

Microfluidic Assembly of Magnetic Hydrogel Particles with Uniformly Anisotropic Structure

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Functional gel particles produced through the incorporation of an inorganic material are used in a wide range of applications^[1] ranging from cosmetics^[2] to optics^[3,4] and biotechnology.^[5,6] Such particles with uniform morphologies are desirable because of their consistent and reproducible behavior. Particularly, micro-particles consisting of magnetic materials encapsulated in a polymer matrix are of great interest in drug delivery,^[7] image enhancement,^[8] hyperthermia,^[9] sorting, separation,^[10] and immunoassays^[11] due to their ability to be manipulated remotely. Due to the sensitive response to an external field and its gradients, and bio-comparability, magnetic gel particles with anisotropic features are attractive in many domains of technology, such as electronic paper,^[4] rheological probe,^[12–14] and biomedical applications.^[15–18]

Various polymerization methods, including microemulsions and suspension polymerization, were established and implemented to synthesize both polymeric and composite particles.^[19–21] However, these bulk methods do not offer control of particle morphology to achieve uniform distributions of inorganic inclusions in the polymer network, especially for magnetic materials. To generate particles with various controlled morphologies, several chemical methods were developed, based on manipulation of growth and nucleation of molecular species during precipitation, or the template-assisted manipulation of spherical particles.^[22–25] However, these techniques impose limitations on size and morphology, as well as material selection, due to the requirements for the initial particle formation. Thus, fabrication of anisotropic magnetic gel particles with uniform anisotropic features requires new techniques.

Microfluidic devices provide an alternative technique for the generation of monodisperse droplets by coflowing two

immiscible fluids to induce the drop formation. Many studies have successfully demonstrated microfluidic synthesis of microgels, polymeric particles, and composite particles for different purposes.^[12,26–33] However, most of them focus on making particles with homogeneous internal structure. Very few studies have been reported in which a microfluidic device was used to produce anisotropic magnetic gel particles, apart from recent important work.^[1,12] Hwang et al.^[1] have demonstrated magnetic manipulation of their homogenous particles; however, the control of particle rotation was still lacking. Recently, poly(dimethylsiloxane) (PDMS) microfluidic double emulsion devices have provided a straightforward and robust approach to forming highly monodisperse double emulsion droplets.^[34–36] The double emulsions generated by PDMS drop makers can be functionalized to form composite gel particles with anisotropic inhomogeneous internal structure for advanced applications.^[34,37] The use of microfluidics techniques using double emulsion templates allows making hydrogel particles with uniform and well-defined anisotropic features.^[34]

In this paper, magnetic hydrogel particles with uniform anisotropic internal structure were produced by a flow focusing drop maker using double emulsions as templates. These particles provide excellent rotational control by applying an external field. Moreover, with the advantage of double emulsion core-shell structure, the inorganic magnetic inserts were fully covered by a biocompatible polymer network, which allows the particles to be used in biomedical applications.

Our device is made from a PDMS elastomer using soft-lithography methods. We coat the channels with a sol-gel layer that is functionalized with photoreactive silanes. This chemical treatment allows the wettability of the channels to be spatially patterned, and thus allows the formation of double emulsion droplets.^[35] The sol-gel mixture is prepared by combining tetraethylorthosilicate (TEOS) (0.2 mL), methyltriethoxysilane (MTES) (0.2 mL), (heptadecafluoro-1,1,2,2-tetrahydrodecyl) triethoxysilane (0.1 mL), photoinitiator-silane (0.2 mL), water adjusted with HCl (0.2 mL, pH 2), and methanol (2.6 mL). The PDMS channels are first treated with plasma to form silanol groups and are then immediately bonded to a glass slide. These channels are filled with the photoreactive sol-gel mixture. The device is then placed on a hotplate set to 225 °C, which results in evaporation of the solvent and curing of the sol-gel on the channel walls. The sol-gel is fluorinated by fluorosilanes and is, therefore, very hydrophobic by nature. To spatially pattern the wettability, we graft hydrophilic patches of polyacrylic acid onto the channels. To accomplish this, we fill the sol-gel coated channels with an aqueous monomer solution comprising acrylic acid (0.2 mL) with NaIO₄ water (0.8 mL, 5 mM), ethanol (1 mL),

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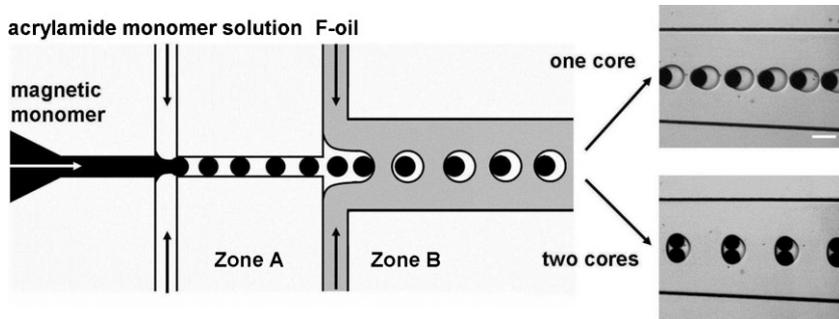


Figure 1. Scheme of the PDMS device for forming double emulsion droplets. The droplets consist of the hydrophobic monomer core with magnetic material (black) that is encapsulated by a hydrophilic monomer droplet (white) suspended in fluorocarbon oil (gray). By increasing the inner flow rate, two magnetic cores could be encapsulated in the droplets, which demonstrates excellent control of emulsion morphology by our devices. The scale bar for the two images corresponds to 50 μm .

and acetone (1 mL) containing 10% benzophenone by weight. To prepare the benzophenone solution, we dissolved benzophenone (0.1 g) in acetone (0.9 g). We expose the channels under a focused spot of UV light to control the location where polyacrylic acid is grafted to the channel walls, making them locally hydrophilic.

To form magnetic hydrogel particles with uniform anisotropic features, oil-water-oil double emulsion droplets were made from polymerizable monomer mixtures as templates. We graft polyacrylic acid to the region of the device between the first and second drop maker, making it hydrophilic; the default properties of the sol-gel make the rest of the device hydrophobic, as shown in Figure 1. Thus, in the first stage, the oil-dispersed monomer is encapsulated by the aqueous solution of monomer, which wets the hydrophilic walls, forming an oil-in-water single emulsion (zone A). The droplets then flow into the second drop maker, where the wettability is inverted. This causes the water to lift off the hydrophobic interface and become encapsulated by the fluorocarbon oil, forming the oil-water-oil double emulsions, zone B. All channels were 50 μm deep; the width of the A-channel was 20 μm , the B-channel was 120 μm . The volume flow rates for forming the double emulsions with one bead were optimized to 55 $\mu\text{L h}^{-1}$ for the inner flow rate; 50–75 $\mu\text{L h}^{-1}$ for the middle flow rate, and 850–1100 $\mu\text{L h}^{-1}$ for the outer flow rate. Two inner beads were encapsulated by one droplet by increasing the inner flow rate twice to about 110–140 $\mu\text{L h}^{-1}$, which offered different emulsion morphologies (see Figure 1).

The inner oil core drop was composed of styrene Reagentplus (Aldrich) (8 mL) with divinylbenzene (Aldrich) (2 mL), thermal initiator V-65B (0.2 g), as well as photoinitiator Darocur 1173 (0.2 g) all mixed with ferrofluid EFH1 (Ferrotec) (1 g). The outer hydrophilic shell of the double emulsion drop was made of acrylamide (Sigma) (10% w/w), *N,N'*-Methylenebisacrylamide (Fluka) (4% w/w), Darocur 1173 (Ciba) (2% w/w), and water (87%) with

surfactants, SDS (0.25%) and Tween 25 (0.25%). For the continuous phase we used fluorocarbon oil, HFE-7500 (3 M), with surfactant Krytox 157FSL (Dupont).

After collecting the resulting double emulsion in a container, there are two steps for the full polymerization. The aqueous hydrogel solution of the droplet shells was solidified by exposing to UV-light for 10 min.^[34] In this step it is important to maintain low UV intensity and continuous low-amplitude vibration of the emulsions to allow the forming of separate particles without linking them across. Polymerization of the hydrophobic ferrofluid was achieved by leaving the solutions under 60 °C over night for thermal crosslinking. One may wonder why we mixed two kinds of initiator in the organophilic monomer solution. In our experiments, the photo-initiator (Darocur) was

not able to activate the polymerization of styrene and divinylbenzene in the core region. However, the Darocur initiator happens to be soluble both by styrene and water. Therefore, the aim of adding the same concentration of this initiator to the inner core mixture was to prevent the styrene from absorbing it from the outer shell, causing the incomplete polymerization of the hydrogel shell.

Once polymerized, the magnetic gel particles were robust and could be washed, dried, and re-dispersed into water. The collected double emulsions in the fluorocarbon oil are shown in Figure 2a and b. The water monomer shell of the particles is immiscible with the fluorocarbon oil; hence, the hydro-gel particles adopt a spherical shape to minimize their surface energy, as shown in the magnified view of Figure 2a. By controlling the flow rates, the morphology of the particles could be designed. The particles with two cores collected in the fluorocarbon oil are shown in Figure 2b. Upon evaporating the volatile fluorocarbon oil and water, the particles become more compact and adopt an ovular shape with uniform anisotropic morphology, as shown in Figure 2c. The

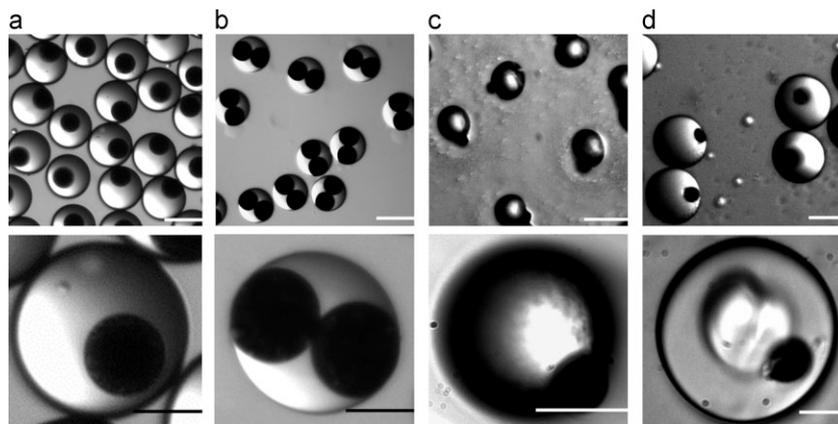


Figure 2. Optical microscopy images of magnetic gel particles with uniform anisotropic features. a) Particles with a single magnetic core, and b) with two magnetic cores, in fluorocarbon oil. c) Single-core particles dried, and d) re-dispersed in water. The images in the second row show magnified views of the same particles. The scale bar in the top row is 50 μm and in the bottom row is 20 μm .

magnified view clearly shows that the small beads on one side of the particles are the magnetic cores. When the dried particles were re-dispersed into water, the water was absorbed into the hydrophilic shell causing it to swell. The particle diameters increase from 55 μm in fluorocarbon oil to 75 μm in water (Fig. 2d). The swelling of particles could be controlled by varying the cross-linker concentration of the polyacrylamide gel.^[34,38]

The particles combine the biocompatibility of hydrogel with the ability to be manipulated and rotated on the micro-scale using an externally applied magnetic field. This makes them useful for sorting applications, as contrast enhancers in magnetic imaging and for micro-mixing applications. To demonstrate the magnetic response of the particles, we observed their rotation in the presence of a magnetic field. The sample holder was fabricated by sealing a plastic ring onto a glass slide coated with a hydrophobic sol-gel layer preventing the hydrogel particles sticking to the surface. After washing the slide with the sol-gel solution, it was heated to 225 °C for 2 min to allow the hydrophobic layer build on the surface of the glass. The reservoir was then filled with magnetic hydrogel particles, suspended in deionized water with 5% v/v tracing colloidal particles (diameter 3 μm) introduced to visualize the fluid flow. The reservoir was then placed in a rotating magnetic field produced by a standard heating plate. In addition to visually observing the flow around the gel particles, the high speed camera (Phantom V7, Vision Research) was used to analyze the flow velocity around a magnetic particle by recording the movements of the tracing colloids.

In the presence of an external magnetic field, the iron-oxide magnetic nanoparticles of the ferrofluid acquire dipole moments. The saturation value of magnetization in our (very typical) ferrofluid is ~ 400 Gauss (0.04 T). Given the fraction of ferrofluid in the core matrix ($\sim 9\%$ w/w), and the manufacturer-quoted fraction of magnetic particles in it ($\sim 5\%$), we can estimate the magnetic moment of the magnetic core ($\sim 20 \mu\text{m}$ diameter) to be $m \sim 6 \times 10^{-11} \text{ A m}^2$ (or J/T units) at saturation. Since magnetic nanoparticles are immobilized by polymerization, the rotating external field would exert a torque $\sim mB$ on the whole hydrogel particle (for a typical field of a magnetic stirrer, $B \sim 1000$ Gauss (0.1 T), the torque is of the order $\sim 6 \times 10^{-12} \text{ Nm}$). Importantly, the axis of this torque is located in the magnetic core, i.e., eccentric for the whole particle. As a result, eccentric rotation is induced, which generates a significant shear flow of the suspending fluid. Since the geometric center of the particle is in translational motion, the estimate of the resistance torque is $3\pi\eta D a v$ where η is the fluid viscosity, D is the particle diameter and $v = a\omega$ is the linear velocity, with ω the angular velocity of the external field rotation, and a the distance between the geometric particle center and its magnetic center. The balance of torques gives the estimate of the maximal angular

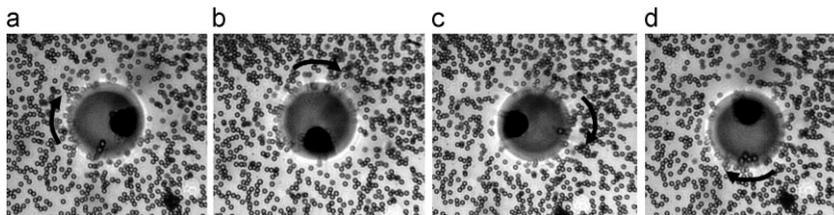


Figure 3. A series of optical microscopy images, a) to d), showing the particle rotating around its magnetic bead.

velocity ω_{max} that a given field B can rotate in a given particle/fluid system:

$$\omega_{\text{max}} = \frac{mB}{3\pi a^2 \eta D} \quad (1)$$

This could reach several kHz in water, for the typical magnetic values and dimensions discussed above. Figure 3a–d show optical images of the rotation of a magnetic hydrogel particle in a rotational magnetic field. The resulting torque causes the particle to rotate in a well-controlled manner. In contrast to the usual homogeneous magnetic gel particles, the anisotropic magnetic hydrogel particles rotate eccentrically around a point in the magnetic core.

The vector field of the flow velocity around the magnetic hydrogel particle could be obtained by recording the instantaneous movements of the tracing particles. Figure 4a shows the superposition of these instantaneous flow velocities over the full rotation cycle; the full hydrogel particle with its magnetic inclusion is sketched on top of the map to illustrate the point about its eccentric rotation. The highest average velocity of the superposed flow occurs at a distance $\sim 75 \mu\text{m}$ from the rotation axis, which is approximately the diameter of the particle. At a distance further than 130 μm from the rotation axis the constant

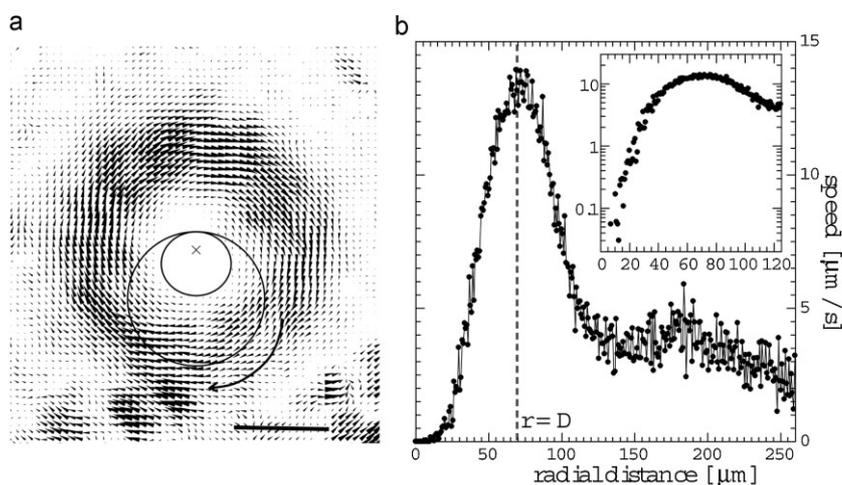


Figure 4. The superposed vector field of fluid velocity a) was obtained by recording trace colloid movements over the full rotation cycle. The scale bar is 50 μm ; the X on the particle sketch marks the rotation axis. Plot b) shows the azimuthal average of flow velocity around the particle, showing that the highest flow is at 75 μm from the rotation axis.

flow velocity is assumed to represent an undisturbed Brownian motion of the tracing colloids (Fig. 4b).

This unique magnetic response of magnetic hydrogel particles with internal anisotropy has great potential for many microfluidic applications. In particular, the asymmetric particles offer a possibility of eccentric rotation and thus induce significant shear flow in the vicinity of each particle, with a potential for micro-mixing of fluids, e.g. in a microfluidic reactor or directly in vivo. Additionally, these particles could serve as probes for microrheological characterization of complex fluids and biomaterials. Finally, biocompatibility and the capacity to adjust/modify the anisotropic internal microstructure within the generic core-shell morphology offers new opportunities in biomedical applications. The suggested stable and reproducible way to fabricate such particles could provide major benefits in all these advanced applications.

In conclusion, magnetic hydrogel particles with uniform anisotropic features were synthesized using double emulsions as templates. Microfluidic assembly by using flow-focusing double emulsion drop makers provides excellent control over the size, morphology, and monodispersity. The particles exhibit excellent rotational control by an external field, with a possibility of eccentric rotation inducing a significant localized shear flow.

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