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Microfluidic preparation of monodisperse ethyl cellulose hollow microcapsules with non-toxic solvent

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ABSTRACT

Monodisperse ethyl cellulose (EC) hollow microcapsules are successfully prepared by using a simple and novel method which combines microfluidic double emulsification and solvent diffusion. To dissolve EC, we use a non-toxic solvent ethyl acetate (EA), instead of methylene chloride which is commonly used but carcinogenic. By introducing chitosan (CS) into outer fluid, we can increase the viscosity of outer fluid and obtain smaller microcapsules which are desired. On the other hand, introducing CS only into outer fluid could lead to osmotic pressure gradient between the inner and outer fluids which could cause the undesired collapse of microcapsules. To avoid the collapse phenomena, we try adding iso-osmotic NaCl into inner aqueous fluid but failed in achieving osmotic pressure balance possibly because the small Na^+ and Cl^- ions could penetrate the EC matrix during solidification. However, success is achieved when we introduce CS into both inner and outer fluids because CS polymer is too big to permeate through the EC matrix and thus could maintain iso-osmotic state. The microcapsules prepared under iso-osmotic state show perfect spherical shape and no collapse. The method developed in this work provides a novel and versatile route for fabricating monodisperse biocompatible microcapsules composed of water insoluble polymers.

1. Introduction

Uniform particle size is important for microcapsules as drug delivery systems, because the distribution of the microcapsules in vivo, and the interaction with biological cells, is greatly affected by the particle size [1]. Monodisperse microcapsules can increase the bioavailability and decrease the side effects. In addition, the practical and theoretical evaluation such as drug release kinetics will become simple and precise if the size distribution of microcapsules is narrow [2–8].

Microcapsules are generally prepared by interfacial polymerization reaction, controlled phase separation and coacervation. These methods often produce microcapsules with insufficient control over the size distribution and morphology. Although layer-by-layer (LBL) assembly of polyelectrolytes can control the wall thickness of capsules precisely, the microcapsules show poor mechanic strength. Shirasu porous glass (SPG) emulsification followed by batch or continuous solidification can produce microcapsules with narrow size distribution, but its monodispersity greatly depends on the size distribution of the membrane pores [9]. Recently developed microfluidic technique provides a new route to prepare microcapsules with controlled morphology and uniform size [9–17].

So far, microcapsules obtained in microfluidic devices are synthesized by either interfacial polymerization or solidification of double emulsion. The materials used for interfacial polymerization are scarcely biocompatible and have very limited potential in medical application [16,17]. Although microfluidic preparation of biocompatible alginate microcapsules via interfacial crosslink reaction have been reported, the preparation process was not feasible for preparation of microcapsules based on water-insoluble polymers [18]. Because a large amount of polymeric materials used for drug encapsulation show poor water solubility, microfluidic fabrication of microcapsules based on hydrophobic polymers is in demand. Since microfluidic technique can produce perfect double emulsions, fabrication of microcapsules via solidification of double emulsions have attracted more and more attention [6,13,14,19,20]. Recently, biocompatible and biodegradable poly(ethylene-glycol)-*b*-poly(lactic acid) microcapsules have been prepared by Weitz's group using microfluidic technology [20]. However, the employment of toluene and chloroform is not desirable for human safety concern. Even in the process of bulk emulsification/evaporation methods to prepare microspheres or microcapsules, methylene chloride, a solvent commonly chosen to dissolve water-insoluble polymeric materials, is also toxic [21,22]. The use of such toxic solvent is of environmental concern because it is known to destroy ozone layer in the atmosphere, and the residue solvents may harm human health due to their carcinogenic effects [23,24].

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Here, we report on a novel and convenient method for preparation of monodisperse ethyl cellulose (EC) hollow microcapsules without using toxic solvents. In our experiments, EC polymer was dissolved in a nontoxic solvent, ethyl acetate (EA). Using microfluidic devices, we obtained monodisperse water-in-oil-in-water (W/O/W) double emulsions which were used as templates to fabricate monodisperse EC microcapsules. EC microcapsules with different size and morphology can be achieved by using different inner and outer fluids. The prepared monodisperse EC microcapsules have large cavity and narrow size distribution, which could have high drug loading and high encapsulation efficiency, and may improve the drug bioavailability. The method proposed in this study can also be adapted to manufacture other biocompatible microcapsules compose of other water-insoluble polymers such as polylactic acid (PLA) and poly(lactic acid-co-glycolic acid) (PLGA) which have various applications.

2. Materials and methods

2.1. Materials

Ethyl cellulose (EC, 9 m Pa S) and Span 20 were purchased from Chengdu Kelong Chemical Reagent Co., China. Chitosan (CS, Mw = 100 kDa, degree of deacetylation > 85%) was provided by Ji'nan Haidebei Marine Bioengineering Co. Ltd., China. Pluronic F127 was purchased from Sigma-Aldrich. Acetic acid (HAc) and ethanol were purchased from Shanghai Organic Chemical Institute, China. Ethyl acetate (EA) was purchased from Tianjin Zhiyuan Chemical Reagent Co. Ltd., China. All of these chemicals were of reagent grade and used without further purification. Deionized water (DI water) used throughout the experiments was from a Millipore Milli-Q water purification system.

2.2. Microfluidic device

Microfluidic device for generation of monodisperse W/O/W double emulsions was fabricated according to literature [25]. Briefly, the microfluidic device was fabricated by assembling glass capillary tubes on glass slides. To assemble the capillaries, a cylindrical capillary was inserted into and coaxially aligned with a square capillary tube by matching the outer diameter of the cylindrical tube to the inner dimension of the square one. The inner diameters of the injection tube, the transition tube, and the collection tube were 580, 200, and 580 μm, respectively. A micropuller (Narishige, Japan) was used to taper the end of cylindrical capillaries, and the orifice dimensions of tapered ends were adjusted by a microforge (Narishige, Japan). The inner diameters of the tapered ends of the injection and transition tubes were 40 and 200 μm, respectively. A schematic illustration of the microfluidic device was shown in Fig. 1.

2.3. Fabrication of W/O/W emulsions and EC microcapsules

To prepare the W/O/W double emulsions, the inner aqueous fluid, middle organic fluid, and outer aqueous fluid were separately pumped into the injection tube, transition tube and collection tube. Due to the coaxial co-flow geometry, monodisperse W/O single emulsions were generated in the transition tube and monodisperse W/O/W double emulsions were generated in the collection tube (Fig. 1). The flow rates were adjusted to achieve optimum emulsification conditions for generating double emulsions. Recipes for preparing EC microcapsules (No. MC-W-W, MC-W-CS, MC-NaCl-CS, and MC-CS-CS) and the viscosity coefficients of solutions are listed in Table 1. Both inner and outer fluids were pre-saturated with 8% (v/v) EA. The viscosity coefficients of solutions were

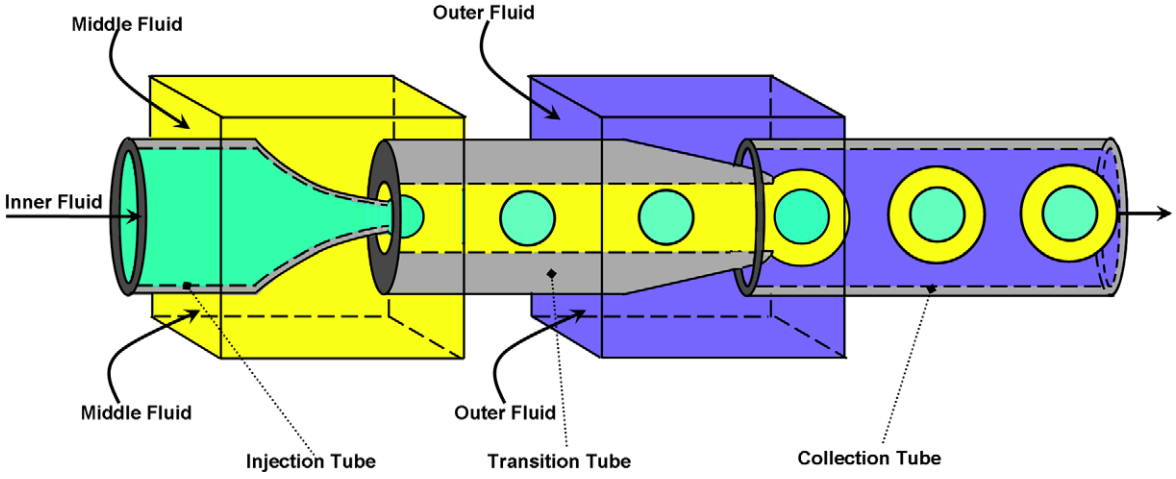

Fig. 1. Schematic illustration of the microfluidic device for fabricating monodisperse W/O/W double emulsions.

Table 1
Recipes for using microfluidic device to prepare EC microcapsules.

Microcapsule code	Inner fluid*					Outer fluid*			
	F127 (w/v)	NaCl (g/L)	HAc (v/v)	CS (w/v)	Viscosity (m Pa s)	F127 (w/v)	HAc (v/v)	CS (w/v)	Viscosity (m Pa s)
MC-W-W**	1%	–	–	–	1.35	1%	–	–	1.35
MC-W-CS	1%	–	–	–	1.35	1%	1%	1%	13.0
MC-NaCl-CS	1%	5.1	–	–	1.35	1%	1%	1%	13.0
MC-CS-CS	1%	–	1%	1%	13.0	1%	1%	1%	13.0

* Inner and outer fluids were pre-saturated with EA (8%, v/v). Middle fluid was the EA solution containing 5% (w/v) EC and 2% (w/v) Span 20. The viscosity of middle fluid was 8 m Pa s.
** MC-W-W was solidified in mixture of ethanol and water (1:4 v/v).