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Rapid production of single- and multi-compartment polymeric microcapsules in a facile 3D microfluidic process for magnetic separation and synergistic delivery

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ABSTRACT

A facile liquid-driven compound-fluidic flow focusing (LCFF) platform is employed to produce single- and multi-compartment poly (lactic-co-glycolic acid) (PLGA) microcapsules at high production rates. Single-compartment microcapsules encapsulating magnetic nanoparticles (MNPs) exhibit very good magnetic responsiveness. The magnetic nature allows them to concentrate at specific sites by applying permanent magnetic fields, and the magnetic microcapsules can be separated quickly from the non-magnetic microcapsules. Moreover, multi-compartment microdroplets are produced to encapsulate different kinds of interactive materials individually. It is demonstrated that after the controlled reaction of inner materials, the generated precipitates can be obviously observed. This study provides the LCFF method for one-step preparing uniform-sized single- and multi-compartment microcapsules with solid shell and spherical shape at high throughput, which can be potentially used for several applications, such as sensors, microreactors, diagnostics and drug delivery.

1. Introduction

Polymeric microcapsules have been widely used in biomedicine, sensors, environmental protection, and new materials [1]. The polymeric shell of the microcapsules can mask bitter taste [2], prevent vaporization and oxidation [3,4], control drug release rates [5,6] and insulate the encapsulated probes from the environment [7–9]. The applications of microcapsules are strongly dependent on their characteristics, such as size, uniformity, composition, structure and morphology.

Conventional industrial methods for synthesis of polymeric microcapsules include spray drying [10], interfacial polymerization [11], and solvent evaporation [12]. The advantageous feature of them lies in the high production rates, but the microcapsule size and uniformity are often out of control, and the encapsulation efficiency is often low, especially when hydrophilic and/or amphiphilic small molecules are needed to be encapsulated [13,14]. In addition, it is technically challenging to prepare multi-compartment and anisotropic microcapsules by the traditional methods. Multi-compartment microcapsules are of significant value in co-encapsulating different types of reagents for activate therapy, controllable reaction, synergistic delivery and production of multi-compartment materials [15–22].

To overcome these shortcomings, the emerging microfluidic processes show the technical potential for producing diversified polymeric microcapsules with uniform size distribution, controlled structural characteristics, designated loading capacity, and high encapsulation efficiency [23–27]. Microfluidic devices based on microchannel chips and glass microcapillaries are most commonly used in previous studies for producing polymeric microcapsules [28–35]. The diameters of the produced microdroplets mainly range from a few microns to hundreds of microns. However, the production rates are always limited due to their geometric and physical characteristics. Here, a microfluidic liquid-driven compound-fluidic flow focusing (LCFF) platform is employed to produce single- and multi-compartment poly (lactic-co-glycolic acid) (PLGA) microcapsules at high production rate, which is very different from the commonly used microfluidic devices due to the relatively high

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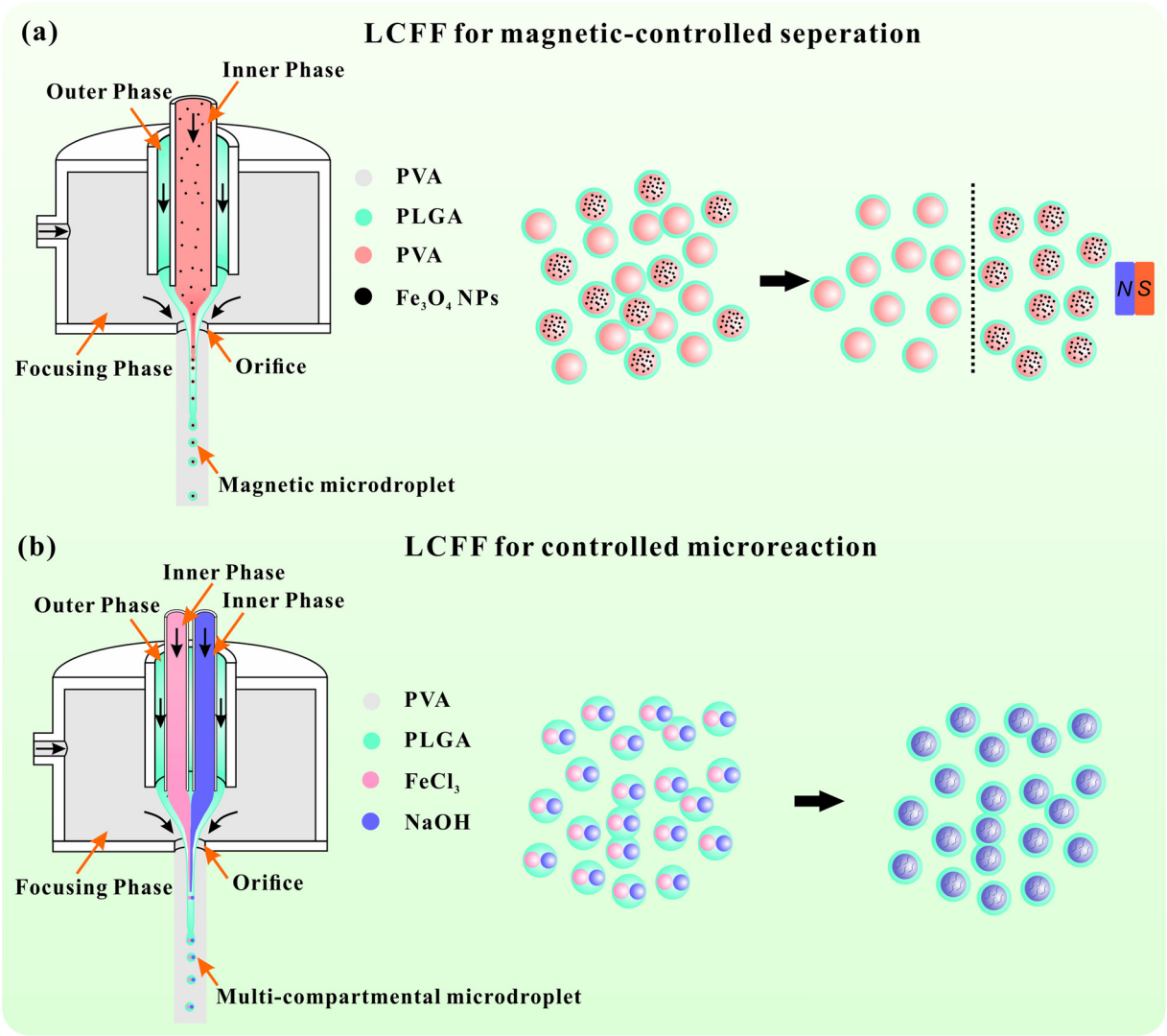

Fig. 1. Schematic illustration of (a) the LCFF process and the production of the magnetic PLGA microcapsules; (b) the LCFF process and the production of the multi-compartment microcapsules.

Reynolds numbers and Weber numbers in 3D flow focusing methods [23,36–41].

PLGA is a kind of biocompatibility material and can be widely used in drug delivery system [42–45]. In our previous studies, uniform drug-loaded single core liposomes are produced based on the 3D coaxial flow focusing platform [46]. Here, PLGA is used as the shell of microcapsules and single- and multi-compartment PLGA microcapsules are produced by the LCFF process. Magnetic nanoparticles (MNPs) encapsulated PLGA microcapsules are produced and the magnetic-controlled locomotion and separation are investigated, as depicted in Fig. 1(a). Besides, the LCFF process is used to produce PLGA microdroplets with two interactive materials encapsulated and the interactive process of the two inner cores is performed, as depicted in Fig. 1(b). The produced single- and multi-compartment PLGA microcapsules can be useful in sensors, microreactors, diagnostics and drug delivery. It will be verified that the LCFF technique is able to produce single- and multi-compartment PLGA microcapsules at low cost, good uniformity, high production rate and precise process control.

2. Materials and methods

2.1. Reagents preparation

PLGA (lactide : glycolide = 50 : 50, molecular weight = 12,000 Da) was purchased from Shandong Institute of Medical Instrument (Shandong, China). Poly (vinyl alcohol) (PVA, molecular weight = 13000–23000 Da, 87–89% hydrolyzed) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Dichloromethane, ferric chloride hexa-hydrate, ferrous sulfate hepta-hydrate and sodium hydroxide were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Ultrapure deionized water was generated by a water purification system (Direct-Q, Millipore Corporation, USA) and used in our experiment.

2.2. Synthesis and characterization of iron oxide nanoparticles

Synthesis of the superparamagnetic nanoparticles follows a standard one-step synthetic protocol [47,48]. 1.623 g ferric chloride hexa-hydrate and 0.834 g ferrous sulfate hepta-hydrate were dissolved in 30 ml distilled water to prepare an iron solution. 1.2 g sodium hydroxide was dissolved in 150 ml distilled water in a three-necked flask. The flask was in a 80 °C water bath and protected by nitrogen atmosphere flow. Iron