COENZYME Q_{10} MICROPARTICLES FORMATION WITH SUPERCritical CARBON DIOXIDE

FORMACIÓN DE MICROPARTÍCULAS DE COENZIMA Q_{10} CON DIÓXIDO DE CARBONO SUPERCRÍTICO

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Recibido 4 de Noviembre 2014; Aceptado 15 de Febrero de 2015

Abstract

Coenzyme Q_{10} is a powerful antioxidant used on cardiovascular, neurodegenerative and cancer diseases. Its hydrophobic nature do limit its applications, because human body absorbs it with difficulty, that is why it was proposed to increase its bioavailability by diminishing the particle size using supercritical carbon dioxide. It was determined experimentally the phase behavior of the coenzyme in a supercritical system. The equilibrium data and a factorial 2^k experimental design were utilized to find how the shape and size of the microparticles are affected by temperature, coQ_{10} concentration and nozzle diameter. Microparticles were characterized using infrared spectrometry and chromatography. For verify the fundamental chemical structure, the size and the shape of the microparticles was used scanning electronic microscopy. It was found a significant decrease in particle size and a modification of physical structure. The antioxidant power of coQ_{10} after micronization was measured, showing an increase of this property. Finally, in order to evaluate the bioavailability, the kinetic of solubility was determined in ethanol, having a substantial increase on solubilization speed of micronized coQ_{10} compared with the commercial one.

Keywords: coenzyme Q_{10}, bioavailability, micronization, supercritical carbon dioxide.

Resumen

La coenzima Q_{10} es un potente antioxidante utilizado en las enfermedades cardiovasculares, neurodegenerativas y el cáncer. Su naturaleza hidrofóbica limita sus aplicaciones, ya que el cuerpo humano la absorbe con dificultad, es por eso que se propone aumentar su biodisponibilidad al disminuir el tamaño de partícula utilizando dióxido de carbono supercrítico. Se determinó experimentalmente el comportamiento de fases de la coenzima en un sistema supercrítico. Los datos de equilibrio y un diseño experimental factorial 2^k se utilizaron para encontrar cómo la forma y el tamaño de las micropartículas se ven afectados por la temperatura, la concentración de coQ_{10} y diámetro de la boquilla. Las micropartículas se caracterizaron mediante espectrometría de infrarrojo y cromatografía. Para verificar la estructura química fundamental, el tamaño y la forma de las micropartículas se utilizó microscopía electrónica de barrido. Se encontró una disminución significativa en el tamaño de partícula y una modificación de la estructura física. El poder antioxidante de coQ_{10} micronizada se incrementó de manera importante. Por último, con el fin de evaluar la biodisponibilidad, se determinó la cinética de la solubilidad en etanol, y se encontró un aumento sustancial en la velocidad de solubilización de la coQ_{10} micronizada en comparación con la coenzima Q_{10} comercial.

Palabras clave: coenzima Q_{10}, biodisponibilidad, micronización, dióxido de carbono supercrítico.

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Publicado por la Academia Mexicana de Investigación y Docencia en Ingeniería Química A.C.
1 Introduction

CoQ$_{10}$ is an orange colored substance present in every cell in the human body accomplishing an essential roll on adenosine triphosphate (ATP), which is the source of energy used by cells to carry on several chemical reactions needed to sustain (Pecar and Dolecek, 2007).

Utilization of coQ$_{10}$ on medical treatments was made in Japan for the first time, in order to attack cardiovascular diseases and other heart conditions. Sometime later it was implemented in medical treatments against cancer, reporting several benefits to health (Pecar and Dolecek, 2007; Laplante et al., 2009). The therapeutically value of coQ$_{10}$ has been also proved with success along with standard medical therapy on diabetes, pediatric cardiopathies and neurodegenerative diseases like Parkinson and Huntington (Pecar and Dolecek, 2007; Bhagavan and Chopra, 2007; Galpern and Cudkowic, 2007).

However the hydrophobic nature of this compound makes difficult its absorption in the human organism. Several commercial formulations have been proposed with coQ$_{10}$, but the challenge of increasing its capability to be dispersed in aqueous solutions has not been solved and hence its bioavailability. This work has the aim to increase coQ$_{10}$ bioavailability by raising its solubility in aqueous media, through the increase of superficial contact area with solvents decreasing the particle size of microcapsules obtained by micronization. An application of supercritical fluids is in fact the production of micronized particles by using several techniques: Rapid Expansion Supercritical Solutions (RESS), which has been used successfully to process high valued compounds, being able to control particle sizes and size distribution by handling variables involved on RESS (Santos and Meireles, 2013). Finally and due to the low solubility of the coenzyme in CO$_2$SC, it has been proposed the use of acetone as a cosolvent.

2 Materials and methods

2.1 Materials

CoQ$_{10}$ was provided by Nano Nutrition S. de R.L. de C.V. (Mexico), carbon dioxide (CO$_2$) high purity (99.99%) was acquired from Infra S.A. de C. V. (Mexico), acetone (99.8%) was obtained from J.T. Baker degree HPLC (Mexico).

2.2 RESS technique and equipment

The RESS process consists of two phases, a phase of solubilization of the solute in a supercritical fluid (FSC) (in case of a solute with low solubility on FSC, it is possible to use a co-solvent) and then a fast expansion or depressurization. Those phases are illustrated on figure 1.

The equipment used to produce microparticles by RESS technique is shown on figure 2. It consists of two systems, a system with high pressure and a system to feed and pressurize CO$_2$. The high pressure system is composed by a CO$_2$ compression cylinder (pressure generator High Pressure Equipment, HIP) and a high pressure cell (HPC), where the supercritical solution is prepared and maintained on equilibrium until the expansion that produces microparticles; this system is provided with a pressure (SENSOTEC, model TJF/7039-03), indicator device (SENSOTEC model GM), a temperature regulator (Cole-Palmer, model Polystat®) and a thermometer (FLUKE, model 1504).
2.3 Formation of microparticles using RESS technique

The high pressure cell was loaded with an approximately 5 g of the coQ10-acetone solution, depending on conditions to be studied and established by an experimental design type $2^k$, with $k=4$ (table 1, three levels of temperature were used to observe their effect). A mass between 10 and 20 g of CO$_2$ was added, previously calculated with density determined at P and T from inside the addition tank), in order to keep the desired CO$_2$ percentage (50 and 80%). The system is fixed on process conditions ($P = 200$ bar and temperature determined by experimental design), letting the system to reach a stable homogeneous phase during 30 minutes. The nozzle is then inserted in the aluminum box, followed by the expansion of the supercritical solution through a nozzle with a predetermined diameter (50 or 100 µm), being necessary to maintain a constant pressure during the process.

2.4 Scanning Electron Microscopy (SEM)

The micrographs of commercial and micronized coQ$_{10}$ were obtained with a scanning electron microscopy low vacuum JEOL JSM-5900 LV. The measurement of the particles diameter has been made with the software Digital Micrograph® (Version 1.71.38. Gatan, Inc.). A minimum of 100 microparticles per treatment were observed.

2.5 Infrared Spectrophotometry (IR)

The Infrared spectra of commercial or micronized coQ$_{10}$ were determined with a Perkin Elmer Spectrophotometer, model 1600, using a resolution of $4 \text{ cm}^{-1}$ and 3 times scan. Potassium bromide has been used to place the samples.

2.6 Liquid Chromatography with reverse phase (HPLC-r)

Chromatograms of commercial or small size micronized coQ$_{10}$ were obtained by Liquid chromatography with a Hewlett Packard, series II1090, equipped with a flame ionization detector. A column Purospher $125 \times 1 \text{ RP18}$ of 5 µm (C18). The fluid phase was a solution of methanol:n-hexane (9:1) flowing at 1.5 ml min$^{-1}$. 

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Table 1. Experimental design.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CO$_2$ in supercritical solution (%weight)</th>
<th>Temperature (°C)</th>
<th>coQ$_{10}$ in supercritical solution (%weight)</th>
<th>Nozzle diameter (µm)</th>
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2.7 Antioxidant capability (Method reducing the radical DPPH)

Determination of antioxidant capability of micronized coQ10 was carried out with the radical DPPH (1,1-diphenyl-2-picryl-hidrazyl) discoloring method (García-Márquez et al., 2012; Cotelle et al., 1996; Gámez et al., 1998; Cavin et al., 1998). This method is based on the capability of antioxidant compounds to catch electrons from the free radical DPPH. First, it was prepared a blend with 50 µL of a coenzyme solution and 150 µL of an ethanolic solution of DPPH (concentration of 1000 µM coQ10 / DPPH and 100 µM DPPH/ethanol). The blend was incubated during 30 minutes at 37°C constantly stirred. The absorbance was measured at 515 nm on an Ultra Microplate Reader, model ELX 808, Bio Tek Instruments Co. Percentage of antioxidant activity against radical DPPH was calculated with the following equation:

\[
\%\text{inhibition} = \frac{\text{Absorbance}_{\text{control}} - \text{Absorbance}_{\text{problem}}}{\text{Absorbance}_{\text{control}}} \times 100
\]  

(1)

2.8 Kinetics of solubility in ethanol

Solubility curves of commercial or smaller micronized coQ10 were measured by UV - VIS spectrophotometry. Model Cary 50 CONC, Varian. Absorbance at 407 nm was correlated to concentration of coQ10 in ethanol, by preparing solutions from 0.00 to 0.16% (w/w) of coQ10 (0 to 1270 mg/L). To determine solubility kinetics, absorbance was measured as a function of time, initiating with a saturated solution (7 mg of coQ10 and 5 ml of ethanol). A measurement was made every 1 hour until accomplishment of 10 points.

3 Results and discussion

Obtained results emerging from the experimental design are showed on table 2, besides characterization results of commercial coQ10 particles.

Table 2. Summary results of microparticles

<table>
<thead>
<tr>
<th>Process variables</th>
<th>Response variables</th>
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<tr>
<td>coQ10 concentration in supercritical solution (% weight)</td>
<td>Temperature (°C)</td>
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<tr>
<td>coQ10 commercial</td>
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<td><a href="http://www.rmiq.org">www.rmiq.org</a></td>
<td>52</td>
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</table>
A decrease of particle size of commercial $\text{coQ}_{10}$ particles was observed, which originally had an average diameter of 79.78 $\mu$m. In this case particles with average diameter 0.84 to 21.71 $\mu$m were obtained. Besides, micronized particles had size distributions narrower than the commercial ones, which mean that their differential between maximal and minimal values (DMM) was around 11.5 $\mu$m and 316 $\mu$m respectively.

There existed also modifications of $\text{coQ}_{10}$ morphology, as showed on figure 3. Clusters or accumulations of encapsulating material on the surface of commercial coenzyme were essentially amorphous (figure 3A), whereas those on micronized particles were generally spherical (figure 3C). It was observed that micronization reorganized structures (figures 3B and 3D), by doing smaller, thinner and cordoned flakes, allowing to imagine the growing dynamic of microparticles, having at the same time an increase of superficial area of the coenzyme.

3.1 Effect of process variables on microparticles shape, size and size distribution

3.1.1 Effect of temperature

The figures 4 and 5 show the effect of the temperature for concentrations of 0.2% and 2.5% to nozzle diameters of 50 $\mu$m (figure 4) and 100 $\mu$m (figure 5) where it is observed that to a concentration of $\text{coQ}_{10}$ to 0.2% doesn’t show up an effect of the temperature with distributions in the closed particle size, contrary to concentration of 2.5% where the particle size is increased with the increment of the temperature with more deviations standard. For all the following figures, the dotted shown lines are tendencies.

At a concentration of 0.2% (w/w) of $\text{coQ}_{10}$ in the supercritical solution, it was not observed a significant effect of temperature on microparticles size or morphology; particles diameter was around the value of 3.4 $\mu$m, with standard deviations between 0.96-1.16. The same effect was observed for a concentration of 0.5% of $\text{coQ}_{10}$ (3.57 $\mu$m average size, with standard deviations between 0.88-1.05). However, for concentrations of 1.0% and 2.5%, an increase on temperature induced a race on particle diameter with more deviations standard; taking into account both nozzle diameters. At 2.5% of $\text{coQ}_{10}$ and nozzle diameter of 50 $\mu$m, an increase on temperature induced bigger particle sizes, with a nozzle of 100 $\mu$m, a less significant increase of diameter was the result.
Particle sizes average from 5 µm to 21.71 µm with deviations standard up of 3 µm.

The morphology of \( \text{coQ}_{10} \) to concentration of 0.2% is solid particles of uniform size shown in the figures 6A-D at 35° and 55°C. In the case of \( \text{coQ}_{10} \) concentration of 1.0% it was found that an increment in the temperature induces an increase in the particle diameter; to both temperatures they are formed spherical accumulations of flakes (figures 7A and C), however at 35°C solid microparticles and flakes (figure 7B) are observed also, while at 55°C, circular accumulations of flakes (figure 7D).

For a concentration of 2.5%, the forms of the particles are accumulations of flakes of sizes to 5 µm. In the figures 8A and B morphologies are shown to 35°C and 8C and D at 55°C.

Summarizing, at low concentrations of \( \text{coQ}_{10} \) in a supercritical solution (0.2 and 0.5% w/w), temperature had not an effect on particle size neither on their morphology, but at higher concentrations (1.0 and 2.5% w/w), an increase of temperature carried an increase on microparticles size, and a modification on their morphology, as well as an effect on particle size distribution (Kwauk and Debenedetti, 1993; Carrillo-Navas et al., 2011), developing a mathematical model for the RESS technique, founded that an increase of temperature produced more important
particle diameters. The same effect was observed by micronizing salicylic acid (Reverchon *et al*., 1993; Yildiz *et al*., 2007), naphthalene (Liu and Nagahama, 1996; Türk, 1999), hyaluronic acid (HYAFF-11) (Benedetti *et al*., 1996), benzoic acid (Türk, 2000; Helfgen *et al*., 2001; Türk *et al*., 2002), perfluoro polyether diamide (PFD) (Chernyak *et al*., 2001), tetraphenyl porphyrine fluorated (TBTPP) (Sane and Thies, 2005) and chitin (Salinas-Hernández *et al*., 2009). On the other hand, it has been determined that temperature has no effect on size or morphology of cholesterol (Türk, 1999; Helfgen *et al*., 2001), griseofulvin (Helfgen *et al*., 2001; Türk *et al*., 2002), β-sitosterol (Türk *et al*., 2002), aspirine (Huang and Moriyoshi, 2006) or felodipine (FLD) (Chiou *et al*., 2006) microparticles. This could be related to a low solubility of those compounds in supercritical solvents, which produces no detectable changes on microparticles shape and size.

3.1.2 Effect of nozzle diameter

At concentrations of coQ10 in a supercritical solution of 0.2, 0.5 and 1.0% w/w, the nozzle diameter had no significant effect on shape, size or size distribution of microparticles, however at 2.5% w/w and 35°C, an increase of the nozzle diameter induced an increase of the particle diameter, whereas 45°C and 55°C the opposite effect was observed (figure 9). Morphology and size distribution were not affected by the nozzle diameter, being the average DMM of 5.53 µm with a nozzle of 50 µm, and of 5.58 µm with a nozzle of 100 µm.

Foster and coworkers (Foster *et al*., 2003), reported no effect of the nozzle diameter on shape or particle size of micronized ibuprofen manufactured with the RESS technique, perhaps this is due to its low solubility. The team work of Huang, also observed the phenomenon during production of aspirin microparticles (Huang *et al*., 2005). On the other hand, progesterone was micronized and the results founded were that bigger nozzle diameters produced more important particle sizes (Alessi *et al*., 1996), being the same phenomenon observed for micronized loperamide (Huang and Moriyoshi, 2006).

3.1.3 Effect of coQ10 concentration in the supercritical solution

At 35°C an increase of the coQ10 concentration in the supercritical solution produced a small increase of microparticles diameter.
Figure 11. Effect of coQ10 concentration on the size of microparticles at 55 °C.

and of the width of the size distribution or DMM, besides a modification of microparticles morphology at 55°C. This same effect has been found by Tom and Debenedetti (Tom and Debenedetti, 1994) when they produced polymeric microparticles, by Lele and Shine (Lele and Shine, 1994) with PMMA. At unsaturated conditions of the supercritical (0.08% w/w) dusts were formed, whereas at conditions closer to saturation (0.263% w/w) bigger fibers were produced.

Santoyo-Arreola (Santoyo-Arreola, 2006), determined that at concentrations around 20% of 1,1-Dihydroperfluorooctyl Methacrylate (PFOMA) bigger microspheres were obtained (5 µm) than at 5% (2 µm). Salinas-Hernández et al. (2009) found that using chitin, an increase of its concentration is followed by an increase of the average particle diameter, of the standard deviation and of the width of particle size distribution DMM.

The augmentation of the average particle diameter motivated by an increase of the concentration could be due to a higher quantity of solute in the supercritical solution, facilitating contacts and interactions between particles of coQ10, inducing bigger circular accumulations. According to Türk (2009), the speed of particles collision is directly proportional to the solute concentration to the power of two.

3.2 Spectrophotometry IR

IR spectra of commercial or micronized coQ10 are shown in figure 12. In this work, conditions such as pressure, temperature and contact with organic solvents (supercritical carbon dioxide and acetone) suffered by the coenzyme during RESS technique, they did not induced any modification of wavelength of vibration of the electron bonds in the coQ10 molecule that could insinuate interactions of functional groups. We can also note that there was no remaining molecule of acetone, because if there were, this solvent would absorb IR light at 1240 cm$^{-1}$, wavelength characteristic of the keto group.

3.3 Liquid chromatography with reverse phase (HPLC-r)

Chromatograms of commercial or micronized coQ10 are represented on figures 13 and 14 respectively.
Retention times of both samples are similar (9.787 and 9.871 minutes), putting in evidence that micronized molecules of coQ$_{10}$ have not been modified in their fundamental chemical structure by the conditions of the process during the RESS technique.

### 3.4 Antioxidant capability

The antioxidant capability of commercial coQ$_{10}$ and microparticles of coQ$_{10}$ elaborated with a treatment allowing to obtain the smallest particle diameter (concentration of 0.5% in a supercritical solution at 55°C and 200 bar of pressure, with a nozzle diameter of 50 µm) was determined using the method of radical reduction of DPPH. A statistical analysis of results (test t) was made using the software Minitab® 15 (Statistical software. Minitab, Inc.). Obtained results are shown in table 3.

Normality and variance equality test were carried out, having a P=0.443 and 0.581, respectively. The difference between the average value of both groups was 5.86%, reporting a t value of 4.875 with 8 degrees of freedom (P=0.001) and with a confidence interval of 95% of the interval between average values from 3.087 to 8.629. The alpha value used for the test was 0.050. With this statistical analysis it was proved that the difference between average values for micronized coQ$_{10}$ and commercial coQ$_{10}$ is more important the one expected randomly and, hence there is a significant difference between antioxidant capabilities of both groups.

As shown in table 3, the average of the antioxidant capability of commercial coQ$_{10}$ is 2.14%, whereas for micronized coQ$_{10}$ is 8.00%, showing this way a significant increase of the antioxidant capability of the coenzyme micronized.

This phenomenon is possibly due to a reduction of the particle size that induces an increase of the contact surface between the coenzyme and free radicals present in the surrounding medium, making possible to accomplish the oxidant trapping function of the coQ$_{10}$.

### 3.5 Kinetics of solubility in ethanol

The kinetic of solubility of coQ$_{10}$ in ethanol at 25°C is reported on figure 15, reaching a maximal concentration for both coenzymes after 10 hours and being of 1200 mg/L. Since the first hour the micronized coenzyme showed a solubility of 53% (640 mg/L) and it continues to increase toward the hour 7 where solubility reaches saturation, whereas coQ$_{10}$ reaches this concentration 6 hours later, getting saturation after 10 hours. The concentration of micronized coenzyme, compared with the commercial one is higher after 10 hours, being 4 times superior at one hour after the kinetic begins, 3 times higher between the hour 1 and the hour 6 and 2 times bigger between hour 6 and 7.

### Conclusions

Micronization decrease the particle size of commercial coQ$_{10}$, producing microparticles diameters in a range from 0.84 to 21.71 µm, with particle size distribution narrower than commercial particles, modifying at the same time the morphology, going from amorphous accumulations to spheres.

The studied variables showed an effect on the particle size. Temperature has a significant effect at 1.0 and 2.5% w/w of coQ$_{10}$ in a supercritical solution. An increase of temperature induces bigger particle sizes and a more important distribution of sizes. The effect of the nozzle diameter is related to temperature. With a concentration of coQ$_{10}$ in the supercritical solution of 2.5% w/w and 35°C, an increase of the nozzle diameter induces bigger particle diameters, opposing to 55°C where the contrary effect is observed. Concerning concentration of coQ$_{10}$ in the supercritical solution, its increase induces more important particle sizes and size distributions, and morphological modification. This effect is more
significant at higher temperatures.

A reduction of particle size possibly induces an increase on contact surface, obtaining thus a significant augmentation of the antioxidant capability of the coenzyme; micronized coQ$_{10}$ can achieve a 4 times higher antioxidant capability than the commercial one. Finally, the decrease of the particle size of coQ$_{10}$ considerably increases its solubilization speed in ethanol, although it has been proved in organic solvents, this possibly an indicator of the bioavailability increase.

Acknowledgements

Authors wish to acknowledge the grant obtained from the Mexican National Council of Sciences and Technology, given through the project 83842.

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