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Original Research Paper

Preparation of hydroxypropyl methyl cellulose phthalate nanoparticles with mixed solvent using supercritical antisolvent process and its application in co-precipitation of insulin

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ABSTRACT

To obtain hydroxypropyl methyl cellulose phthalate (HPMCP)/insulin nanospheres by supercritical antisolvent process, the formation of HPMCP nanoparticles was first investigated. The effects of ratio of the mixed solvent, pressure, temperature, concentration, flow rate of CO_2 and solution on forming HPMCP nanoparticles are discussed. It was found that different morphologies of HPMCP could be produced by varying the ratio of DMSO to acetone in the solvent. The operating parameters were optimized for making HPMCP nanoparticles. Formation of HPMCP/insulin nanospheres was further inspected. The nanospheres with the size ranging from 138 nm to 342 nm were obtained. The loading of insulin in the nanospheres ranged from 10.76% to 16.04% and the encapsulation efficiency reached 100%. The release of insulin is also discussed.

1. Introduction

In recent years, more attentions have been paid to the generation of biopolymer particles encapsulating additives, such as pharmaceuticals, natural products, and cosmetics. In particular, the formation of biopolymer particles containing pharmaceuticals is a good way to produce drugs with controlled release and targeted locations. Supercritical fluid technology has been one of the most promising methods because it can form superfine particles at mild conditions with a narrow size distribution and no organic solvent remains.

The supercritical fluid based techniques for producing micro/nanoparticles can be classified into two main processes: rapid expansion of supercritical solutions (RESS) and supercritical antisolvent process (SAS). According to the properties of the selected biopolymers and additive compounds, a suitable process can be chosen in order to produce the designed particles or co-precipitates. For example, the RESS process is suitable for highly soluble biopolymer in supercritical fluid.

Supercritical antisolvent process (SAS) and its multiform modifications, such as GAS, ASES, PGSS, SAA and SEDS, have been widely used in preparing micro/nanoparticles and micro/nanospheres [1–5]. Song et al. [6] and Sarkari et al. [7] successfully produced L-PLA particles by the SAS process. Their studies highlighted that temperature, pressure, and concentration affected the particle size and morphology. Taki et al. [8] encapsulated diuron in L-PLA by SAS process. The biopolymer and additive compound were dissolved in dichloromethane. The degree of loading was obviously affected by the initial concentration of polymer and diuron.

However, most pairs of biopolymers and additive compounds can not be dissolved in one solvent, so mixed solvents must be used to dissolve two substances. Elvassore et al. [9] used the mixture solvent of DMSO and dichloromethane with 50% ratio to dissolve L-PLA and insulin. After SAS process, it was shown that more than 80% of insulin initially sprayed into vessel was encapsulated in the L-PLA particles. Grassi et al. [10] loaded theophylline into poly(hydroxypropyl methylcellulose) (HPMC) particles by SAS process using a mixture of dichloromethane and ethanol (50/50). It was found that the drug release of the processed samples was slower than that of unprocessed ones. From these results, we can see that the application of mixed solvent can broaden the choice of coating materials in SAS.

Insulin is the most effective drug in diabetes therapy. Generally, diabetes patients have to take it for their whole life. Injection is the most common way to deliver insulin, but it is not convenient for patients. Now oral administration of insulin is regarded as a promising way. Encapsulation is a good method in which insulin could be protected from biodegradation by oral administration. The rate of release can be controlled and the duration of bioactive protein could be prolonged [11–14].

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Hydroxypropyl methyl cellulose phthalate (HPMCP) is cellulose derivate. It is a pH-sensitive polymer which is stable in acidic conditions of the stomach but degradable in enteric conditions. HPMCP is often used as an enteric drug carrier. The aim of this paper is to make nano-encapsulation of insulin by SAS using HPMCP as a coating material to develop the orally administrated insulin. The factors affecting HPMCP nanoparticle formation are discussed followed by nano-encapsulation of insulin and release them from HPMCP matrix.

2. Materials and methods

2.1. Materials

DMSO (AR) and acetone (AR) were purchased from SCR Co., Ltd. (Shanghai, China).

PBS solution was supplied by Beyotime Institute of Biotechnology (Jiangsu, China). The composition of PBS was 1.35 M NaCl, 47 mM KCl, 100 mM Na_2HPO_4, and 20 mM NaH_2PO_4. The pH value of PBS was adjusted to 7.4. HPMCP (Hydroxypropylmethyl Cellulose phthalate, HP55) was purchased from Hopetop Co., Ltd. (Jiangsu, China). Insulin was obtained from WanBang Pharm., Co., Ltd., China. CO_2 of 99.99% purity was supplied from Rui Li, Ltd. (Shanghai, China).

2.2. Phase equilibrium experiments

The phase equilibrium experiments were carried out in an adjustable windowed high pressure vessel. The temperature was controlled by a thermostat having precision of 0.1 K. A certain amount of CO_2 and organic solvent were injected into the vessel with a specific mole ratio forming a two-phase region. Then, the volume of the vessel was gradually decreased until the last gas bubble disappeared. The pressure at which the two-phase region transfers to one-phase was recorded. The process was repeated three times and the average values were reported. A series of data was obtained regarding the relationship of the pressure and compositions by varying sample compositions. The phase equilibrium of the system of CO_2, solute and solvent was obtained.

The VLE data of the CO_2–DMSO–acetone mixture at different temperature was shown in Fig. 1.

2.3. SAS experiment

The SAS experiment apparatus is shown in Fig. 2. CO_2 from the cylinder (A) was condensed by a chiller and pumped into the precipitating vessel (G) by the piston pump (C) via the heat exchanger (D). CO_2 then went into the separator from the precipitating vessel and back to the chiller for circulation. After the pressure and temperature reached the desired values, the liquid solution was injected though inner part of the coaxial nozzle (*I*, Φ_{inner} = 200 μm, Φ_{outer} = 1000 μm) and premixed with SC-CO_2 before entering the vessel (Due to the application of the coaxial nozzle, the current method could be also regarded as a modified SAS technique, SEDS). The flow of the liquid solution could be adjusted by an HPLC pump (E). After all of the solution was injected in the vessel, supercritical CO_2 continued to be pumped into the vessel (G) to remove the remaining solvent, thus ensuring products contain no solvent. The organic solvent could be separated from CO_2 in the separator (H).

2.4. Morphology

Morphological characterization of products was observed by SEM (JOEL, JEM-7401F). A small amount of specimen is placed on

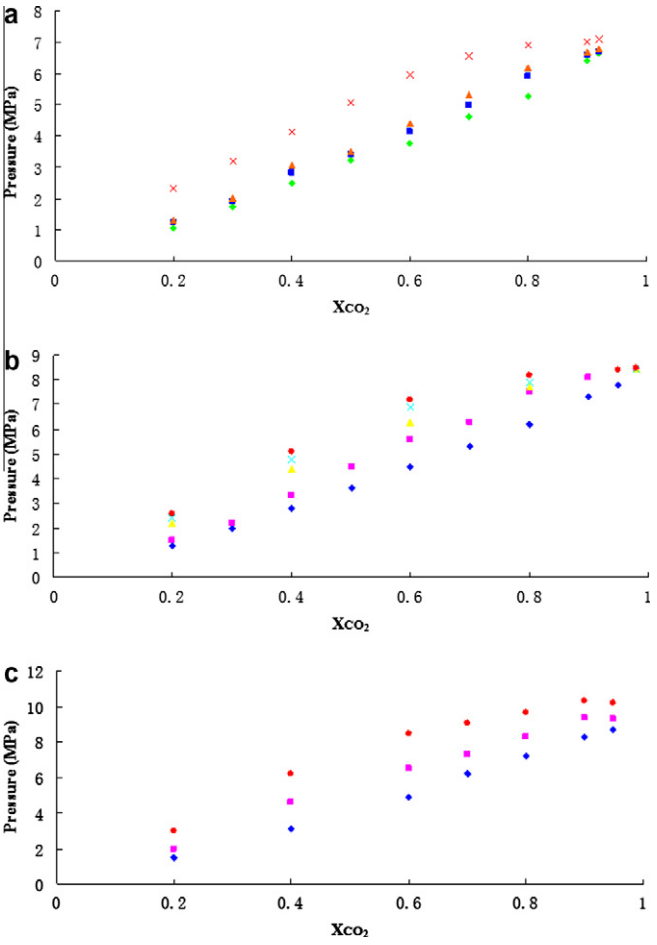

Fig. 1. VLE experimental data: (a) CO_2–DMSO, 305.13 K (×); CO_2–acetone, 305.13 K (●); CO_2–DMSO–acetone (DMSO/acetone = 1:3, volume ratio), 305.13 K (▲); CO_2–DMSO–acetone (DMSO/acetone = 1:5, volume ratio), 305.13 K (■). (b) CO_2–DMSO, 313.13 K (●); CO_2–acetone, 313.13 K (◆); CO_2–DMSO–acetone (DMSO/acetone = 3:1, volume ratio), 313.13 K (×); CO_2–DMSO–acetone (DMSO/acetone = 1:3, volume ratio), 313.13 K (▲); CO_2–DMSO–acetone (DMSO/acetone = 1:5, volume ratio), 313.13 K (■). (c) CO_2–DMSO, 321.13 K (●); CO_2–acetone, 321.13 K (◆); CO_2–DMSO–acetone (DMSO/acetone = 1:3, volume ratio), 313.13 K (■). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

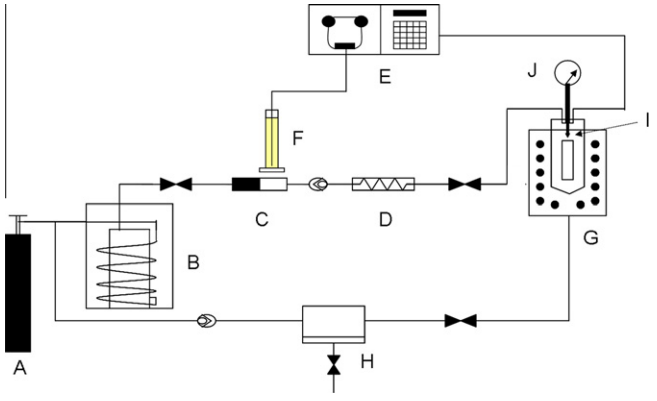

Fig. 2. The apparatus of SAS experiment: (A) CO_2 cylinder; (B) chiller; (C) piston pump; (D) heat exchanger; (E) HPLC pump; (F) solution; (G) vessel (precipitator); (H) separator; (I) nozzle; (J) pressure gauge.