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Measurement and correlation for the solubilities of cinnarizine, pentoxifylline, and piracetam in supercritical carbon dioxide

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ABSTRACT

The equilibrium solubility of cinnarizine, pentoxifylline, and piracetam in supercritical carbon dioxide ($SCCO_2$) were experimentally measured using a semi-flow apparatus. These compounds are active pharmaceutical ingredients (APIs) that are applied as circulatory improvers. Solid solubility data for three binary mixtures of CO_2 with each API were determined at three isotherms of 308.15, 318.15 and 328.15 K. The experimental pressure range was from 12 to 24 MPa. The solubility of cinnarizine in $SCCO_2$ is from 0.29×10^{-5} to 2.05×10^{-4} mole fraction in this pressure range. The solubilities of pentoxifylline and piracetam are from 0.3×10^{-4} to 1.37×10^{-3}, and from 0.75×10^{-5} to 3.73×10^{-5} mole fraction, respectively. We applied three semi-empirical models presented by Mendez-Santiago and Teja, Chrastil, and Bartle to correlate our measured solubility data. The average absolute relative deviation (AARD) in solid solubility correlation is from 5 to 7% using these models. Our measured data satisfied the self-consistency tests. The optimally fitted model parameters as well as the crossover region results for each binary mixture are reported.

1. Introduction

Supercritical fluids (SCF) process is a relatively innovative technology and has widely been used in natural product extraction, chemical reaction, material processing and pharmaceutical industry [1–6]. Carbon dioxide is always preferred as the supercritical fluids owing to its nontoxic and inflammable characteristics. The threshold limit value (TLV), an index for occupational health, for CO_2 is 5000 ppm that is much higher than 25 ppm for ammonia or 200 ppm for methanol [7]. For the safety and energy cost concern, CO_2 also has the advantage of nearly ambient critical temperature at 304 K and moderate critical pressure at 7.38 MPa. The application of supercritical fluid technology requires basic physical property data for CO_2 with other components in a mixture. Taking pharmaceutical industry as an example, the solubility of an API in supercritical CO_2 is a key point for selecting the appropriate particle formation process. Recent examples for the measurement and correlation of solid APIs in supercritical CO_2 have been presented in literature [8–12]. The reported solubility data have also been collected and compiled [13–15] for future design and development of feasible chemical processes. The motivation of this study is to measure novel solid solubility data of APIs with important value for pharmaceutical industry. The three APIs investigated in this study are cinnarizine ($C_{26}H_{28}N_2$), pentoxifylline ($C_{13}H_{18}N_4O_3$) and piracetam ($C_6H_{10}N_2O_2$). They are generally used as blood flow improvers and classified as vasodilators. Cinnarizine is orally used for treating cerebral apoplexy and cerebral arteriosclerosis. It is also used for the therapy of nausea and vomiting [16]. Pentoxifylline and piracetam are used in the treatment of peripheral vascular disease and dementia, respectively [16].

Cinnarizine has very low water solubility (2 μg/mL) and this limits the rate of absorption in medical treatment. This disadvantage can be resolved by micronizing the original API. Supercritical fluid process can be employed in micronizing APIs by either the supercritical anti-solvent (SAS) or rapid expansion of supercritical solution (RESS) method. These supercritical fluid processes have been discussed and review in literature [17–23]. The selection of either process depends on the solubility of an API in supercritical CO_2.

Some APIs such as pentoxifylline and piracetam are freely soluble in water. On the contrast, a controlled release formulation would be clinically beneficial for those APIs. Formation of a cocrystal for the API with another conformer is an intensively investigated topic, and the guidance on pharmaceutical cocrystals has been recently issued by FDA [24]. A cocrystal is defined as a crystalline material composed of two or more molecules in the same crystal lattice. The API interacts with a conformer or another API through hydrogen bonding that has been studied by examining the structures of the products [25–27]. The benefits of a cocrystal include the improvement of the bioavailablity and stability of the original API

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Notations

a_0, a_1, a_2 parameters in the Mendez-Santiago and Teja model
b_0, b_1, b_2 parameters in the Chrastil model
c_0, c_1, c_2 parameters in the Bartle model
M molecular weight (kg/mol)
n number of data points
obj. objective function defined in Eq. (5)
P pressure (MPa)
S solid solubility defined in Eq. (3)
T temperature (K)
T_m melting temperature (K)
y mole fraction

Greek letters
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

[28–30]. The feasibility for the production of cocrystals using the supercritical fluid method has been presented in recent literature [31,32]. The solubility data of an API or a conformer in supercritical CO_2 are again essential for crystal engineering design using supercritical fluid technology. To our knowledge, the solid solubilities of three APIs of cinnarizine, pentoxifylline and piracetam in supercritical carbon dioxide have not been available in literature. The motivation of this study is to measure the novel solid solubility data and to correlate these data with semiempirical equations.

In our previous investigations, we have measured the solubilities of organic and pharmaceutical components in supercritical CO_2 using a semi-flow apparatus [33–35]. The similar experimental apparatus and method were applied in measuring the new solubility data. The experimental temperatures were conducted at 308.15, 318.15 and 328.15 K in this study. The experimental pressure range was from 12 to 24 MPa. Repeated measurements were carried out for each experimental condition to obtain the results with acceptable standard deviations. The experimental data were correlated using three density based semiempirical models proposed by Mendez-Santiago and Teja (MST) [36], Chrastil [37] and Bartle [38], respectively. Thermodynamic consistency was tested for each system. The crossover region data are also reported for each binary mixture.

2. Experimental

2.1. Materials

Carbon dioxide was purchased from Air Product San-Fu Company, Taiwan, with a minimum purity of 99.9 mass%. The APIs of cinnarizine, pentoxifylline and piracetam were purchased from Sigma–Aldrich Company. All of these APIs had a minimum purity of 99 mass% that were stated in the certificates of analysis provided by Sigma–Aldrich Company. The purity of these APIs had also been tested in this study using HPLC with UV/Vis detector (Jasco UV-975). No detectable impurities were observed and these APIs were used without further purification. The melting temperatures for three APIs in this study were measured using DSC (PerkinElmer, Jade) with a scanning rate of 5 K/min and a standard uncertainty of 0.1 K. The results are presented in Fig. 1. The DSC result of piracetam shows two endothermic peaks. The first peak indicates the melting temperature of a polymorph form III with a peak value at 398.0 K. The second peak for piracetam represents another polymorph of form I with the peak melting temperature at 426.2 K. These results are consistent with those shown in literature [39]. The API of piracetam used in our solubility measurement is confirmed as form III. The melting temperatures of cinnarizine and pentoxifylline measured in this study are also consistent with those shown in literature [40,41]. The IUPAC names, melting temperatures and molecular structures of these pure APIs are listed in Table 1.

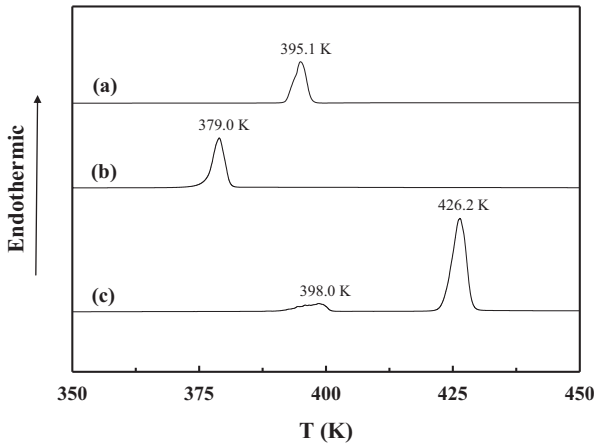

Fig. 1. DSC measurement results of pure APIs in this study: (a) cinnarizine, (b) pentoxifylline and (c) piracetam (scanning rate is 5 K/min).

2.2. Experimental apparatus and procedures

A semi-flow type apparatus was used in this study for measuring the solid solubilities of three APIs. The experimental apparatus is similar to those of our previous studies, and has been described elsewhere [33–35]. The main parts are a pre-equilibrium cell and an equilibrium cell, each with a volume of 75 ml. These two cells were immersed in a water bath to reach thermal equilibrium at a set temperature. An amount of 10 to 15 g API was loaded layer by layer with glass beads in each cell. The experimental temperatures were detected by a PT-100 resistance thermometer with the accuracy of ±0.1 K. Pure CO_2 was liquefied in a cooling unit to 278.15 K before charging to the equilibrium cells. It was pressurized to the equilibrium cells by a HPLC pump (SSI, Series II) at a desired pressure. The experimental pressure in the equilibrium cells was detected by a transducer (Druck, PDCR-4031). The estimated accuracy in pressure measurements was ±0.03 MPa.

The solid API packed in the equilibrium cells was extracted by supercritical CO_2 at a given temperature and pressure. The gas was then expanded into a flask at the atmospheric pressure through the decompression needle valve that was wrapped with a heating tape. The dissolved solid API compound in the supercritical CO_2 was separated from the gas phase after the depressurization process. It was dissolved into a flask with organic solvent that was immersed in an ice bath. In this study, ethyl acetate was selected as the solvent to dissolve the APIs of cinnarizine and pentoxifylline. Methanol was taken as the solvent to dissolve piracetam. The flow rate of CO_2 was recorded by a wet test meter (Ritter, TG1). The solution collected in the flask was sonicated for more than 10 min before its composition was measured by a UV/Vis detector (Shimadzu, UV-1800). The wavelengths in the UV/Vis measurements were 253, 275 and 205 nm for cinnarizine, pentoxifylline and piracetam, respectively.