles are (1) the possibility of manipulating them inside microfluidic channels by utilizing high gradient magnetic fields,[9–11] (2) detection by integrated microsensors, and (3) flexibility due to functionalization by means of surface modification and specific binding. Techniques employing magnetism in biomedicine are amenable to automation and miniaturization.

The motivation of this research is to realize a compact and cost-effective biosensing device for a broad range of biochemical samples. A novel concept is presented, which exploits the advantages of magnetic microparticles for the qualitative detection of analyte, e.g., pathogens. Experiments for the proof of concept are reported and discussed.

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II. EXPERIMENTAL

A. Working principle

In the proposed system magnetic microparticles (MPs), having a volume V, are coated with the ligands of specific affinity to the (nonmagnetic) analyte to be detected and are mixed with the sample fluid under investigation in a microfluidic channel.[12] If analyte is present in the fluid it binds to the coated MPs forming loaded magnetic microparticle compounds (LMPs). These are compounds with total volume V' [see Figs. 1(a) and 1(b)]. Upon the application of an external magnetic field, MPs and LMPs experience the same attractive forces but will accelerate to different velocities due to the difference in volume; the drag force increasing in the opposite direction to that of the magnetic force. Therefore, the difference of the velocities determines the presence of analyte in the fluid under examination. The discrimination method is based on the fact that the LMPs need more time to travel a certain distance than MPs.

As a proof of concept COMPEL superparamagnetic microparticles coated with streptavidin (~6.2 μm in diameter) and nonmagnetic polystyrene microparticles coated with biotin (~0.97 μm in diameter) were utilized and purchased from Polysciences Europe GmbH and Bangs Laboratories, Inc. The streptavidin coated MPs which were suspended in PBS (phosphate buffered saline, pH 7.2), and the biotin coated polystyrene microparticles were gently mixed at room temperature to form LMPs (~8.2 μm in diameter) (see Fig. 2). Both LMPs and MPs were suspended in PBS containing 1% (w/v) BSA (bovine serum albumin, to reduce particle channel–surface interactions) and were introduced into the microfluidic

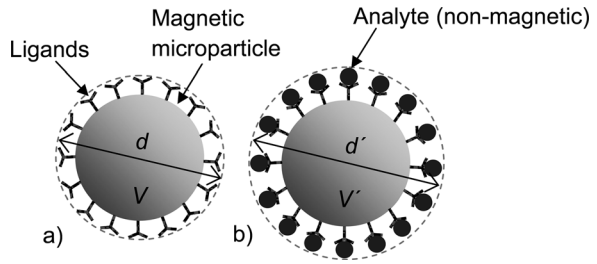

FIG. 1. (a) Magnetic microparticle coated with ligands having an aggregate diameter d and a volume V and (b) magnetic microparticle coated with ligands and attached analyte of total diameter d' and total volume V'.

channel. The MPs and LMPs were accelerated using a permanent magnet. The time it took for the LMPs and MPs to cover a distance of 95 μm was measured using an optical microscope and a semiautomatic stopwatch computer program.

B. Microfluidic device

The microfluidic device that was utilized for the experiments consisted of two sandwiched calcium-fluoride (CaF_2) wafers, each one with a thickness of 1 mm. Three microfluidic channels were fabricated from SU-8 in between the CaF_2 wafers using a fabrication procedure as found in.[13] The height of the channels was 23 μm and the channel volume was approximately 0.2 μl. A photograph of the device is shown in Fig. 3. The inlet and outlet holes, which were positioned on each side of the channel, were used to fill the device with the sample fluid. In order to prevent evaporation the holes were sealed with PDMS (poly-dimethyl-siloxane) strips which stick to the CaF_2 surface. The fabricated microfluidic channels were cleaned with ethanol prior to the introduction of the LMPs and the plain MPs.

C. Instrumentation

Experiments were carried out in order to measure the velocity decrease due to the volumetric increase of the MPs. LMPs and plain MPs were suspended in PBS containing 1% (w/v) BSA. Then this solution was introduced from the inlet

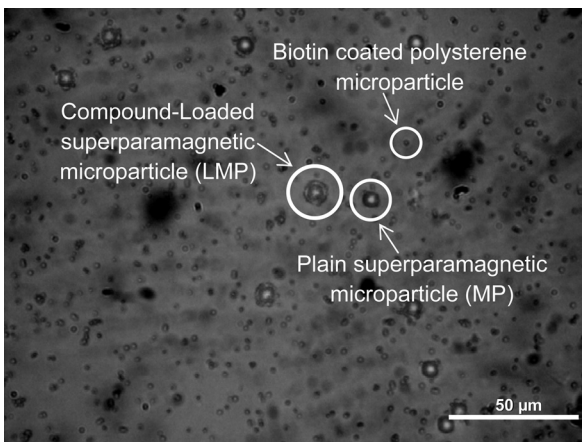

FIG. 2. Microscopic image of the plain superparamagnetic microparticles with a diameter of ~6.2 μm (MP), polystyrene microparticles coated with biotin with a diameter of ~0.97 μm and streptavidin coated, superparamagnetic microparticles with biotin coated, polystyrene microparticles attached with a total diameter of ~8.2 μm (LMPs).

FIG. 3. (Color online) Photograph of the microfluidic device with three different microfluidic channels, one of which was utilized for the experiments.

into the microfluidic channel using a syringe. The MPs and LMPs were accelerated using a NdFeB permanent magnet of $5 \times 5 \times 1$ mm^3. The magnet was positioned 2 mm apart from the microchannel, near the outlet. The movement of the microparticles was captured by a Samsung VP-HMX20C camcorder mounted on a Carl Zeiss Axiotron Microscope.

III. RESULTS AND DISCUSSION

Analytical calculations regarding the experiments were carried out. Specifically, the magnetic force F_{mag} acting on a single microparticle, approximated by a pointlike magnetic dipole with a magnetic moment m is proportional to the magnetic flux density B. In the case of a superparamagnetic microparticle this force is given by Eq. (1), assuming the magnetic susceptibility of the surrounding medium is zero

$$\vec{F}_{\text{mag}} = \frac{V\chi}{2\mu_0}\vec{\nabla}\vec{B}^2 \tag{1}$$

Thereby, V is the volume of the magnetic microparticle, χ is the susceptibility of the microparticle, and μ_0 is the permeability in vacuum. The hydrodynamic drag force acting on the MP is proportional to the radius of the microparticle and a consequence of the velocity difference Δu between the magnetic microparticle and the fluid. In the presented case the fluid is static; therefore, Δu is equal to the velocity of the microparticle u_p. For a spherical particle with radius r it is

$$\vec{F}_d = 6\pi\eta r u_p \tag{2}$$

where η is the viscocity of the surrounding sample fluid. By equating Eqs. (1) and (2), one can determine the particle velocity that can be generated by a magnetic force in a surrounding static fluid. Analyte attaching to the MP will form an enclosing layer and increase the radius to $r' \approx r + 2r_p$, where r_p is the radius of the analyte [see Figs. 1(a) and 1(b)]. This increase will only have an influence on Eq. (2) and thus the velocity will be given by

$$u_p = \frac{r^3\chi}{9\mu_0\eta r}\vec{\nabla}\vec{B}^2 \tag{3}$$

These calculations yielded ~25% decrease in the velocity of the LMPs

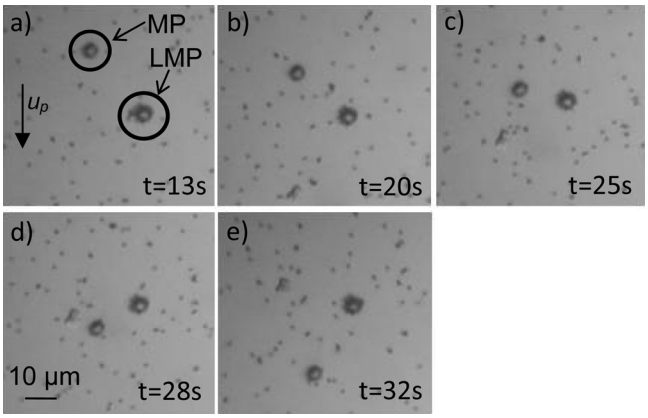

FIG. 4. Optical microscopic images of a typical measurement of the movement of the plain MPs and the LMPs inside the microfluidic channel when accelerated by an external magnetic field at (a) 13 s, (b) 20 s, (c) 25 s, (d) 28 s, and (e) 32 s.

During the experiments several movies were obtained in order to investigate the movement of LMPs in comparison to the movement of the MPs during their acceleration by the external magnetic field. Figure 4 is a sequence of optical microscope images of a typical measurement, at different time intervals, showing the movement of an MP and an LMP toward the externally applied field. The sequence clearly shows that the LMP is traveling at lower speed than the MP. After comparing the movement of five different pairs of LMPs and MPs over a distance of 95 μm, the velocity u_p of the LMPs was calculated with Eq. (4)

$$u_p = \frac{d}{t}, \tag{4}$$

where d is the distance covered by the MPs and LMPs while accelerated by the external magnetic field and t is the time they required to cover that distance. On average, LMPs were found to be ~52% slower (SD 7.5%) than MPs.

The difference between the analytical calculations and the experimental results is due to several reasons. First of all, the sample liquid contained several biotin coated polysterene microparticles which were not attached to the streptavidin coated MPs because they could not be completely removed. As it could be observed, the movement of some LMPs was sometimes slowed down due to collisions with the polysterene microparticles. As a consequence, this yielded an additional decrease in their velocity, which has not been considered in the model and can be avoided by removing the remaining biotin coated microparticles from the liquid. Moreover, additional forces such as inertia and gravitational sedimentation also have an influence in the particle velocity. Other forces that affect the movement of particles inside a microfluidic channel are the buoyancy force and the Magnus force, which is a lift force due to particle rotation.[14] Even though such forces are usually considered negligible in microfluidics the fact that the size of the microparticles is in the range of a few micrometers could have caused such phenomena to become relevant.

The proposed method offers a simple solution for the detection of analyte, with potentially high sensitivity, in comparison to other methods where the shift in the frequency-dependent magnetic susceptibility of magnetic particles suspended in a fluid is utilized.[9] In the presented system what is measured is the time that the LMPs and MPs need in order to travel a certain distance. Thus, the difference in their velocities is calculated.

IV. CONCLUSION

In conclusion, the innovative concept of the velocity decrease of magnetic microparticles, which are attracted toward a magnetic field when their volume increases due to an analytical load, was experimentally proven. Experiments utilizing different pathogens are planned. The possibility of using magnetic sensors for the detection of the movement of the magnetic microparticles is currently being investigated as well as the design of an integrated solution for the application of the magnetic field.

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