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Alginate droplets pre-crosslinked in microchannels to prepare monodispersed spherical microgels

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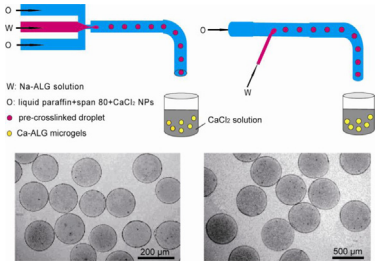
HIGHLIGHTS

- Na-ALG droplets pre-crosslinked by $CaCl_2$ nanoparticles formed *in situ* in oil phase.
- The pre-crosslinked droplets possess sufficient rigidity to avoid the deformation.
- The collection height is no longer influence on the shape of the Ca-ALG microgels.
- The spherical microgels move more fluently than the tailed ones in the microchannel.

GRAPHICAL ABSTRACT



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ABSTRACT

Monodispersed spherical calcium alginate microgels (denoted as Ca-ALG) with uniform and controllable size were prepared by using a microfluidics technique. Herein, an aqueous solution of sodium alginate (denoted as Na-ALG) was used as a dispersed phase, and the liquid paraffin containing $CaCl_2$ nanoparticles formed *in situ* was used as a continuous phase. Na-ALG droplets were first pre-crosslinked by $CaCl_2$ diffused from the oil phase in the microchannel, and then crosslinked completely in the collection bath containing an aqueous solution of $CaCl_2$. In comparison with conventional external crosslinking, this method can avoid deformation of microgels which usually occurs in the process of external crosslinking. Due to the pre-crosslinking of Na-ALG droplets in the microchannel, the spherical morphology of the microgels could not be affected by the preparation conditions, such as types of microfluidic devices, flow rate ratios of the continuous phase and dispersed phase, size of the droplets, collection height and so on. In addition, the size of the spherical Ca-ALG microgels can be well controlled from 40 to 700 μm in diameter by changing the dimension of the microchannels and the flow rate ratios of the dispersed phase and continuous phase. Furthermore, such spherical Ca-ALG microgels can improve their movement and packing state in a microchannel, which is beneficial for their use as embolic materials for interventional therapy.
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1. Introduction

Sodium alginate, a kind of natural polymers, can be crosslinked by metal ions like calcium ions to become bulk hydrogels or microgels depending upon the preparation method. Calcium alginate (denoted as Ca-ALG) microgels have received great attention in recent years due to their biocompatibility and biodegradation. Their application involves encapsulation of cells [1–4], drug delivery system [5–8], interventional embolization [9,10] and cellular therapeutics [11], etc.

For the preparation of Ca-ALG microgels, common methods include external ionic crosslinking combined with a dripping technique or bulk emulsification. However, the former usually results in tailed particles (non-spherical) [12], while the latter always leads to

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a wide size distribution. Nevertheless, the dripping technique well overcomes the disadvantages of traditional bulk emulsification method, namely, uncontrollable shapes and wide size distribution. As reported, shape, size and size distribution of microgels greatly influence the rheological behavior of microgel suspensions [13], and biodistribution after intravascular injection [14]. For instance, the movement of spherical particles is easy to predict due to their inherent symmetry, but non-spherical particles may align or tumble during flowing process [15]. As used as embolic materials in interventional therapy, microspheres with uniform size and shape are easy to deliver through a microcatheter in comparison with non-spherical particles [16,17]. In addition, the non-spherical fat particles can generate larger viscosities than spherical particles at the same volume fraction [13,18]. In case of their use as drug carriers, non-spherical particles could offer unpredictable degradation profiles due to the irregular shapes and different thicknesses, resulting in uncontrollable drug release profiles [15,19]. In addition, particles with an irregular shape also affect their vascular adherence, circulation time, endocytosis, intracellular trafficking and phagocytosis of the encapsulated drugs [20]. Therefore, it is crucial to control a narrow size distribution and a uniform spherical shape of Ca-ALG microgels for biomedical applications.

During the past decade, a droplet-based microfluidics technique has been developed to fabricate various polymeric microparticles with precisely controllable size and shapes with narrow distribution [18,21,22]. For the preparation of Ca-ALG microgels with this technique, the crosslinking of sodium alginate (denoted as Na-ALG) droplets usually use either external gelation [23–26] or internal gelation [27–31]. In the case of external gelation, the Na-ALG droplets produced in microchannel drip down into a collection bath containing an aqueous $CaCl_2$ solution and followed by a crosslinking reaction of Ca^{2+} and carboxyl groups of alginate [23]. However, the formation of tail-shaped or tadpole-shaped Ca-ALG microgels is unavoidable due to the gravitational force and interfacial effect when they drip into the collection bath [24–26]. We note that internal gelation takes place in the microchannel and is nearly simultaneous with the formation of Na-ALG droplets [27–32]. In this method, to supply of Ca^{2+} for crosslinking of Na-ALG droplets, $CaCO_3$ powder [27] or $CaCO_3$ nanoparticles (NPs) [29,30] are usually suspended in the Na-ALG solution or oil phase, combined with another acidic aqueous or oil phase. These methods need an accurate control of the concentrations of the calcium salts, the acidity and the preparation conditions, as well as a complicated device. Otherwise, an unexpected clogging in microchannels or uncompleted crosslinking of Na-ALG may occur.

In this work, we propose a simple method to fabricate Ca-ALG microgels with a perfect spherical shape and a controllable size with narrow distribution. Herein, $CaCl_2$ NPs, *in situ* formed in an oil phase, were used as a pre-crosslink reagent. Na-ALG droplets were slightly crosslinked in the microchannel, leading to a certain rigidity. Thus, the pre-crosslinked droplets can resist the deformation that arises from the preparation conditions including microfluidic devices, flow rates of the continuous phase and dispersed phase, droplets size and collection height. The completed crosslinking was carried out in the collection bath. The resultant Ca-ALG microgels show a great potential application in the field of interventional therapy.

2. Materials and methods

2.1. Materials

Sodium alginate (low viscosity) was purchased from Sigma–Aldrich. Anhydrous calcium chloride, ethanol, liquid paraffin and span 80 were of analytic grade and purchased from sinopharm chemical reagent Co. Ltd., Sylgard 184 silicone elastomer kits including poly(dimethysiloxane) (PDMS) and the curing agent were purchased from Dow Corning Co. Tetrafluoroethylene–hexafluoropropylene copolymer (FEP) tubing was purchased from Cole-Parmer instrument company and polytetrafluoroethylene (PTFE) tubing was produced by Shanghai Jufu Wujin Ltd., Co., China.

2.2. Fabrication of microfluidic devices

As shown in Scheme 1, two types of microfluidic devices were used to prepare Ca-ALG microgels. One of them was a microfluidics flow-focusing device based on PDMS (denoted as microfluidic FFD) fabricated using standard soft lithography techniques as described previously [9]. The width of the channel for continuous phase and dispersed phase, orifice and collection were 270, 180, 50, and 480 μm, respectively. The height of the channel was 180 μm. The other was a T-junction device based on FEP tubing (denoted as T-junction device). The devices were fabricated with a blunt syringe needle (ID 0.16 mm, OD 0.31 mm) pierced vertically into a FEP tubing (ID 0.8 mm, OD 1.6 mm). Epoxy glue (ITW Devcon) was used to seal the hole and fix the tubing on a glass slide.

2.3. Preparation of spherical Ca-ALG microgels

Liquid paraffin containing $CaCl_2$ nanoparticles (NPs) was prepared according to a method described elsewhere [33], and used as a continuous phase. Briefly, a designed amount of $CaCl_2$ powder was dissolved in a small amount of ethanol under sonication. Subsequently, a certain volume of liquid paraffin containing 2 wt% of span 80 as surfactant was added into the $CaCl_2$ ethanol solution. The mixture was firstly sonicated for 5 min and followed by heating to 60 °C in an oil bath. The mixture was maintained at 60 °C in the oil bath overnight with stirring to remove ethanol. After the ethanol was completely evaporated, the mixture was allowed to cool to room temperature. Meanwhile, $CaCl_2$ NPs was *in situ* formed in liquid paraffin. The concentration of $CaCl_2$ NPs in liquid paraffin was set at 0.5, 0.8 and 1.0 wt%, respectively.

This continuous phase and an aqueous solution of Na-ALG (2 wt%) as a dispersed phase were pumped into microchannels of the microfluidic device using digitally controlled syringe pumps (NE-1000, New Era). Na-ALG droplets were fabricated and pre-crosslinked by $CaCl_2$ NPs in the microchannel. Subsequently, the droplets dripped into a collection bath containing an aqueous solution of $CaCl_2$ (0.2 mol L^{-1}) and maintained in the bath for several hours as shown in Scheme 1. The resultant Ca-ALG microgels were collected *via* centrifugation and purified by washing several times with alcohol and DI water. As a reference, liquid paraffin without $CaCl_2$ NPs was also used as a continuous phase. The clean Ca-ALG microgels were dispersed in DI water for further characterization.

The distance from the outlet of the droplets to the liquid surface of the collection bath was defined as collection height (h) and varied to study the effect of h on the shape of the prepared Ca-ALG microgels. Ca-ALG microgels with various sizes were fabricated by changing the ratio of flow rates of the continuous phase and the dispersed phase.

2.4. Characterization

The diameter and polydispersion index (PDI) of $CaCl_2$ NPs *in situ* formed in liquid paraffin were measured at 25 °C by using dynamic light scattering (DLS) (Nano-ZS 90, Malvern). The refractive index of liquid paraffin and $CaCl_2$ were 1.480 and 1.520 [33], respectively. The viscosity of liquid paraffin was 70 cp.

The dilute aqueous dispersions of Ca-ALG microgels were dripped on a clean glass slide. And the shape and size of the Ca-ALG

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