Solubility and micronisation of phenacetin in supercritical carbon dioxide

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The rapid expansion of a supercritical solution (RESS) process represents an attractive prospect for producing sub-micron and nano-particles of medical compounds with low solubility. The solubility of phenacetin in supercritical carbon dioxide was measured by the analytical-isothermal method at pressures ranging from 9.0 MPa to 30.0 MPa and temperatures ranging from 308.0 K to 328.0 K. The results show that the mole fraction solubility of phenacetin in supercritical carbon dioxide is up to $10^{-5}$. Four density-based semi-empirical models were introduced to correlate the experimental data. Agreement between the model predictions and experimental data is greater with the Adachi–Lu-modified Chrastil model than with the Chrastil model, Méndez-Santiago–Teja model, and the Bartle model and the average absolute relative deviation (AARD) observed is 0.0483. The preparation of fine phenacetin particles by the RESS process under different conditions of extraction temperatures (308.0–328.0 K), extraction pressures (9.0–30.0 MPa), nozzle temperatures (373.0–393.0 K), nozzle diameters (0.1–0.8 mm), and collection distance (20.0–40.0 mm) was investigated. The size and morphology of the resultant particles were analysed by SEM. A remarkable modification in size and morphology can be obtained by condition-optimisation.

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Introduction

With ever greater emphasis being placed on environmental protection in the chemical process, and increasing demand for more advanced and safer products, supercritical fluids technologies have been widely investigated for use in industrial applications such as ceramics, catalysis, and pharmaceuticals (Cocero et al., 2009; Dohrn et al., 2010; Fages et al., 2004). In recent years, the applications of supercritical fluids technologies in the controlled production of fine drug powders with the requisite physical and surface properties for delivery have attracted considerable attention in the pharmaceutical industry (Kawashima, 2001; Kawakami, 2012; Tong et al., 2002; Yasuji et al., 2012). Many new technologies based on the use of supercritical fluids to obtain fine particles were investigated, such as SAS (Supercritical anti-solvent), SAA (Supercritical-assisted atomisation), GAS (Gas anti-solvent), ASES (Aerosol solvent extraction system), and RESS (Rapid expansion of supercritical solutions) (Fages et al., 2004; Jung & Perrut, 2001). Due to the attractive advantages offered by the RESS process, such as products without residual solvents, controllable particle size and mild operating conditions, the RESS process has been widely applied to the micronisation of drug particles. Precipitation from a supercritical solution as one of the basic mechanisms for material processing is often limited by the solute solubility (Palakodaty & York, 1999). To study these technologies, knowledge of the equilibrium solubility of the solute in the supercritical fluids is required. Many data on the solubility of pharmaceutical compounds in supercritical carbon dioxide have been reported (Lucien

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Supercritical carbon dioxide (SC-CO\textsubscript{2}) is a solvent commonly used in the RESS process, in which it can function under moderate operating temperatures (\(T_e = 304.19\) K, \(P_e = 7.38\) MPa) (G"ucl"u-Ust"unda˘g & Temelli, 2006; Higashi et al., 2011).

In this study, phenacetin was chosen due to its wide use in antipyretics and analgesics. The solubility of phenacetin in the SC-CO\textsubscript{2} was determined at pressures of 9.0–30.0 MPa and temperatures of 308.0–328.0 K. Four density-based semi-empirical solubility models were applied to accurately correlate the experimental data, specifically the Méndez-Santiago and Teja model (Méndez-Santiago & Teja, 1999), the Bartle model (Bartle et al., 1991), the Chrastil model (Chrastil, 1982), and the Adachi–Lu-modified Chrastil model (de Lucas et al., 2007). The influence of RESS conditions, including nozzle temperature and diameter, extraction temperature and pressure, and collection distance on the morphology, size, and its distribution of the resultant particles was investigated and the optimised conditions were finally obtained.

### Experimental

Phenacetin (CAS registry no. 62-44-2, more than 0.98 mole % purity, RG grade, Basel, Switzerland) supplied by Aladdin Chemistry Co., was used as the solvent. High purity CO\textsubscript{2} (CAS registry no. 124-38-9, more than 0.999 vol. % purity, SFC grade) was supplied by Yueyang MingZhuo Gas Co. (Yueyang, China). Absolute ethanol (CAS Registry no. 64-17-5, 0.997 mole purity, GC grade), supplied by Tianjin Chemical Reagent Co. (Tianjin, China), was used as a solvent to collect the solute.

A schematic diagram of the supercritical experimental equipment used in this study to obtain the solubility data of phenacetin and the RESS process is shown in Fig. S1 (see the Supplementary Data associated with this article). The supercritical equipment consists of a carbon dioxide cylinder, a cooling water recirculation system (Taizhou Yuhua Refrigeration Equipment Manufacturing Co., Taizhou, Zhejiang, China), a compression pump (Huaan supercritical fluid extraction Co., Nantong, Jiangsu, China), an extraction cell with a circulating water system, a collection vessel for the solute solubility determinations, and an expansion chamber equipped with nozzles of different diameters (Huaan supercritical fluid extraction Co., Nantong, Jiangsu, China). The cooling water recirculation system used to cool the CO\textsubscript{2} was controlled by an automatic temperature controller for maintaining a constant temperature (273.0 K). Pressure applied in the extraction experiments was measured by a pressure transducer (Tianli Control Instrument Manufacture Co., Changzhou, Jiangsu, China) accurate to within 0.50 MPa over a range of 0.0–50.0 MPa. During the extraction experiments, the temperature was readily controlled by a thermo regulator (Jiangshu Jinzhao Temperature Instrument Co., Changzhou, Jiangsu, China) up to 373.0 K within ±0.1 K. The maximum working pressure and temperature of this system were 50.0 MPa and 373.0 K, respectively. The nozzle was heated by a circulating oil system equipped with a thermocouple (Jiangshu Jinzhao Temperature Instrument Co., Changzhou, Jiangsu, China) for controlling the temperature at the nozzle.

The solubility of phenacetin in supercritical carbon dioxide (SC-CO\textsubscript{2}) was measured by the isothermal method, viz.: equilibration is attained at a constant temperature, whereas the other equilibrium properties such as pressure and phase composition adjust themselves depending on temperature, total composition and volume of the equilibrium cell. There are three fundamental steps to the isothermal methods: (a) preparation of the mixture, (b) equilibration, and (c) sampling and analysis of the phase compositions (Dohrn et al., 2012). The experimental procedure is as follows: the temperature of the pure CO\textsubscript{2} solvent was reduced to 273.0 K by the cooling water recirculation system, then, the CO\textsubscript{2} was compressed to the desired pressure by a high pressure pump. The liquid CO\textsubscript{2} at the desired pressure was pumped into the preheated extraction cell (5.0 L), where the excess phenacetin (20 g) was previously placed. This was held at the requisite constant temperature and pressure for at least 3 h to ensure that equilibrium was achieved. Next, the mixed supercritical fluids were transferred to the collection vessel, the volume of which was known to be 41.5 mL. At the same time, the CO\textsubscript{2} was pumped slowly into the extraction cell at a rate of 1.0 L min\(^{-1}\), so as to maintain a constant pressure. Samples from the exiting fluid phase were collected by rapid depressurisation and expansion into a small glass trap (100 mL), which was filled with 50.0 mL of absolute ethanol. These samples were dissolved in the absolute ethanol and analysed by an ultraviolet spectrophotometer (TU-1901, Beijing) to measure the solubility of phenacetin quantitatively. According to previous reports in the literature (Rajasekhar et al., 2010), the maximum wavelength was at 248 nm. The calibration was obtained by using standard samples of concentrations ranging from 1 mg kg\(^{-1}\) to 10 mg kg\(^{-1}\). The calibration curve obtained (with a regression coefficient better than 99.7 %) was used to establish the concentration of phenacetin in the glass trap. All the sampling processes were performed in triplicate under identical conditions and the relative standard deviation was in the range of 3 %. To prepare the particles by RESS, causing the SC-CO\textsubscript{2} to expand from the nozzle outlet into atmosphere through the expansion device, the precipitated particles were collected in an expansion unit. The size and morphology of the resultant particles were analysed by SEM (JSM-6610LV, JEOL, Tokyo, Japan).