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Coenzyme Q10 solubility in supercritical CO_2 using a dynamic system

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ABSTRACT

Coenzyme Q10 (coQ10) is a lipid-soluble antioxidant naturally present in all human cells, which plays a fundamental role during aerobic cellular respiration. The objective of this study was to investigate the solubility of coQ10 in supercritical carbon dioxide (SC-CO_2) using a dynamic semi-continuous process at different conditions of pressure (10.0 to 30.0 MPa), temperature (32 °C to 50 °C) and addition of co-solvent (ethanol at 5 and 10 mol %) for potential scale up. Melting point depression of coQ10 in SC-CO_2 decreased from 51.3 °C at ambient pressure to 32.6 °C after saturation with CO_2 at 8.0 MPa. As expected, coQ10 solubility in SC-CO_2 increased with CO_2 density, from 6.5×10^{-6} g/g_{CO2} at 628.61 kg/m^3 to 3.4×10^{-3} g/g_{CO2} at 909.89 kg/m^3. The addition of 10 mol% of ethanol increased the solubility up to 7.8×10^{-3} g/g_{CO2}. Better understanding of the coQ10 solubility behavior in SC-CO_2 presents potential for developing novel processes for the production of ingredients for functional foods and natural health products.

1. Introduction

Coenzyme Q10 (coQ10) (Fig. 1) is a natural substance present in all human cells and plays a fundamental role during aerobic cellular respiration [1]. It is a lipid-soluble antioxidant [2], commonly sold in the form of supplement capsules, which helps to maintain and/or support cardiovascular health, according to Health Canada [3]. It also helps to reduce the frequency of migraine headaches and associated nausea and vomiting when taken as a prophylactic [3]. CoQ10 deficiency due to genetic mutations can result in different nephropathies, which can be controlled if detected early by coQ10 supplementation, preventing the development of neurological and renal manifestations [4].

The incorporation of coQ10 into functional foods is typically difficult, due to its poor solubility in water and its crystalline nature [5,6]. In order to overcome this challenge, different approaches have been developed for the enhancement of the bioavailability of coQ10 [7]. These include particle size reduction [8], solid dispersion [9], cyclodextrin complexation [10], oily formulations [11] and self-emulsifying drug delivery systems (SEDDS) [12]. Another approach to increase the bioavailability of coQ10 includes the preparation of delivery systems using supercritical carbon dioxide (SC-CO_2) processes. Meng et al. [13] studied the formation of nanoparticles of coQ10 by rapid expansion of supercritical solution (RESS), in an effort to improve its oral bioavailability. Nanoparticles in the range of 151.7 ± 29.1 nm to 299.6 ± 48.3 nm were obtained, which, unlike the unprocessed coQ10, dispersed in water resulting in a solubility of 0.19 mg/mL.

To better understand the mechanisms of particle formation targeting delivery systems using SC-CO_2, research concerning the behavior and applications of coQ10 in SC-CO_2 has been undertaken. However, developing such novel processing approaches requires fundamental information. The density of mixtures of coQ10 and SC-CO_2 was measured by Pečar and Doleček [14] in the range of 35–60 °C and 10.0–40.0 MPa and partial molar volume, isothermal compressibility, isobaric thermal expansivity, internal pressure and cluster size were calculated from the values obtained. The melting point depression and the binary three-phase solid-liquid-gas equilibrium of coQ10 in SC-CO_2 were studied by Li et al. [15]. The solubility of coQ10 in SC-CO_2 in batch mode was investigated by Matias et al. [16] in the pressure range of 9.2–26.2 MPa and temperature range of 32–50 °C. They reported solubilities in the range of 10^{-5}–10^{-4} mole fraction. It was also found that an addition of 5 to 15% of ethanol as co-solvent improves the solubility by up to eight times. Considering this solubility behavior, several authors have studied the extraction of coQ10 from different sources using SC-CO_2, such as *Pseudomonas diminuta* [17], activated sludge [18,19], the photosynthetic bacterium *Rhodobium marinum* [20] and *Artemia* (brine shrimp) [21].

Building on the existing fundamental data, the objective of this work was to investigate the solubility of coQ10 in SC-CO_2 using a dynamic semi-continuous process at different conditions of pressure, temperature and co-solvent (ethanol) addition in order to assess the feasibility of developing continuous processes involving coQ10 using SC-CO_2. Melting point depression of coQ10 in SC-CO_2 was also

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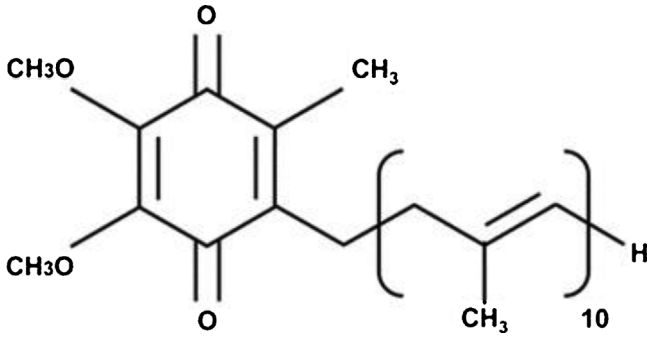

Fig. 1. Molecular structure of coenzyme Q10.

investigated at pressures of up to 15.0 MPa to assess the range of temperatures to be studied for solubility determination. Based on the melting point depression observed, the conditions chosen to be tested for the solubility of coQ10 in SC-CO_2 were in the ranges of 10.0–30.0 MPa, 32–50 °C and 0–10 mol % of ethanol addition.

2. Materials and methods

2.1. Materials

Coenzyme Q10 (98.34% purity) was purchased from PureBulk (Roseburg, OR, USA). CO_2 (99.9% purity, < 3 ppm H_2O) was purchased from Praxair Canada Inc. (Mississauga, ON, Canada), while ethanol (food grade) was purchased from Commercial Alcohols Inc. (Toronto, ON, Canada).

2.2. Melting point determination

2.2.1. Experimental unit

The unit used for the determination of the melting point depression of coQ10 in SC-CO_2 was described in detail previously [22]. Briefly, this unit consisted of a 10 mL high pressure view cell equipped with sapphire windows (Phase equilibria unit, Sitec Sieber Engineering, Zurich, Switzerland). The temperature was controlled by a recirculating water bath (Lauda, RM 6, Delran, NJ, USA) attached to the jacket around the cell. CO_2 was pumped into the cell and pressurized by a syringe pump (Teledyne ISCO, model 260D, Lincoln, NE, USA).

2.2.2. Experimental protocol

For the melting point experiments, coQ10 was placed inside an HPLC glass insert (4.6 mm in diameter, 31.4 mm in length), which was placed inside an HPLC vial and melted on a heating plate. Due to the extent of volume contraction when coQ10 melts, more coQ10 was introduced into the HPLC insert and melted again. The HPLC vial and insert with coQ10 were quickly transferred to the previously heated high pressure cell to maintain coQ10 in the liquid state. Then, the high pressure cell was filled with CO_2 at the desired pressure and left to stabilize for 1 h. This allows enough equilibration time for the CO_2 to dissolve in the molten coQ10 and saturate it. Then, the temperature was lowered to a level of 5 °C below the point at which solidification was observed. The temperature was then slowly increased (0.6 °C/min) until the first light across the coQ10 was observed, indicating the first point of melting.

2.3. Solubility determination

2.3.1. Experimental unit

The unit used for the determination of coQ10 solubility in SC-CO_2 is presented in Fig. 2. CO_2 was pumped by means of a syringe pump (Dionex, Series 600 SFC, Sunnyvale, CA, USA) into a high pressure vessel where coQ10 was placed. The high pressure vessel was a stainless steel tube (7 mm ID and 191 mm length), capped at both ends with glass wool and on the exit side with a sintered metal filter to avoid dragging of unsolubilized coQ10. A co-solvent can also be pumped co-currently with the CO_2 into the vessel by a liquid pump (Gilson 305, Middleton, WI, USA). Co-solvent was mixed with SC-CO_2 in a tee connection prior to entering the high-pressure vessel. Between the tee connection and the vessel, a long loop (stainless steel tube, 100 cm length × 1.25 mm ID) was introduced to guarantee enough contact time between SC-CO_2 and ethanol to ensure complete miscibility before entering the vessel. This loop also served as a preheater to ensure that SC-CO_2 or SC-CO_2 + ethanol had enough residence time inside the oven to reach the desired temperature before entering the high pressure vessel. The high pressure vessel was kept inside an oven (Dionex, Series 600 SFC/GC, Sunnyvale, CA, USA) to control temperature. At the exit of the oven, SC-CO_2 with solubilized coQ10 was decompressed into a collection vessel by means of a micrometering valve (Parker Autoclave Engineers, 10VRMM2812, Erie, PA, USA). The flow rate was measured at the exit of the collection vessel by a flow meter (Canadian Meter Company Limited, Type AL225, Cambridge, ON, Canada). The collection vessel was kept refrigerated by a cooling bath (Haake F3 circulator with Haake K bath, Berlin, Germany) to ensure precipitation of coQ10 and minimize any loss in exhausted CO_2. The line at the exit of the oven was heated by a heating rope and the temperatures of all the heated zones were controlled by a 6-channel temperature controller (OMEGA, CN616TC1, Norwalk, CT, USA).

2.3.2. Experimental protocol

An appropriate amount (ca. 0.5 g) of coQ10 was weighed and introduced into the high pressure vessel, capped at both ends with glass wool and a sintered metal filter at the exit side, both to avoid coQ10 particles from falling out of the vessel while handling it and to avoid it from being dragged out of the vessel without being dissolved by SC-CO_2 during the operation. The vessel was assembled in the unit and temperatures were stabilized before introduction of SC-CO_2. CO_2 was pumped into the vessel at the desired pressure by the syringe pump. In those experiments where ethanol was used as a co-solvent, ethanol was pressurized and pumped in by the liquid pump. Once the temperature and pressure of the system were stabilized, flow of CO_2 through the vessel was started. The flow rate of SC-CO_2 was regulated by the opening of the micrometering valve, according to the values read on the flow meter. Extract samples were collected every 30 min, at which time the cumulative amount of CO_2 that passed through the flow meter was recorded and the amount of coQ10 collected was measured gravimetrically. At the end of each experiment, the micrometering valve and exit tubing were also disassembled and washed with ethanol to collect the precipitated coQ10. The amount of coQ10 collected in the collection vessel was also measured and combined with the amount of coQ10 precipitated in the tubing. For those samples where ethanol was used as co-solvent, ethanol was evaporated under a gentle flow of nitrogen prior to the gravimetric measurement and ensuring that constant weight is reached.

2.4. Experimental design

For the melting point determination, 5 pressures were tested (0, 4.0, 8.0, 10.0 and 15.0 MPa). One of the pressures (10.0 MPa) was selected to perform triplicates in order to assess the reproducibility of the method.

For the solubility determination three parameters were tested: temperature (32, 40 and 50 °C), pressure (10.0, 15.0, 20.0, and 30.0 MPa) and addition of co-solvent (5 or 10 mol% of ethanol). At 32 and 40 °C, the four pressures were tested without the addition of co-solvent, while at 50 °C only 20.0 MPa was tested. All experiments were performed at the SC-CO_2 flow rate of 0.5 L/min (0.91 g/min) (measured at ambient conditions). This flow rate value was chosen based on preliminary testing at different flow rates and taking into consideration

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