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Generation of quercetin/cellulose acetate phthalate systems for delivery by supercritical antisolvent process

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ABSTRACT

Supercritical antisolvent process (SAS) has been used to precipitate microparticles of quercetin, a plant pigment found in many foods and used for medical treatments, pharmaceutical and cosmetic industries, together with nanoparticles of cellulose acetate phthalate (CAP), a polymer quite frequently used in drug delivery. Previously, precipitation of nanoparticles of CAP by the same process was studied at different conditions of pressure, temperature, CO_2 and solution flow rates, nozzle diameter and initial concentration of the solution. Morphologies of the precipitates were analyzed by scanning electron microscopy (SEM). A range between 84 and 145 nm of diameter in spherical particle were achievement in CAP precipitation. A same range of semi-spherical particles of CAP around 145 nm and needle-like particle of quercetin was obtained in the coprecipitation experiments. X-ray diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FTIR) were carried out to find out the possible loss of crystallinity of the coprecipitates and the possible interactions between the polymer and quercetin, respectively. Release profiles of quercetin were carried out in simulated gastric and intestinal fluids. Higher quercetin:polymer ratios in the coprecipitates are recommended to achieve faster release and higher solubilities of quercetin in the assayed time. This fact would allow its use in pharmaceutical, cosmetic or nutraceutical applications.

1. Introduction

Quercetin is a flavonoid present in many fruits and vegetables, also in different drinks (Formica, 1995; Singhal et al., 2011). The main property of this molecule is its antioxidant action, but it shows different benefits as anti-inflammatory, cardiovascular health, antibacterial and anticancer effects (Boots et al., 2008; Sahoo et al., 2011a). The efficacy of quercetin is limited because of its low solubility in aqueous media and poor gastrointestinal absorption which complicates their possible oral delivery and decreases its bioavailability and biological activity (Van der Merwe et al., 2012; Srinivas et al., 2010).

Cellulose acetate phthalate is a cellulose derivative used in various controlled and sustained drug delivery applications (Garg et al., 2016a). In terms of safety, CAP is generally nontoxic for use in human biological system (Neurath et al., 2001). Particularly, it is used in intestinal delivery because CAP resists gastric media fluids and degrades around pH 6.8 (Sousa e Silva et al., 2013). CAP has been used with different techniques as oil-water solvent evaporation (Hanafi et al., 2013), emulsification-solvent evaporation (Rahman et al., 2010; Shalin Thakker et al., 2014) and spray drying (Sansone et al., 2009) to encapsulate drugs for oral delivery and thus avoid partially gastric degradation of the molecules and improve its bioavailability from solid oral dosage forms. Concretely, Scarfato et al. (2008) prepared successfully the microencapsulation of quercetin contained microspheres using CAP with an oil/water evaporation method, showing its efficiency protecting quercetin in gastric fluid.

Supercritical CO_2 ($scCO_2$) has been widely use to obtain nanoparticles of nutraceutical, drugs, polymers and so on. It has low toxicity, low cost and relatively low critical temperature (31.1 °C) and pressure (73.8 bar), so quite adequate to process thermolabile solutes in agreement of environment (Jung & Perrut, 2001; Martin & Cocero, 2008). Moreover, using $scCO_2$ processes offer several advantages such as higher product quality in terms of purity, more uniform dimensional characteristics and its properties can be also adjusted continuously by altering the experimental conditions (Martín & Cocero, 2008; Cocero et al., 2009).

Particularly, supercritical antisolvent process (SAS) is appropriated to precipitate polyphenols as quercetin due to its low solubility in supercritical CO_2. In this process a solution of the active substance is sprayed through a nozzle into the vessel containing CO_2 at supercritical conditions. Then $scCO_2$ diffuses into the drops of solvent and vice versa leading to a high supersaturation of the mix solution and taking place a powder precipitation.

Precisely, in a previous work the optimization of quercetin precipitation by SAS process was carried out (Montes et al., 2015). In spite of the

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micronization of quercetin improves considerably the dissolution rate, the use of a coating agent would contribute to a protection against degradation. CAP has never been precipitated by SAS process and also never used in coprecipitation experiments of any active substance by this technique. However, previous studies carried out by Fraile et al. (2014) achieved the quercetin coprecipitation using Pluronic F127 as polymer by SAS technique getting a no degradation of the product and a faster dissolution than raw quercetin.

In this work quercetin was coprecipitated with CAP in order to prepare new drug delivery systems by SAS process. In a first step, SAS was applied to CAP, tailoring the operating conditions to use it in the quercetin co-precipitation experiments. Different mass ratios quercetin polymer were assayed. Drug delivery and dissolution profiles were carried out in simulated fluids.

2. Experimental section

2.1. Materials

Quercetin ($C_{15}H_{10}O_7$), cellulose acetate phthalate ($C_{116}H_{116}O_{64}$) and acetone (99,5%) were purchased by Sigma-Aldrich (Spain). CO_2 with a minimum purity of 99.8% was supplied by Linde (Spain).

2.2. Particle formation with SAS

SAS precipitation technique was used to produce nanoparticles of CAP, microparticles of quercetin and coprecipitates composed by nanoparticles of CAP covering microparticles of quercetin. The experiments were carried out in a pilot plant developed by Thar Technologies® (SAS200). A schematic diagram of SAS process is represented in Fig. 1 and the system was described in detail in a previous publication (Tenorio et al., 2007).

In a first step, CAP was precipitated using acetone as organic solvent. The influence of SAS parameters as pressure (P), temperature (T), initial concentration of the solution (cc), liquid solution (Q_L) and CO_2 (Q_{CO2}) flow rates and nozzle diameter (Θn) on particle size and size distribution were evaluated. In Table 1 is shown the assayed operating conditions.

Each experiment was performed following the same procedure. Initially, CO_2 was injected by a high-pressure pump into a stainless steel precipitator vessel and waited for supercritical conditions were fixed. Then, the CAP dissolved in acetone was pumped into the precipitator vessel and sprayed through a nozzle. Thus, a rapid mass transfer occurs between the solution and supercritical CO_2 so this one is dissolved into the solvent inducing a supersaturation of the solution, triggering the precipitation of the CAP as a powder, which is deposited mostly at the bottom of the vessel (Fig. 2a).

The same procedure is carried out when the solution of CAP/Quercetin was injected into the vessel. The operating conditions of these experiments were chosen on basis of the CAP precipitation results focusing on the higher particle size to be near of the range of quercetin microparticles and on the higher amount of powder precipitated (Table 2). So pressure of 90 bar, temperature of 40 °C, nozzle diameter of 100 μm, CO_2 and solution flow rates of 30 g/min and 6 mL/min respectively were selected. In these experiments, the mass ratio between CAP and quercetin was modified holding constants the rest operating conditions. The powders were precipitated mostly on the frit as can be seen in Fig. 2b. Pressures below 90 bar were not chosen because the addition of another solute as quercetin could modify the phase equilibrium and the experiments could be situated below mixture critical point (MCP) leading a powder precipitation from two phases, a liquid and a supercritical phase.

Microparticles of quercetin as flowers (1.24 ± 0.25 μm) (Fig. 3a) was also precipitated by SAS process at the same conditions of coprecipitation experiments in order to compare the influence of the

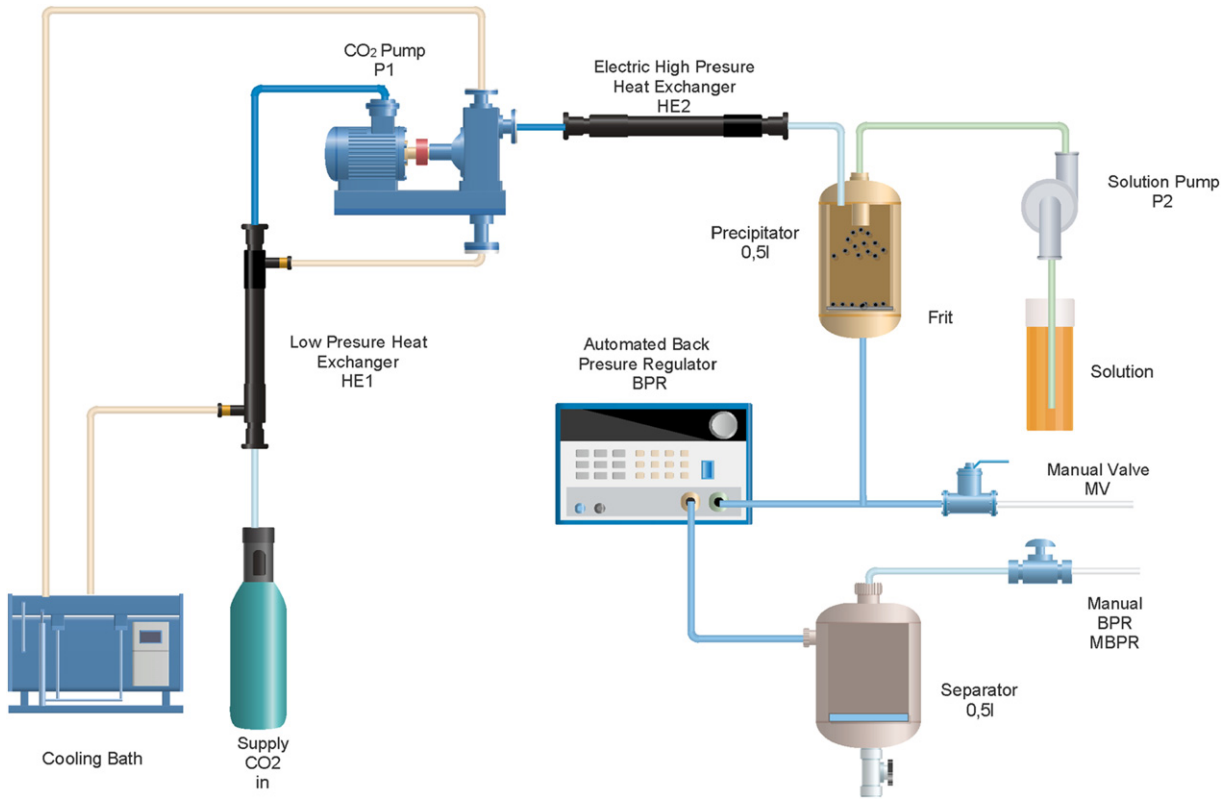

Fig. 1. Schematic SAS.