A CENTRIFUGE-BASED DROPLET SHOOTING DEVICE FOR THE SYNTHESIS OF MULTI-COMPARTMENTAL MICROSPHERES UNDER ULTRA-HIGH GRAVITY

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ABSTRACT

This paper reports the centrifuge-based synthesis method of monodisperse hydrogel microspheres possessing multiple compartments under ultra-high centrifugal gravity, and the demonstration of magnetic self-assembly of chain-structures using cell-laden Janus-spheres. Our method, enabling gelification of droplets of sodium alginate solution into microparticles without oil, heat or UV, is easy to use, simple and biocompatible. The synthesis procedure takes only a few minutes and can be conducted on a lab-bench, using our Centrifuge-based Droplet Shooting Device (CDSD) and a tabletop centrifuge. The CDSD will be a valuable tool in various fields, such as drug delivery, biotechnology and tissue engineering.

KEYWORDS: Anisotropic particle, Hydrogel, Microfluidics, Centrifuge

INTRODUCTION

Hydrogel-based microparticles have found applications in various fields including drug delivery, tissue engineering, photonics, medical diagnosis and self-assembly [1]. Recently, anisotropically modified particles have been drawing attention owing to their multi-functionality [2-3]. Especially, multi-compartmental particles are useful since they acquire multi-functionality by carrying multiple materials in their compartments [4-5]. In addition, control over size and shape of the compartments can modify the functionality without changing materials carried in the particles.

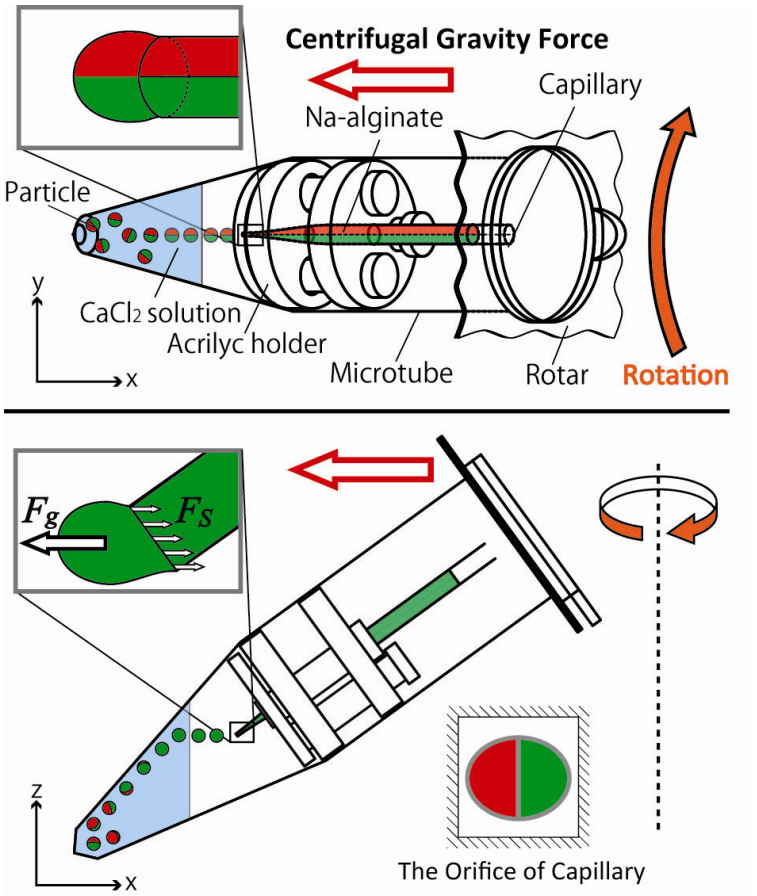

Figure 1. Schematic depiction of a Centrifuge-based Droplet Shooting Device (CDSD) and the concept of our hydrogel micro sphere synthesis method using the CDSD. The CDSD is composed of a capillary, an acrylic holder and a microtube. The acrylic holder of the CDSD holds the capillary in which sodium alginate solutions are introduced in the capillary. The sodium alginate solution is pushed out from the capillary and form droplets under ultra-high gravity. The droplets are gelified in a $CaCl_2$ solution.

Currently, on-chip droplet-based microfluidic systems utilizing immiscible two-liquid flows, such as flow-focusing and T-junction, are center pieces in the field of monodisperse microparticle synthesis. Those synthesis methods allow functionalization of particles simply by encapsulation of various materials in the particles. In those methods, however, providing multiple compartments in monodisperse particles requires complicated devices, and available compartmentalization has been limited. Besides, those methods compromise biocompatibility owing to their oil, UV or heat use, in spite of the growing demand of hydrogel particles in biological applications. In these points, a simple and biocompatible method for the synthesis of hydrogel microparticle with flexible controllability over compartmentalization is desirable.

Here we present a simple and rapid method for the synthesis of monodisperse multi-compartmental hydrogel microspheres using a Centrifuge Droplet Shooting Device (CDSD) and a table-top centrifuge. We confirmed biocompatibility of the method by the encapsulation of magnetic colloids and cells with 91% viability inside Janus particles. The cell-laden magnetic Janus particles self-assembled into a pearl-chain structure under applied magnetic field.

A CENTRIFUGE DROPLET SHOOTING DEVICE

A device with built-in microtubes – a centrifuge-based droplet shooting device (CDSD) – and a tabletop centrifuge are the only components required in our hydrogel microsphere synthesis method (Fig. 1). The device, CDSD, is composed of a capillary, an acrylic holder, and a microtube. The barrel-configuration of the capillary gives designated compartmentalization in the hydrogel spheres. Firstly, sodium alginate solutions are introduced in each capillary barrel. We set the capillary in the acrylic holder and insert the holder in a microtube whose bottom is filled with a 500 mM $CaCl_2$ solution. Then we conducted centrifugation on the microtube. The sodium alginate solutions in capillary-barrels are pushed out by centrifugal gravity and synthesized into pendant-drop at the orifice. Following Tate's law, when the the centrifugal force exerted by centrifugal gravity, F_g, surpasses the surface tension drawing force exerted from the capillary orifice, F_s, the drop gets detached and formed droplet [6]. The balance of the forces acting on the drop when it detaches from the capillary orifice is as follows:

$$F_g = F_s . \qquad (1)$$

Using this equation, the diameter of the droplet can be written as

$$d_p = a \sqrt[3]{\frac{d_o}{G}} , \qquad (2)$$

where d_o is the diameter of capillary orifice, G is centrifugal gravity and a is a constant defined by density and surface tension coefficient of the sodium alginate solutions [7]. This droplet travels in the air gap and gets gelified in the $CaCl_2$ solution. According to equation (2), Theoretical diameter of the 3% (w/w) sodium alginate droplet is 110 μm when the capillary orifice is 100 μm and applied centrifugal gravity is 3000 G.

MULTI-COMPARTMENTAL SPHERE SYNTHESIS

Fig.2 shows two-compartmental –Janus– spheres obtained from a double-barreled capillary and three-compartmental spheres obtained from a triple-barreled capillary. We used 3% (w/w) sodium alginate solutions and a 500 mM $CaCl_2$ solution. For optical visibility in microscopic observation, we added 4% (w/w) aqueous suspensions of fluorescent nanobeads to the sodium alginate solutions. In a centrifuge, applied centrifugal gravity was 3000 G. Both Janus and triple-compartmental spheres presented narrow size distribution (CV: 2.0 %). Mean diameter of those spheres corresponds to the theoretical diameter of the droplet predicted using equation (2), if we consider the shrinking behavior of sodium alginate solution in the process of gelification in $CaCl_2$ solution. Both Janus and triple-compartmental spheres possess fine interfaces between their compartments.

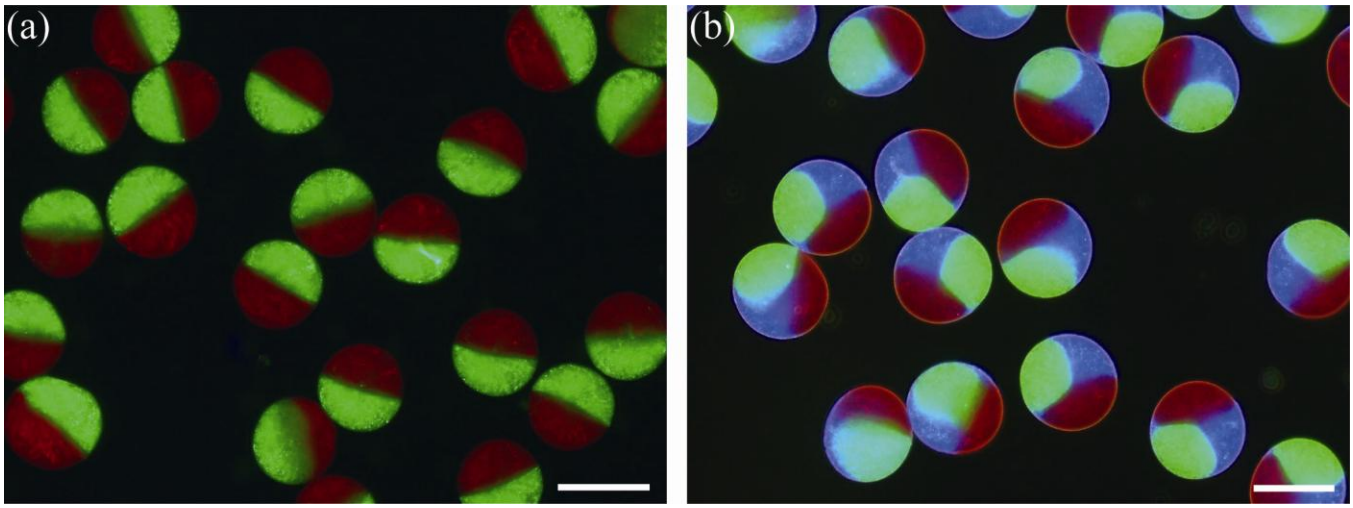

Figure2. Multi-compartmental spheres. (a) Janus spheres obtained from a double-barreled capillary. (b) Triple-compartmental spheres obtained from a triple-barreled capillary. Both Janus and triple-compartmental spheres are made from droplets of 3% (w/w) sodium alginate solutions gelified in a 500 mM $CaCl_2$ solution. The diameter of the capillary orifice is 100 μm. Applied centrifugal gravity is 3000 G. Scale bars are 100 μm.

ORGANIC/INORGANIC-ENCAPSULATION

To functionalize our multi-compartmental spheres and to test biocompatibility of our method, we demonstrated organic/inorganic encapsulation into Janus spheres by adding magnetic colloids and living Jurkat cells to 3 % (w/w) sodium

alginate solutions. A 50 mM $CaCl_2$ solution was used for gelification. Fig. 3 shows an image of Janus spheres with one hemisphere carrying magnetic colloids and the other carrying living Jurkat cells. The viability of the cells after encapsulation was 91%. This high biocompatibility is presumably due to our simple liquid-air droplet formation system without any use of oil, UV or heat. Under applied magnetic field (20mT in plane), the spheres self-assembled into pearl-chain structure along the direction of the magnetic field. Encapsulation of this combination of materials, magnetic colloids and living cells, into monodisperse particles have not been previously reported yet. Our successful organic/inorganic encapsulation suggests our method can be used for encapsulation of various types of materials, from colloids to cells.

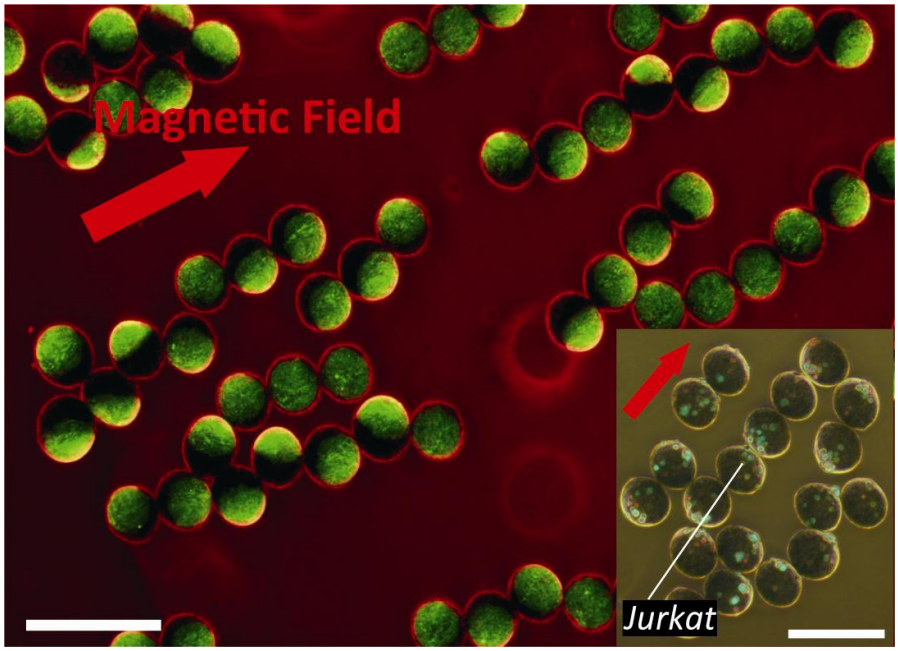

Figure3. Cell-laden Janus spheres. Jurkat cells and magnetic colloids are successfully encapsulated in hemispheres of the particles. Cell variability is 91 %. The cell-laden Janus particles are self-assembled into pearl-chain structure under applied magnetic field. Scale bars are 200 µm.

CONCLUSION

In conclusion, we successfully fabricated monodisperse multi-compartmental hydrogel microspheres in a simple method using our CDSD and a tabletop centrifuge. Our liquid-air droplet based particle synthesis is highly biocompatible and can provide particles with various functionalities by encapsulation of unattained combinations of materials. Our method would widespread throughout materials science communities and enhance applications of compartmentalized particles.

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