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Solubilities of chlormezanone, metaxalone and methocarbamol in supercritical carbon dioxide

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ABSTRACT

The solubilities of three active pharmaceutical ingredients (APIs) in supercritical carbon dioxide were measured in this study using a semi-flow apparatus. These APIs are chlormezanone ($C_{11}H_{12}ClNO_3S$), metaxalone ($C_{12}H_{15}NO_3$) and methocarbamol ($C_{11}H_{15}NO_5$) that are all used as skeletal muscle relaxants. The solubility data are reported for three isotherms at 308.2, 318.2 and 328.2 K, with the pressure range from 12 to 24 MPa. Most solubility data are within the range of 10^{-6} to 10^{-4} mole fraction for each API. The crossover phenomena were observed from the experimental results for all three systems. These solubility data satisfied the thermodynamic consistency tests. They were then correlated using three semi-empirical models. With the optimally fitted binary interaction parameters, satisfactory correlation agreement is presented for each binary mixture.

1. Introduction

The application of green chemistry is becoming a major concern in future industrial process. Taking the pharmaceutical industry as one example, the minimization of organic solvent usage can be approached by employing advanced solvents like supercritical carbon dioxide [1–3]. The basic thermodynamic and transport properties of pharmaceutical compounds with these alternative solvents supply essential information for the design of feasible process as well as equipment. Solubility of active pharmaceutical ingredients (APIs) in supercritical fluid, usually carbon dioxide, provides useful information for selecting appropriate processing method for particle recrystallization and micronization. The rapid expansion in supercritical solution (RESS) method is considered applicable for micronizing an API with high enough solubility, for example, in the order of 10^{-2} or 10^{-3} mole fraction in supercritical carbon dioxide. For the APIs with relatively lower solubility, the supercritical anti-solvent (SAS) method maybe considered. Solid solubility data in sub- and supercritical fluids has been reviewed in the literature [4–6]. Literature data from 1978 to 2010 can be searched from these reviews and their references. Compilation and correlation of experimental data have also been presented for many organic compounds and APIs [7]. In the recent literature, Sabegh et al. [8] presented the measured solubility of a non-steroid anti-inflammatory drug, ketoprofen, in supercritical carbon dioxide using a variable volume equilibrium cell. Shariati et al. [9] measured the phase behavior for a ternary mixture of carbon dioxide, methanol and a drug compound of prednisolone using visible Pyrex glass tube equipment. Their results provide information for the concentration effect of carbon dioxide in the gas anti-solvent process of the model drug. The motivation of this study is to obtain novel solubility data in supercritical carbon dioxide for three APIs that are used as skeletal muscle relaxants in medical treatment. These new data can be used for further particle formation process using supercritical CO_2.

We have presented the solubility data of APIs in supercritical CO_2 in our previous researches using a semi-flow apparatus [10–12]. The similar equipment and method have been employed in this study for measuring the solubility of chlormezanone, metaxalone and methocarbamol in supercritical carbon dioxide. These three APIs are used by oral clinic route as skeletal muscle relaxants. Their IUPAC names, chemical formula, molecular weights, pure fluid melting temperatures and chemical structures are listed in Table 1. The solubility data were measured in this study at three isotherms of 308.2, 318.2 and 328.2 K. The experimental pressure range for all three binary systems was from 12 to 24 MPa. We then employed three density based semi-empirical models to correlate the experimental solubility results. The optimally fitted binary interaction parameters are obtained and satisfactory correlation results are demonstrated. The experimental results also satisfy the self-consistency tests. The feasibility of using the correlated model parameters at extrapolated temperatures is ensured.

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List of symbols

a, b, c	parameters in the Mendez-Santiago and Teja model
k, d, e	parameters in the Chrastil model
f, g, h	parameters in the Bartle model
M	molecular weight (g/mol)
n	number of data points
obj.	objective function defined in Eq. (5)
P	pressure (MPa)
S	solubility defined in Eq. (3)
T	temperature (K)
T_m	melting temperature (K)
u	standard uncertainty
u_r	relative standard uncertainty
y	mole fraction

Greek letter

ρ	density (kg/m^3)

Subscripts

1	component 1, CO_2
j	solid solute component j
k	kth experimental data point

Superscripts

cal	calculated value
exp	experimental value

2. Experimental

2.1. Materials

Carbon dioxide was purchased from Air Products San-Fu Company, Taiwan with certified purity greater than 99.9 mass%. Two APIs of chlormezanone ($C_{11}H_{12}ClNO_3S$) and metaxalone ($C_{12}H_{15}NO_3$) were supplied by Syn-Tech Chem. & Pharm. Company, Taiwan. Methocarbamol ($C_{11}H_{15}NO_5$) was bought from Sigma–Aldrich Company. The purity of all three APIs was better than 99 mass%, and they were used without further purification. The IUPAC names, chemical formula, molecular weights, melting points and the structures of pure solid API compounds used in this study are listed in Table 1.

2.2. Experimental apparatus and procedures

A semi-flow equipment, similar to that described in our previous investigation [10–12], was employed in this study for the solubility measurements of APIs. The major parts include a pre-equilibrium and an equilibrium high pressure cells, each has a volume of 75 mL. The API material was packed layer by layer with glass beads in these cells. The total weight of each loaded API solid was about 10–15 g. The high pressure cells were immersed in a temperature controlled water bath in our experiments. Pure CO_2 was firstly liquefied at 278.2 K. It was then charged into a high pressure pump (SSI, series II) and was compressed to a desired pressure. The compressed CO_2 flew through the pre-equilibrium and equilibrium cells, and was expanded to atmospheric pressure into a flask filled with the solvent of ethyl acetate after this extraction process. The entrainment effect was avoided by equipping filters at both ends of the pre-equilibrium and equilibrium cells. Heating tapes were used after the extraction process to eliminate any precipitation of solid API in the experimental line. A wet test meter (Ritter, TG1) was used to record the amount of CO_2 that had flown through the cells. The total number of moles of CO_2 in the extraction process was then determined. The concentration of the extracted API, collected in the flask, was measured by an UV/vis photometer (Jasco, UV-975). The wavelengths for the UV/vis measurements were 266, 280 and 276 nm for chlormezanone, metaxalone and methocarbamol, respectively. The number of moles of each extracted API was then evaluated according to its accurately calibrated curves. The solubility of each API in supercritical CO_2 was finally calculated at the given experimental temperature and pressure condition. The experimental temperatures were detected by a PT-100 resistance thermometer with accuracy of ±0.1 K. Pressure readings were measured by a transducer (Druck, PDCR-4031) with accuracy of ±0.03 MPa. At least three measurements were conducted for each solubility data point. Different CO_2 flow rates were used for repeated experiments in order to confirm that the true thermodynamic equilibrium data were obtained. Standard deviation for each data point was recorded. The coefficients of variance, defined as the standard deviation over the mean solubility value, were also evaluated. The coefficients of variance must be smaller than 5% before the experimental data were accepted in this study.

3. Results and discussion

3.1. The experimental results for the solubility of APIs

The measured solubility data for three APIs of chlormezanone, metaxalone and methocarbamol are presented in Tables 2–4, respectively. Generally, these solubility data ranged from 10^{-6} to 10^{-4} mole fraction. The standard deviations shown in these Tables are also small enough to justify the reproducibility of our experimental results. Graphical illustrations of the solubility results are depicted in Figs. 1–3 for these three APIs, respectively. The solubility increases with increasing pressure at each isotherm due to the enhancement of supercritical CO_2 density. The three isotherms for each API solute demonstrate a crossover region resulting from the competing effect of the solvent density and the vapor pressure of solid solute. On examining the solubility data of this study, it is observed that methocarbamol has relatively the highest solubility in supercritical carbon dioxide. Its solubility is greater than 10^{-4} mole fraction at pressure higher than 16 MPa. Metaxalone has the relatively lowest solubility in these three APIs, with mole fraction smaller than 10^{-4} under 22 MPa. Chlormezanone shows the intermediate solubility in comparison to the other two APIs. This trend of solubility is consistent with their magnitude of melting temperatures as shown in Table 1. Methocarbamol has the lowest melting temperature and the corresponding highest solubility in supercritical CO_2. The solubility data of these three APIs are within the similar range as those for other APIs presented in our previous studies [10–12].

3.2. Correlation of solubility data of APIs

We apply three semi-empirical models to correlate our measured solubility data of APIs in supercritical CO_2. They have simple equation forms and are the mostly commonly used models for correlating the solid solubility data in supercritical CO_2. Similar correlation methods have been presented by other investigators (e.g. Sparks et al. [13], Asiabi et al. [14], Shojaee et al. [15]). The first one is the Mendez-Santiago and Teja (MST) model [16] for a binary mixture of supercritical CO_2 (component 1) and the solid API (component j). It expresses the solubility of an API (mole fraction, y_j) as a function of temperature, pressure and the density of supercritical CO_2 (ρ_1):

$$T(\mathrm{K})\ \ln(y_j P(\mathrm{MPa})) = a + b\rho_1\,(\mathrm{kg/m^3}) + cT\,(\mathrm{K}) \quad (1)$$

There are three adjustable parameters (a, b and c) in Eq. (1) that are obtained from data regression.