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Preparation of starch nanoparticles in water in oil microemulsion system and their drug delivery properties

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ABSTRACT

In this research, 1-hexadecyl-3-methylimidazolium bromide C_{16}mimBr/butan-1-ol/cyclohexane/water ionic liquid microemulsion was prepared. The effects of *n*-alkyl alcohols, alkanes, water content and temperature on the properties of microemulsion were studied by dilution experiment. The microregion of microemulsion was identified by pseudo-ternary phase diagram and conductivity measurement. Then starch nanoparticles were prepared by water in oil (W/O) microemulsion-cross-linking methods with C_{16}mimBr as surfactant. Starch nanoparticles with a mean diameter of 94.3 nm and narrow size distribution (SD = 3.3) were confirmed by dynamic light scattering (DLS). Scanning electron microscope (SEM) data revealed that starch nanoparticles were spherical granules with the size about 60 nm. Moreover the results of Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) demonstrated the formation of cross-linking bonds in starch molecules. Finally, the drug loading and releasing properties of starch nanoparticles were investigated with methylene blue (MB) as drug model. This work may provide an efficient pathway to synthesis starch nanoparticles.

1. Introduction

Ionic liquids (ILs), organic salts with melting point at or close to room temperatures, have been widely studied and have specific chemical and physical properties, such as negligible vapor pressure, thermal stability, high ionic conductivity and more (Bates, Mayton, Ntai, & Davis, 2002; Dupot, Souza, & Suarez, 2002). Owing to their unique chemical and physical properties, ILs have currently attracted much interests for applications as novel solvents in organic synthesis (Welton, 1999), catalysis (Gordon, 2001), electrochemistry (McEwen, Ngo, Lecompte, & Goldman, 1999). Particularly, they have an advantage as an environmentally benign solvent, i.e., "green solvent," since their nonvolatile nature can prevent the environmental pollution. As an important series of ionic liquids 1-alkyl-3-methylimidazolium salts, $C_n$mimX, where n is the carbon number in the alkyl group, are extensively investigated because they are easy to prepare and relatively cheap to manufacture (Fletcher & Pandey, 2004). Long-chained $C_n$mimX ILs have amphiphilicity like traditional cationic surfactant because of their hydrophobic chains and polar imidazolium groups, and have been called "surface active" or "surfactant-like" ionic liquids (Dong, Li, Zheng, Yu, & Inoue, 2007; Thomaier & Kunz, 2007). In microemulsion systems, Long-chained $C_n$mimX ILs can be used as substitute for surfactants to stabilize IL microemulsions.

Microemulsions are isotropic, clear, or translucent, thermodynamically stable dispersions comprising water, oil, surfactant, and cosurfactant, usually alcohol (Acosta, Szekeres, Sabatini, & Harwell, 2003; Moulik, Digout, Aylward, & Palepu, 2003; Paul & Moulik, 1998). Because of their unique properties, such as ultralow interfacial tension, large interfacial, and the ability to solubilize otherwise immiscible liquids, microemulsions have been widely used in various fields such as tertiary oil recovery, separation (Firman & Kahlweit, 1996), pharmaceutics (Acosta, Nguyen, Witthayapanyanon, Harwell, & Sabatini, 2005), nanoparticles synthesis (Ethayaraja & Bandyopadhyaya, 2006; Khomane, Manna, Mandale, & Kulkarni, 2002; Xing, Li, Davis, & Mann, 2006), chemical engineering (Candau, Zekhini, & Heatley, 1986).

Starch, a kind of natural polymer with good degree of biodegradability, has been modified through physical, chemical or enzymatic processes, which broaden its application in

Abbreviations: ILs, ionic liquids; $C_n$mimX, 1-alkyl-3-methylimidazolium salts; W/O, water-in-oil; C16mimBr, 1-hexadecyl-3-methylimidazolium bromide; SEM, scanning electron microscopy; DLS, dynamic light scattering; XRD, X-ray diffractometry; FTIR, Fourier transform infrared spectroscopy; B, bicontinuous; MB, methylene blue; PBS, phosphate buffer solution.

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food, textile, papermaking, pharmaceutical and other industries as thickener, retention and drainage agent, drug-loading material, etc. (Ghafoori, Mohammadi, & Ghaffarian, 2006; Nikazar, Safari, Bonakdarpour, & Milani, 2005). Among various modifications, cross-linked starch microspheres show high stability toward swelling, high shear, high temperature and acidic conditions and have been the most investigated drug carriers owing to their total biodegradability, biocompatibility, storage stability and cost-effectiveness (Li, Wang, Li, Adhikari, & Mao, 2012; Kim & Lee, 2002; Mundargi, Shelke, Rokhade, Patil, & Aminabhavi, 2008). However, their poor properties in particle size and size distribution limit the application of starch microspheres in drug delivery systems. Therefore, the quality of starch microspheres is desperately expected to be improved in order to broaden the application.

Several preparation approaches of starch microspheres have been investigated, such as spray dying, precipitation, solvent evaporation and emulsion-cross-linking techniques (Kawashitaa et al., 2005; Sturesson & Carlfors, 2000), among which water-in-oil (W/O) emulsion-cross-linking technique has been extensively used. However, in classic W/O emulsion-cross-linking techniques, large amount use of organic solvents causes environmental pollution and the size of starch microspheres is also relatively big (Fang et al., 2008; Franssen & Hennink, 1998). Therefore, a new pathway is desperately expected to develop for the synthesis of starch nanoparticles.

Long-chained $C_n$mimX ILs have been considered as green solvent and can be used as substitute for surfactants to stabilize W/O microemulsions, which can reduce the use of traditional surfactant and prevent the environmental pollution effectively. Many literatures have reported that W/O IL microemulsions can be used as reaction system of the preparation of nanometer materials (Song & Kim, 1999; Zhang, Kuang, An, Liu, & Huang, 2012; Zhang, Zhou, Hu, Liu, & Kuang, 2009). However, there is no report about the preparation of starch nanoparticles based on W/O microemulsion system with long-chained $C_n$mimX ILs as surfactant until now. Therefore, it is essential to research the possibility of the preparation of starch nanoparticles in W/O microemulsion system with long-chained $C_n$mimX ILs as surfactant.

In this research work, 1-hexadecyl-3-methylimidazolium bromide C_{16}mimBr/butan-1-ol/cyclohexane/water microemulsion was prepared. Then, the phase behavior, thermodynamic properties and the microregion of microemulsion were investigated through dilution experiments, pseudo-ternary phase diagram and conductivity measurement. Starch nanoparticles were prepared based on W/O microemulsion reaction system with C_{16}mimBr as surfactant, acid-treated granular starch as raw material, epichlorohydrin as cross-linker and characterized by scanning electron microscopy (SEM), dynamic light scattering (DLS), X-ray diffractometry (XRD) and Fourier transform infrared spectroscopy (FTIR). Additionally, the drug loading and releasing properties of starch nanoparticles were investigated with methylene blue (MB) as drug model. This work may provide an efficient pathway to synthesis starch nanoparticles and broaden the application of starch nanoparticles in medical filed.

2. Experimental methods

2.1. Materials

1-Hexadecyl-3-methylimidazolium bromide (C_{16}mimBr, >99%) was purchased from Lanzhou Institute of Chemical Physics (Lanzhou, China). Acid-treated granular starch was purchased from Guangzhou Chemical Reagent Co. (Guangzhou, China). All other chemicals were of analytical grade.

2.2. Dilution experiments

An appropriate amount of surfactant (0.5 mmol), water (10 mmol, $\omega_0 = n_w/n_s = 20$), and oil (1 mL) was taken into test tubes, shaken vigorously in a vortex mixer. Then, the tubes were placed in the thermostatic water bath. The cosurfactant alcohol was slowly added in small intervals to the mixture with constant stirring until a clear system appeared. The volume of the alcohol added was recorded. Then, a calculated small volume of oil was added to the system and the solution reverted back to the turbid form.

Alcohol was added again to the turbid system, and another single-phase appeared. The volume of the alcohol added was recorded.

The procedure was repeated several times, the volumes of the oil and alcohol at each step were recorded.

2.3. Calculation of the dilution experiment

For a stable W/O microemulsion system consisting of surfactant (S)/alcohol (A)/alkane (O)/water (W), alcohol mainly distributes between oil phase and interfacial layer. The interfacial composition and structural parameters can be calculated according to the following equations (Chai, Xu, Liu, & Zhu, 2012).

The total number of moles of alcohol n_a can be represented as:

$$n_a = n_a^i + n_a^o \tag{1}$$

where n_a^i and n_a^o are the moles of alcohol at the interfacial layer and in the oil phase, respectively. The solubility of alcohol in the oil phase can be defined as:

$$k = \frac{n_a^o}{n_o} \tag{2}$$

where n_o is the number of mole of oil, combining Eqs. (1) and (2), defining $I = n_a^i/n_s$, and introducing the mole of surfactant n_s, a liner relation can be obtained:

$$\frac{n_a}{n_s} = I + k\left(\frac{n_o}{n_s}\right) \tag{3}$$

In the dilution experiment, n_s is fixed, n_a and n_o are varied, a straight of n_a/n_s versus n_o/n_s can be obtained with slope k ($k = n_a^o/n_o$) and intercept I ($I = n_a^i/n_s$).

The corresponding molar fraction of alcohol in the interface layer (X_a^i) and in the oil phase (X_a^o) can be represented as follows:

$$X_a^i = \frac{n_a^i}{n_a^i + n_s} = \frac{n_a^i/n_s}{n_a^i/n_s + 1} = \frac{I}{I+1} \tag{4}$$

$$X_a^o = \frac{n_a^o}{n_a^o + n_s} = \frac{n_a^o/n_o}{n_a^o/n_o + 1} = \frac{k}{k+1} \tag{5}$$

The distribution constant K can be expressed by I and k

$$K = \frac{X_a^i}{X_a^o} = \frac{I(k+1)}{k(I+1)} \tag{6}$$

The standard free energy change of transferring alcohol from the continuous oil phase to the interfacial layer was calculated from the relation:

$$\Delta G_{0\to i}^0 = -RT\ln K \tag{7}$$

The total volume of liquid drop V_d

$$V_d = V_{H_2O} + V_s + V_a^i \tag{8}$$

$$V_a^i = \frac{In_sM_a}{\rho_a} I = \frac{n_a^i}{n_s} \tag{9}$$