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Solubility of progesterone in supercritical carbon dioxide and its micronization through RESS

Zhen Huang *, Yu-hua Guo, Hui Miao, Li-jun Teng

Department of Packaging Engineering, Institute of Materials & Chemical Engineering, Tianjin University of Commerce, Tianjin 300134, China

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ABSTRACT

To investigate the formation of progesterone fine particles with rapid expansion of supercritical solution (RESS), it is vital to determine the solubility of progesterone under various equilibrium pressure and temperature conditions and to correlate the solubility data with a well-performed model. In this study, the solubility of progesterone in supercritical CO_2 was measured using a dynamic apparatus at pressure ranging from 120 to 260 bar, and temperature from 313.15 to 338.15 K. The determined solubility in mole fraction is in the range of 5.3×10^{-5}–8.9×10^{-4} and correlated with three empirical density-based models and the Peng–Robinson equation of state model. The latter model has better correlation effects than the other density-based models and provides an overall average absolute relative deviation of 11.6% between the calculated and experimental solubility. Then, the performances of RESS under different conditions are evaluated by analyzing the particle characteristics, and the effects of extraction temperature, extraction pressure, and nozzle diameter on the particle size and particle size distribution of the formed particles are discussed. The original progesterone has a particle size of about 150 μm while the average particle size of the micronized particles ranges from 0.11 to 3.22 μm based on different experimental conditions. The particles were characterized using scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infrared analysis (FTIR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and *in vitro* dissolution measurements.

1. Introduction

Particle engineering has been becoming a very important issue in the field of pharmaceutical solid dosage forms and size reduction is the most frequently proposed method to ensure high performance of pharmaceutical particles involved. Thus particle size reduction to nano- or micro-size is then gaining ever-increasing concerns as this can have a great impact on the biopharmaceutical behaviors such as solubility, dissolution rate, and bioavailability of the drug, especially for injectable drug products and for the administration by the inhalatory route. Recently, particle size reduction by means of techniques based on supercritical carbon dioxide ($SCCO_2$), such as particles from gas-saturated solutions/suspensions (PGSS) [1,2], supercritical fluid-assisted atomization (SAA) [1,2], supercritical antisolvent processes (SAS) [1,3–5], and rapid expansion of supercritical solution (RESS) [1,4–36], has attracted particular attention for those thermally unstable substances like pharmaceutics or explosives that may be difficult to comminute. $SCCO_2$ can be used as a solvent [1,4–36], an anti-solvent [1,3–5], a solute [1], a co-solute [1] or a co-solvent [1] for the drug to be recrystallized, due to its low critical temperature, low cost, availability at high purity, and excellent safety properties. Of all, the RESS particle formation technique may be, perhaps, considered the simplest process for producing solvent-free fine particles having a narrow particle size distribution [1,4–36].

In the RESS process, the drug to be comminuted is usually dissolved in a $SCCO_2$ at a desired high pressure and temperature and then the supercritical drug/CO_2 solution is rapidly sprayed through a well-designed nozzle to ambient conditions. Due to the great pressure drop in a short time, the decrease in density renders the solvating strength of CO_2 to the drug being suddenly lost and the dissolved solute becomes insoluble. This subsequently brings very high solute supersaturation, and leads to fast nucleation and uniform crystal growth which hence enables the production of solvent-free fine drug particles with a narrow size distribution. The most outstanding characteristic of particle formation through RESS methodology is the possibility of obtaining solids with unique morphology and small size for a wide range of materials. Obviously, adequate yield by means of this technique can be applied only to drugs having 'high' solute solubility in $SCCO_2$, at least, of the order of 10^{-4} mole fraction. Thus several recent studies have highlighted that the drug solubility in $SCCO_2$ is critical to the RESS micronization method as the solubility affects the supersaturation of the drug in the solvent as well as the mass transfer of the drug-loaded solution [28–30]. Moreover, Kim et al. [28] have reported that the particle diameter of ultra-fine drug particles resulted from the RESS process is found to decrease with the increase in the solubility for lidocaine, griseofulvin

* Corresponding author. Tel.: +86 22 26686264; fax: +86 22 26686251.
E-mail address: huangzhen50@yahoo.com (Z. Huang).

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and benzoic acid three drugs under all operating conditions. As known to all, the factors of strongly affecting the morphology and size of crystallized particles via the RESS process can be classified into two categories: thermodynamical parameters and processing parameters. The former mainly includes extraction temperature (T_E) [5–20,24,25,28,29,32,33] and pressure (P_E) [5–20,24–26,28,29,32–36], pre-extraction temperature (T_{PrE}) [5–7,18,21,25,26,28,29,32–34,36] and pressure (P_{PrE}) [21,29], postexpansion temperature (T_{PoE}) [7,26,27,32,36] and postexpansion pressure (P_{PoE}) [36], and cosolvent content (Cs) [5,8,9,13,14,22,23,31,32], influencing the RESS process in terms of solubility and supersaturation, and mass transfer rate. The latter includes nozzle aspect ratio [28] and length (L_N) [15–20,32,34,35], effective nozzle diameter (D_N) [6,8,10,11,13–20,24–29,33,36], spray distance (D_S) [6,12,13,15–20,35,29,32,34,35] and collision angle [34], affecting the particle size and morphology of the RESS products. The relationship between some RESS process conditions and particle properties has been highlighted in a recent review paper [31] and some recent RESS results are exampled in Table 1. However, the understanding of applying RESS to particle formation and the exploration of its feasibility are still in their infancy and more efforts on it are necessary.

In this work, progesterone (Fig. 1) was used as an interesting drug. It is an extremely important intermediate steroid for the biosynthesis of estrogen and hormone testosterone. It is known that progesterone is essential for correct pregnancy evolution and related to protein transport and the electrolytic balance. Usually, progesterone can be taken orally or used as an injectable drug for achieving biological effects of endogenous hormones or correcting unbalanced hormones, however, its effectiveness is strongly related to the particle size, morphology and other size-dependent properties. As a promising method of comminuting particles, the RESS process was attempted for reproducing progesterone particles. Information for drug solubility is essential for the RESS [37–40] since the degree of supersaturation determines the rates of nucleation and growth, consequently influences strongly the particle size and morphology. Although the solubility of progesterone in $SCCO_2$ have been reported in the literature [36,41,42], there is considerable inconsistency among the experimental data. For these reasons, it seems rewarding to studying the solubility and RESS of progesterone.

The main objectives of this work are as follows: (1) a continuous flow technique coupled with gravimetric analysis was used to measure the solubility of progesterone at 313.15, 323.15 and 338.15 K over a broad pressure range of 120 to 260 bar and a solubility comparison was made with previous solubility data. Then, the experimental solubilities of progesterone in $SCCO_2$ were quantitatively correlated with three density-based correlations and the Peng–Robinson equation of state (PREOS) model. (2) the RESS technique was employed for the particle formation of drug progesterone. The performances of RESS under different conditions in terms of nozzle diameter, extraction pressure and temperature were evaluated by analyzing the particle size and particle size distributions of the precipitated particles. The progesterone particles produced by the RESS process were characterized with numerous analytical methods including SEM, XRD, FTIR, DSC, TGA and *in vitro* dissolution tests.

2. Experimental

2.1. Solubility determination

The solubility of progesterone (99.5 +%, Sigma, USA) in supercritical carbon dioxide was measured using a continuous flow technique. Detailed descriptions of the experimental setup and operating procedure have been given elsewhere [37,38]. Briefly, the apparatus consists of a CO_2 reservoir, an HPLC pump, two extraction vessels in series, an oven, a back pressure regulator, a glass U tube solute collector, a wet gas flow meter, and tubings, valves, and fittings of various types. The solubility determination procedure can be briefed as follows. High purity carbon dioxide (99.99%, Tianjin Sifang Gas Co. Ltd., China), supplied from a gas cylinder, was passing through a dryer of molecular sieve 5A for water vapor removal and then a 0.2 μm on-line filter for particle removal. After liquefied at −268 K and 60 bar, CO_2 was then led into the HPLC pump with a precision of less than ±0.1%. Through the pump, the CO_2 was fed into the extraction unit that was held inside the temperature-controlled oven (±0.01 K). The extraction unit was loaded with alternate layers of solute powder (ca. 10 g) and 0.5–0.6 mm diameter glass beads. Downstream to the extraction unit, the saturated CO_2/solute solution was depressurized to ambient conditions through the needle valve set in the back pressure regulator with the pressure error no more than 0.2%. The precipitated solute was collected in a glass U-tube collector immersed in an ice bath. The gas released was led for atmospheric volume measurement through a wet gas meter (±0.001 l). The precipitation line was flushed by carbon dioxide in order to thoroughly recover the solute at the end of each run. The collected solute was gravimetrically determined by a balance (±0.01 mg) and the typical mass of solute collected in each run is approximately 50 mg, giving a potential error due to weighing of 0.02%. By means of the measured solute mass (Ms) and the solvent volume (V), the solubility value (y_2) in terms of molar fraction was readily obtained [37,38].

2.2. RESS particle formation

The experimental RESS apparatus used to produce progesterone ultrafine particles has been detailed elsewhere [33]. It was a slight modification of the solubility measurement setup and mainly divided into three sections: a supercritical CO_2 liquefying-pressurizing-delivering unit (a gas cylinder, a circulating chiller, a HPLC pump), a solute dissolving and extracting unit (a preheater, a 150 ml stainless steel homemade extraction vessel and an oven, along with a bypass back pressure regulator line for pressure controlling), and a crystallizing–separating unit (a nozzle and a solute collector).

After saturated with progesterone, the CO_2 solution was led from the extraction vessel to the crystallizer instead where it was throttled across an expansion nozzle. A heating tape was used to wrap around the pre-expansion line from the downstream of the extraction vessel to the expansion device to heat the solute loaded solution. The pre-expansion temperature, monitored by the heating tape temperature controller (±1 K), was set around 373.15 K to avoid any undesirable precipitation along the line. The nozzle used was homemade of stainless steel stub with 6 mm in o.d. and 15 mm long. After semihollowed with 4 mm in i.d. by a fine driller, a 0.5 mm thick bottom wall was produced in the stub where a hole in the bottom center was afterwards drilled by high-powered laser light. The nozzle thus obtained was assembled to the fluid downstream exit by a stainless steel screw cap and a set of ferrule and nut. As the supercritical solution was depressurized through the nozzle to ambient conditions, it experienced a rapid expansion, leading to deposition of the dissolved solute on a glass wafer. The distance from the nozzle tip to the collection glass was around 30 mm.

Precipitated progesterone particles after coated with palladium by using a sputter coater were analyzed with respect to their size and shape by scanning electron microscopy (SEM, JEOL JSM-6700F). The average particle size and particle size range of the samples were determined by measuring about 100 particles that were arbitrarily selected. The crystal structures and melting points of original and precipitated progesterone were examined by an X-ray diffractiometer (XRD, Shimadzu, XRD-6000) and differential scanning calorimetry (DSC, TA, Q-20), respectively. The sample weight change with increasing temperature was evaluated by a thermogravimetric analyzer (TGA, Shimadzu, DTG-60).

Quantitative *in vitro* dissolution experiments were also carried out to compare the dissolution rate between the original and RESS-processed progesterone sample as follows. Distilled water was used as the dissolution media. The dissolution was performed by using the ZRS-8G dissolution apparatus (Tianda Tianfa Technology Co., Ltd., China) following the