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On-chip preparation of calcium alginate particles based on droplet templates formed by using a centrifugal microfluidic technique

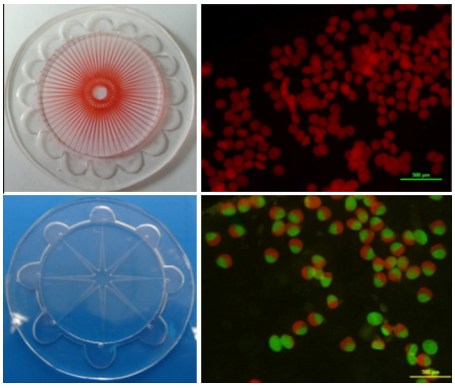
Mei Liu [1], Xiao-Ting Sun [1], Chun-Guang Yang, Zhang-Run Xu *

Research Center for Analytical Sciences, Northeastern University, Shenyang 110819, China

HIGHLIGHTS

- A centrifugal microfluidic chip was developed for producing alginate particles.
- The chip-based system has substantial advantages in simplification and reliability.
- High throughput production was achieved by increasing the number of microchannels.

GRAPHICAL ABSTRACT



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ABSTRACT

A novel chip-based approach for the fabrication of oblate spheriodal calcium alginate particles was developed by combining the droplet template method and the centrifugal microfluidic strategy. Circular chips with multiple radial channels were designed. Sodium alginate solutions in radial channels were flung into $CaCl_2$ solutions in the form of droplets under centrifugal force, and the droplets transformed into particles through cross-linking reaction. The size and morphology of particles could be controlled by regulating the centrifugal force, the channel geometry and the distance between the channel outlet and the $CaCl_2$ solution. The throughput of particle production was evidently enhanced by increasing the number of radial channels to 48 and 64. The coefficients of variation of particle sizes were in the range of 5.2–5.6%, which indicated the monodisperse particles could be prepared by using the present method. With the chip configuration readily modified, the same platform could be used to produce Janus particles. The Janus particles showed clear interfaces owing to the high flight speed and the rapid gelling process of the droplets. This method would be capable of generating particles with complicated morphology and multifunction from diverse polymeric materials.

1. Introduction

Alginate, a water-soluble polysaccharide extracted from brown algae, represents the most widely used polymeric materials due to its biocompatibility, porosity, and low toxicity [1,2]. The preparation of alginate particles is usually based on the gelling reaction of alginate and Ca^{2+} ions [3]. Because of the relatively mild gelling process, Ca-alginate particles have found numerous applications as

* Corresponding author at: Research Center for Analytical Sciences, Northeastern University, No. 3-11, Wenhua Road, Heping District, Shenyang 110819, China.
E-mail address: xuzr@mail.neu.edu.cn (Z.-R. Xu).
[1] Both authors have equally contributed to this article.

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encapsulation vehicles and delivery systems for cells [4], proteins [2,5], enzymes [6] and drugs [7], as well as useful tools for the controlled release of drugs [8,9] in biomedical science and pharmaceutical engineering. The applications of Ca-alginate particles depend strongly on their sizes, shapes and components, thus calling for highly controllable methods to generate Ca-alginate microparticles in a reproducible manner.

Over the past few years, microfluidic techniques capable of manipulating fluids at micro-scale have provided a powerful platform for the synthesis of highly monodisperse polymeric particles [10–14]. Many research groups have developed microfluidic devices to produce alginate particles with precise control over their size, shape, and composition [4,8,15–19]. Microfluidic generation of monodisperse alginate particles was mainly based on T-junction and flow-focusing geometries [20,21]. These particles were produced from the droplets generated by the breakup of the fluid due to the Rayleigh-Plateau instability. However, these methods depend strongly on the precise control over the geometries of the chips and manipulation of the flow rate of each fluid. Centrifugal microfluidics, taking advantage of centrifugal force for particle generation, presented as an available method in manipulating the size and the structure of particles, and exhibited potential in preparing particles with complex structures. Haeberle et al. [22] developed a centrifugally induced method for fabricating alginate beads by using a commercially available polymer nozzle. The diameter of the bead could be adjusted by changing the nozzle geometry and spinning frequency, and the CVs of the bead diameters were 7–16%. After that, Mark et al. [23] used the same experimental setup to fabricate chitosan microbeads. Maeda et al. [24] reported a one-step synthetic method based on centrifugal droplet formation from a multi-barrelled capillary, providing spherical alginate microparticles with a controlled 3D morphology. By using the capillaries with various barrel configurations, Janus and multicompartment particles with highly axisymmetrical morphologies were obtained. The particle sizes could be adjusted, and their shapes could be tuned to ellipses or fibers. Lee and Kim [25] have developed a novel fabrication method of monophasic, biphasic, and triphasic alginate microparticles by centrifuging different polydiacetylene liposome/alginate mixture solutions into a $CaCl_2$ solution using a simple combined needle injection system. The size and the composition of the biphasic microparticles and the triphasic microparticles could be independently manipulated by controlling the centrifugal force and the type of PDA liposomes. Admittedly the capillary/needle-based centrifugal fabrication methods could provide microparticles with complex 3D morphology for unexplored applications, however, the devices were specially manufactured and assembled, and not universal in all microfluidic laboratories.

Centrifugal microfluidics has some distinct advantages over other microfluidic techniques, which makes it a better candidate for synthesis of polymeric particles. More recently, centrifugal microsystems were also developed for the production of inorganic nanoparticles [26,27]. Here, we presented a chip-based method to synthesize monophasic/biphasic polymeric particles based on droplet templates formed by using a centrifugal microfluidic technique. The centrifugal system simply consisted of a spin coater as the centrifugal platform and a chip fabricated using the universal soft-lithographic technique. Sodium alginate solutions were thrown out from the channels and flew into $CaCl_2$ solution chambers when the centrifugal force was exerted on the chip. Both the droplet generation and solidification were conducted within the chip. By designing two channels adjacently parallel with each other, Janus alginate particles with two distinct fluorescent hemispheres could be synthesized. Moreover, particles with magnetic anisotropy could be readily generated by dispersing Fe_3O_4 into one hemisphere. More importantly, the production throughput of the particles could be dramatically increased simply by arranging plenty of parallel channels on the chip.

2. Experimental

2.1. Microfluidic chip fabrication

Polydimethylsiloxane (PDMS, Dow Corning Co., USA) was used for the centrifugal microfluidic chip fabrication. SU-8 (SU-8 2050 Micro-Chem Corp, USA) masters were fabricated using the conventional photolithography technique. The PDMS replica was peeled off from the SU-8 positive mould and bonded to other PDMS layers by air plasma treatment in a plasma cleaner (PDC-32G, Harrick Scientific Co., USA).

The microfluidic chip consisted of four layers, as illustrated in Fig. 1a. The top layer and the bottom layer were PDMS flat plates as top and bottom walls of the particle collecting chambers. The second layer included two zones: a channel pattern zone and a circumjacent chamber zone. The channel pattern part was cut from the second layer in a round shape (43 mm in diameter), and the collection chambers were tailored from the residual circumjacent part. After the top layer and the channel pattern zone were bonded, holes were punched in the corresponding position to form the inlets for $CaCl_2$ solutions and sodium alginate solutions. The third layer was processed in the same way as the second layer to form a channel substrate part and a circumjacent chamber part. The diameter of the chip was 70 mm. In order to guarantee the stability of the chip under high rotating speed, the thickness of the chip was confined to 4–6 mm. The channels were 40–80 μm deep, and were initially 1000 μm wide at the inlets and narrowed down to 100 μm wide at the outlets. The photograph of the 8-channel chip was shown in Fig 1b.

2.2. Reagents and materials

1%, 1.5% and 2% (w/v) sodium alginate solutions were prepared. $CaCl_2$ solutions were prepared at various concentrations from 2.5 wt% to 20 wt%. Tween 20 (final concentration 0.5% v/v) was added into the $CaCl_2$ solution as surfactant to prohibit potential fusion of droplets in the collection chambers. 0.05% (v/v) red fluorescent beads were dispersed into the sodium alginate solution for observation and imaging. For Janus particle synthesis, red and green florescent beads were added to 2% sodium alginate solutions respectively. For magnetic encapsulation, 50 mg Fe_3O_4 powder was dispersed into 1 mL 2% sodium alginate solution to obtain the magnetic alginate phase.

2.3. Preparation of calcium alginate particles

Fig. 2 shows a schematic diagram of the experimental device used for the production of Ca-alginate particles. Sodium alginate solutions and $CaCl_2$ solutions were introduced into the radial channels and circumjacent chambers by syringes respectively. A spin coater was used as the centrifugal platform on which the chip could be fixed by the vacuum chuck. The chip was then centrifuged at 2400–4800 rpm for 1 min. During the centrifugation, the droplets of sodium alginate solutions were formed at the channel outlets due to the combined action of centrifugal force F_c and surface tension F_σ (Fig. 2b). When F_c exceeded F_σ, droplets were thrown out from the channel outlets, centrifuged into particle collection chambers containing $CaCl_2$ solution, and then underwent gelation to produce Ca-alginate particles.

An inverted fluorescent microscope (Ti-U, Nikon, Japan) mounted with a CCD camera (DS-Fi1c, Nikon, Japan) was utilized to observe the particles. An image analysis software, ImageJ