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Coenzyme Q_{10} nanoparticles prepared by a supercritical fluid-based method

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ABSTRACT

A supercritical fluid-based method is proposed to produce coenzyme Q_{10} (CoQ_{10}) nanoparticles. First, CoQ_{10}/polyethylene glycol 6000 composite particles are prepared by a modified PGSS (particles from gas-saturated solutions) process with controlling the flow rate of the gas-saturated solution. Then, CoQ_{10} nanoparticles are obtained by dissolving the composite particles into water. The effect of experimental variables of the modified PGSS process, including pressure, temperature, flow rate of the gas-saturated solution, and mass fraction of CoQ_{10}, on the CoQ_{10} particle size and particle size distribution was investigated. Results show that CoQ_{10} slurry product with a median diameter of 190 nm and yield of 89.8% can be prepared at an optimum condition (operating pressure of 25 MPa, operating temperature of 80 °C, gas-saturated solution flow rate of 1.02 mL/min, CoQ_{10} mass fraction of 40% and nozzle diameter of 100 μm) via the supercritical fluid-based method.

1. Introduction

Coenzyme Q_{10} (CoQ_{10}) is a fat-soluble, vitamin-like substance found in the cells of many organisms. It is widely applied in the pharmaceutical, food, and cosmetic industries [1,2] because it involves in key biochemical reactions that produce energy in cells and acts as an antioxidant [3]. In spite of its wide applications, the long side chain of the 10 isoprenoid units in the molecule makes it poorly water-soluble [4]. It is thought that the poor bioavailability of CoQ_{10} is attributed to the poor water solubility and the high molecular weight [5] and this limits its applications.

To enhance the bioavailability of CoQ_{10}, development of better formulations, such as solid dispersion, cyclodextrin complex inclusion, and liposome, is needed. An effective method for preparing various formulations would however, be to reduce the particle size of CoQ_{10} to as small as possible (to micro- or nano-scale), since the pathways of absorption and efficiency of CoQ_{10} are affected by its particle size. Moreover, the intestine has special mechanism to absorb particles, and there may be a size-exclusion phenomenon in the gastrointestinal absorption of particles, with 100 nm particles showing a significantly higher uptake (10- to 250-fold higher) than larger particles (500 nm to 10 μm) [6]. Some CoQ_{10} formulations containing CoQ_{10} nanoparticles with improved bioavailability were reported. For example, Parkhideh [7] disclosed some CoQ_{10} formulations including nanoparticulate CoQ_{10}, in which the average effective particle size of the CoQ_{10} is less than about 1000 nm.

Nanotechnology has been widely used to prepare CoQ_{10} or CoQ_{10} loaded nanoparticles. Hsu et al. [8] reported on the preparation of CoQ_{10} nanoparticles engineered from microemulsion precursors. Kwon et al. [9] reported on the use of a microfluidization method to prepare CoQ_{10} loaded PMMA nanoparticles, and Nehilla et al. [10] reported on the production of CoQ_{10}-loaded biodegradable PLGA nanoparticles by nano-precipitation. Compared with these methods, supercritical fluid-assisted particle formation technique has many advantages such as simple operation, mild operating conditions and above all, is environmentally benign. Yet, there are few reports on the preparation of CoQ_{10} nanoparticles by supercritical fluid technology. Zu [11] described the preparation of CoQ_{10} nanoparticles by the rapid expansion of supercritical solution (RESS) method. Due to the low solubility of CoQ_{10} in supercritical CO_2, the RESS process needs a huge amount of CO_2 (e.g., 1 g product consumes more than 330 g CO_2 according to the calculated solubility of CoQ_{10} in CO_2 at 25 MPa and 40 °C [12]).

CO_2 consumption in particles from gas-saturated solution process (PGSS™) is much lower than that of RESS. Since the micronization of pharmaceutical nifedipine by PGSS was reported [13], a wide range of pharmaceuticals have been developed using this method [14]. In spite of the versatility of the method, few publications have focused on the preparation of nanoparticles by the process, which is mainly due to the atomization mechanism [15,16]. Nanoparticles are expected to be produced from melt and solution crystallizations with PGSS method [16,17].

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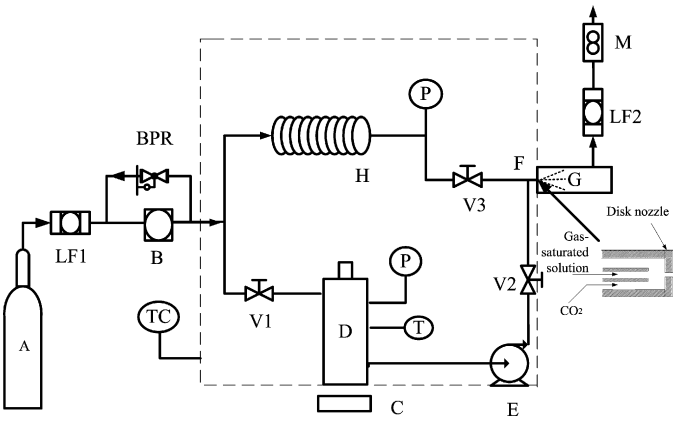

Fig. 1. Schematic diagram of the modified particles from gas-saturated solution process: (A) CO_2 cylinder; (B) compressor; (C) magnetic stirrer; (D) mixer; (E) pump; (F) nozzle; (G) particle precipitator; (H) pre-heater; (BPR) back pressure valve; (V#) valve; (LF#) filter; (T) thermocouple; (P) pressure indicator; (TC) temperature control.

In this study, a modified PGSS process, with the adjustment of the flow rate of the gas-saturated solution, is proposed to prepare nanoparticles of CoQ_{10}. CoQ_{10} is a good candidate for micronization by PGSS process due to its favorable melting temperature of about 49 °C at atmospheric pressure, which further reduces to around room temperature (32.2 °C) in supercritical CO_2 at 7.41 MPa [12]. However, the solidification of pure CoQ_{10} is slow at low temperature (e.g., it takes about 15 min for 1 g of melted CoQ_{10} to be solidified at −30 °C and atmospheric pressure) leading to the formation of large CoQ_{10} particles (>100 μm) by traditional PGSS process due to the coagulation of CoQ_{10} droplets before their solidification. To prevent direct atomization of the melted CoQ_{10} from the formation of microparticles, a water-soluble and non-toxic dispersant, polyethylene glycol (PEG) 6000, is mixed with CoQ_{10} for the modified PGSS process in this study. Through washing with water, the PEG6000 could easily be removed from the CoQ_{10}/PEG6000 composite particles, leaving fine solid CoQ_{10} particles in solution.

2. Experimental

2.1. Materials

CoQ_{10} (purity 99%) was obtained from Kingdomway Vitamin Inc., Xiamen, China. PEG6000 (purity 99%) and anhydrous ethanol (purity 99.7%) were purchased from Chemical Reagent Station, Shanghai, China. Methanol (purity 99.7%) was purchased from Guangfu Fine Chemical Research, Tianjin, China. Carbon dioxide (purity >98%) was provided by Tong'an Air Separation & Special Gas Factory, Xiamen, China.

2.2. Apparatus and procedure

2.2.1. PEG6000/CoQ_{10} composite particles

Fig. 1 shows a sketch of the modified PGSS process apparatus which is composed of a compressor (B) (G447-400, HuizhiP M&E Facilities Co., Ltd, Beijing, China), a pre-heater (H) (a coiled tube) with a magnetic stirrer (C) (2600 rpm), a high-pressure mixer (D), a high pressure liquid pump (E) (J-W 0.5/32, Zhijiang Petrochemical Equipment Co., Ltd, Hangzhou, China), a coaxial nozzle (F) with a house-made disk and a particle precipitator (G). The thickness of the nozzle disk is 0.25 mm with a laser-drilled orifice of 100 μm. The operating temperature is controlled by the water bath with a precision of ±0.1 °C. The pre-expansion pressure of the process is controlled by a back-pressure regulator (BPR) (±0.1 MPa, modified from BY-3, Yantang Equipment Co. Beijing, China). A filter (LF2) is used to recover fine powders before the gas passes through a flow-meter (M) (ML-2, Instrument & Meter Co. Ltd, Changchun, China).

The purpose of using the coaxial nozzle shown in Fig. 1 is to prevent blockage of the nozzle orifice by solid products. In fact, the major difference between this modified PGSS process and conventional PGSS processes is the addition of the high-pressure liquid pump E whose function is to control the delivery of the gas-saturated solution. The advantage of the controlled delivery in the process over conventional ones (in which the melted solute is charged without CO_2 at atmospheric pressure) is: (1) if necessary, the process can be operated at relatively low temperature (due to the depression of the melting temperature of the solid solute in the high pressure CO_2), which is of much importance when thermally sensitive materials are treated or the energy saving issue is concerned; (2) it reduces the problem associated with the nozzle blockage.

The process begins with loading the mixture of PEG6000/CoQ_{10} with fixed mass fraction into the mixer D. Then the temperature of the water bath is increased to expected value according to the mixture's melting temperature at high pressure. CO_2 (from the cylinder) is fed into the PGSS system by the compressor with a pre-expansion pressure (10–25 MPa) controlled by the back-pressure regulator. The CO_2 after the compressor is divided into two parts: one part goes through the pre-heater and V3 (closed before the preparation of the composite particles), and directly into the outer tube of the coaxial nozzle (ID 4.0 mm and OD 6.0 mm) as the atomizing gas. The other part passes through V1 into the high-pressure mixer to form the gas-saturated solution after the CO_2 is well mixed with the PEG6000/CoQ_{10} mixture at a given temperature and stirring (till saturation in about 30 min, this is confirmed by the pressure change in the closed mixer D). The gas-saturated solution then passes through V2 (also closed before the preparation of the composite particles), and is then charged into the inner tube of the coaxial nozzle by the high pressure liquid pump E which controls the flow rate of the solution and is calibrated at different pressures with pure water at ±0.01 mL/min precision. The gas-saturated solution and the atomizing CO_2 then enter the coaxial nozzle and through the disk expand in the precipitator to form the composite particles. The particles are collected by the filter located at the exit of the precipitator and the flow rate of the filtrated gas can finally be measured by the wet flow-meter.

2.2.2. CoQ_{10} nanoparticles

About 5 g of the CoQ_{10}/PEG6000 composite particles (obtained from the above process) was dispersed in 250 mL deionized water at ambient temperature and pressure and stirring for 10 min to completely dissolve the PEG6000 embedded in the particles, leaving the CoQ_{10} particles suspended in the solution which was subsequently separated (from the suspension solution) by a high-speed centrifuge (at a speed of 10,000 r/min in 15 min) to obtain a slurry product containing solid CoQ_{10} nanoparticles. The slurry product was further freeze dried (at 60–70 Pa, −50 °C for 8.5 h) to obtain dry solid CoQ_{10} powders whose yield and purity were then analyzed.

2.3. Analysis methods

The particle size of CoQ_{10} ($D(V, 50)$, volume median diameter, that is, the diameter where 50% of the particle size distribution is above that diameter), and its particle size distribution (PSD) were measured by static method with a laser particle size analyzer (LS908, OMEC, China).

The PEG6000/CoQ_{10} composite particles were used for characterization to investigate the effect of various operating conditions on the size of the produced CoQ_{10} particles. About 10 mg of the PEG6000/CoQ_{10} composite particles was dispersed in 20 mL