SOLUBILITIES OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN SUPERCRITICAL CARBON DIOXIDE

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Abstract

To develop micronization technique for pharmaceutical materials with the rapid expansion of supercritical solution (RESS) method, we need the solubility data of the substances of interest in supercritical fluids. In the present study, the solubility data of two fluorinated and non-steroidal anti-inflammatory drugs (NSAIDs) (flufenamic acid, CAS No. 530-78-9 and niflumic aicd, CAS No. 4394-00-7) in supercritical carbon dioxide were measured with a semi-flow type phase equilibrium apparatus at temperatures ranging from 313.2 K to 353.2 K and pressures up to 31 MPa. The solubilities can be as high as 2.13×10^{-4} and 2.09×10^{-5} in mole fraction for flufenamic acid and niflumic acid, respectively, at their highest equilibrium temperature and pressure. The saturated solubility data were correlated with the Charstil and the Mendez-Santiago-Teja equations. The Chrastil model fitted the experimental data to about within the experimental uncertainty. The correlated results of the Mendez-Santiago-Teja model endorsed the consistency of the solubility data over the entire experimental conditions. The results of this study are useful in the development of micronization process with the RESS method for these two pharmaceutical substances.

1. Introduction

Since mid-1980, various supercritical fluid-assisted processing techniques have been applied to pharmaceutical industry such as extraction of active ingredients from natural resources[1], micronization and nanosization of pharmaceutical compounds[2], formation of microcapsules of medicines[3], production of sustained delivery devices for controlled release applications[4], and serving as a reaction medium for syntheses of pharmaceutical intermediates[5]. Supercritical carbon dioxide is widely used in the practical applications because it is an environmentally benign solvent and is regarded as one of conventional solvents alternatives for a variety of chemical and industrial processes. Furthermore, it is non-toxic, non-flammable, plentiful, inexpensive, and tunable of solvent properties by just adjusting temperature and pressure, and has gas-like viscosities and liquid-like densities. Due to carbon dioxide's relatively low critical temperature (T_C = 304.4 K), it is especially suitable for processing thermo-labile pharmaceutical compounds.

The solubility data of target compounds in supercritical fluids is the most important physical property for development of supercritical fluid-assisted processes. For example, the solubility should be sufficiently high in order to efficiently produce ultra-fine particles by using the RESS method. In the present study, the solubility data of two fluorinated pharmaceutical compounds, flufenamic acid and niflumic acid, were measured with a semi-flow type phase equilibrium apparatus at temperatures from 313.2 K to 353.2 K and pressures up to 31 MPa. These new solubility data were correlated with the Chrastil equation[6] and the Mendez-Santiago and Teja model[7] over the entire experimental conditions.

2. Experimental method

2.1. Materials

Carbon dioxide (99.5+ %) was supplied by Liu-Hsiang Gas Co. (Taiwan). Ethanol (HPLC grade) was purchased from Fisher Scientific (UK). Flufenamic acid (97+ %) and niflumic acid (98+ %) were purchased from Sigma-Aldrich (USA). All the chemicals were used without further purification.

2.2. Apparatus and procedures

A semi-flow type apparatus was employed in the present study to extract the pharmaceutical compounds with supercritical carbon dioxide. The solid-gas equilibrium data were also measured with the same apparatus by running the extraction experiments under sufficiently long contact time. The schematic diagram of the extraction apparatus is illustrated in Fig. 1. Carbon dioxide was cooled and then pressurized by a high-pressure liquid pump (**4**, Minipump, operable up to 40 MPa, LCD Milton Roy, USA). The extractor consists of two stainless steel tubes (**8**, 0.359" I.D. and 10" length of each, Autoclave Engineers, USA) in series. Dried drug particles were blended with glass beads and then packed into the extractor in several sections separated with glass wool. A glass wool plug was placed at the top of the extractor to prevent entrainment of solute. The extractor was submerged in a thermostatic bath (**6**) and controlled to within $\pm$ 0.1 K. A precision thermometer (**9**, Model 1560, Hart Scientific, USA) with a platinum resistance temperature detector (RTD) probe was used for measuring the equilibrium temperature with an uncertainty of $\pm$ 0.02 K. Pressure in the extractor was measured by a pressure transducer (**10**, PDCR-4070, 0-35 MPa, Druck, UK) equipped with a digital indicator (DPI-280, Druck, UK) accurate to $\pm$ 0.1 %.

The gas stream leaving the extractor was expanded to atmospheric pressure through a heated 3-way/2-stem manifold needle valve (**V-1**) and a heated micrometering valve (**12**). The flow rate of the stream and the operating pressure were adjusted with the micrometering valve, the needle valve, and the liquid pump. The expansion zone was maintained at a sufficiently high temperature to prevent the solute from precipitating in the expansion line. The expanded mixture was diverted into a sampling train (**13**), which was composed of two test tubes in series. The test tubes were filled with ethanol to dissolve the extracted drug, and glass beads were also placed in the test tubes to promote the contact of sampling stream with ethanol. A solvent reservoir (**15**), connected to the needle valve (**V-2**), was used for removal of drug left in the expansion zone at the end of each run. The spent solution was also collected in the sampling tubes. The concentration of drug in the collected solution was determined by an UV/visible spectrophotometer (U-1500, Hitachi, Japan), and the total volume of liberated carbon dioxide was measured by a wet test meter (**14**, Alexander Wright Inc., UK) accurate to $\pm$ 0.25 %.

During the equilibrium measurements, the mass flow rate of carbon dioxide was regulated at about 0.0014 g/s for flufenamic acid/CO_2 system and at about 0.0011 g/s for niflumic acid/CO_2 system and the amount of initial packed target material in the equilibrium cells was about 2 g for each case. Under these circumstances, the flow rate was found sufficiently slow to ensure that solvent mixtures can be saturated with the drug before leaving the extractor. The attainment of equilibrium has been verified by measuring the concentrations of drug in carbon dioxide at different lengths of contact time. At least four replicates were taken at each experimental condition. The solubility was obtained by averaging these replications. Generally, the uncertainty of the solubility measurements was estimated to be about $\pm$ 10 %.

2.3 Composition analysis

The concentration of the drug in the collected samples was analyzed with an UV/visible spectrophotometer. The wavelength of the light source was set to 288 nm and 290 nm for flufenamic acid and niflumic acid, respectively. Calibration was made with at least five standard samples over a concentration range of 0.1 ppm to 30 ppm (on the mass basis). A linear equation was applied to correlate the concentrations with absorbencies.

3. Results and discussion

3.1 Extraction of drugs at different lengths of contact time

The concentrations of the drugs in supercritical carbon dioxide were measured at 333.2 K and 21 MPa for flufenamic anid and at 353.2 K and 31 MPa for niflumic acid over a wide range of contact

times. Figs. 2 and 3 illustrate the concentrations (y_2), in mole fraction, varying with contact time (τ) for flufenamic acid and niflumic acid, respectively. The definition of contact time is given by

$$\tau = W/F \quad (1)$$

where W (g) refers to the weight of target solid packed in the extractors (or the equilibrium cells) and F (g/s) represents the mass flow rate of carbon dioxide. It shows that equilibrium state can be attained when the lengths of contact time are longer than 1400 s and 1800 s for flufenamic acid and niflumic acid systems, respectively.

3.2 Equilibrium solubility

During the measurements of equilibrium solubility, the lengths of contact time were kept longer than the minimum values as mentioned above to ensure the saturation of target compounds in the gas phase stream. The equilibrium solubilities of flufenamic acid and niflumic acid in carbon dioxide were measured at temperatures from 313.2 K to 333.2 K over a pressure range of 8 MPa to 21 MPa and at temperatures from 313.2 K to 353.2 K over a pressure range of 19 MPa to 31 MPa, respectively. Over the entire experimental conditions, the mole fractions of the flufenamic acid and niflumic acid are in the range of 10^{-7}–10^{-4} and 10^{-6}–10^{-5}, respectively. Since carbon dioxide is nonpolar, the solid-gas equilibrium behavior may be governed mainly by the physical interactions between carbon dioxide and the drug molecules. Figs. 4 and 5 show the isothermal equilibrium solubility varying with pressure for flufenamic aicd and niflumic acid, respectively. The solubilities increase with increasing pressure for both two systems. While the saturated solubility of flufenamic acid increases about 124-fold as pressure increases from 8 MPa to 21 MPa at 313.2 K, and that of niflumic acid increases about 3-fold at 353.2 K as pressure increases from 19 MPa to 31 MPa.

Figs. 4 and 5 also illustrate that the solubility isotherms have a crossover at pressures around 11 MPa to 15 MPa for flufenamic acid and 19 MPa to 25 MPa for niflumic acid. Below the crossover pressure, the solubility decreases with increasing temperature, whereas an opposite trend was exhibited at pressures higher than the crossover pressure. The crossover phenomena could be attributed to the competitions between solute's vapor pressure and solvent's density, whose temperature-dependences are in opposite directions. At the crossover point, these two competitive factors are even.

4. Data correlation

The new solubility data were correlated with the Chrastil equation[6], which was developed on the basis of the complex formation of solute molecules with solvent molecules in gas phase. The model was defined as

$$\ln C = k \ln \rho + a / T + b \quad (2)$$

where C (g/l) is the concentration of the target compound in the saturated gas phase, k is the number of solvent molecules associating with one molecule of solute to form a solvate complex, ρ (g/l) is the density of supercritical fluid, T (K) is equilibrium temperature, and a and b are constants. The Chrastil equation is linear in a log-log graph of solubility versus density. Figs. 6 and 7 compare the calculated results with the experimental values for flufenamic acid and niflumic acid systems, respectively. In general, the Chrastil equation correlated the equilibrium solubilities to about within experimental uncertainty.

The solubility data were also correlated with a semi-empirical model of Mendez-Santiago and Teja[7], which was derived by using a classical expansion of the Helmholtz energy around the critical point of solvent to describe the mixture properties at infinite dilution. The Mendez-Santiago and Teja model was expressed as

$$T \ln (y_2 P) = A_1 + A_2 \rho + A_3 T \quad (3)$$

where ρ is the density of solvent in (mol/ml), y_2 is the solubility of solute in supercritical fluid, T in K, P in MPa and A_1, A_2 and A_3 are parameters independent of T and P. Rearrangement of the above equation yields

$$T \ln (y_2 P) - A_3 T = A_1 + A_2 \rho \quad (4)$$

Mendez-Santiago and Teja claimed that Eq. (4) could be used to check the consistency of

experimental data. The experimental solubility data are considered consistently well, if all isotherms collapse to a single straight line on a graph of the left hand side of Eq. (4) versus the density of solvent, ρ. Figs. 8 and 9 show that all the experimental data follow the trend of linearity for the systems of CO_2 + flufenamic acid and CO_2 + niflumic acid, respectively. Although the average deviations from this model are slightly greater than those from the Chrastil equation, the deviations are still not far above the experimental uncertainty.

5. Conclusions

The extraction of flufenamic acid and niflumic acid with supercritical carbon dioxide has been investigated with a semi-flow apparatus under a wide range of contact time. The saturated solubilities of these two pharmaceutical compounds in supercritical carbon dioxide have also been measured in a temperature range of 313.2 K to 353.2 K and pressures up to 31 MPa. For both two binary systems, their isothermal solubilities in supercritical CO_2 increase with increasing pressure. Crossover behavior was also found in each binary system. According to the experimental results, flufenamic acid has relatively high solubility in supercritical carbon dioxide. The Chrastil equation correlated the solubility data to about within the experimental uncertainty. The correlated results of the Mendez-Santiago and Teja model showed that the solubility data were consistent well over the entire experiment conditions.

References

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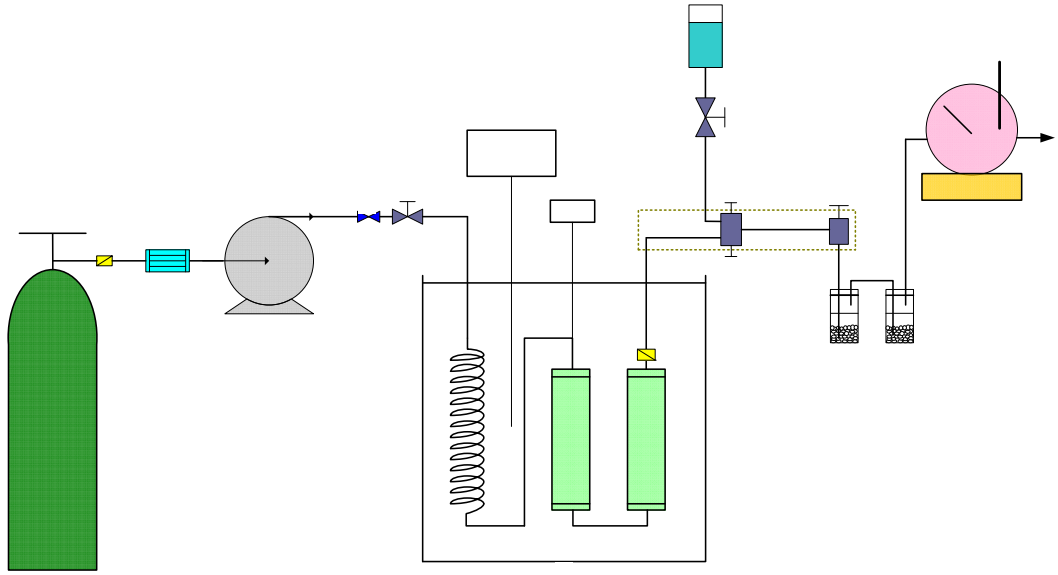

1. CO_2 cylinder
2. Filter
3. Cooler
4. Liquid pump
5. Check valve
6. Thermostatic bath
7. Pre-heater
8. Equilibrium cells
9. Thermometer
10. Pressure transducer
11. Heating tapes
12. Micrometering valve
13. Sampling traps
14. Wet test meter
15. Solvent reservoir

V-1, V-2, V-3: Needle valves

Fig. 1. Schematic diagram of the experimental apparatus.

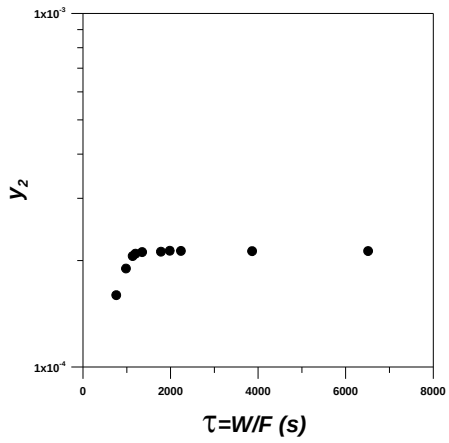

Fig. 2. Concentration of flufenamic acid in supercritical carbon dioxide under different lengths of contact time at 333.2 K and 21 MPa.

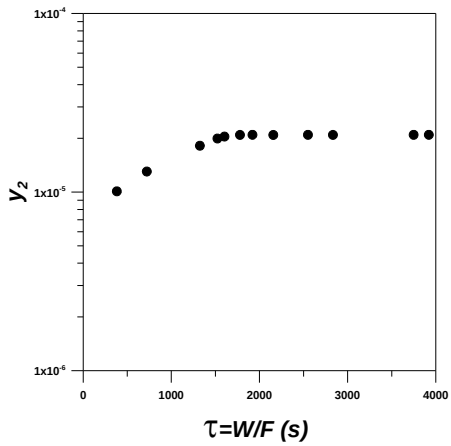

Fig. 3. Concentration of niflumic acid in supercritical carbon dioxide under different lengths of contact time at 353.2 K and 31 MPa.

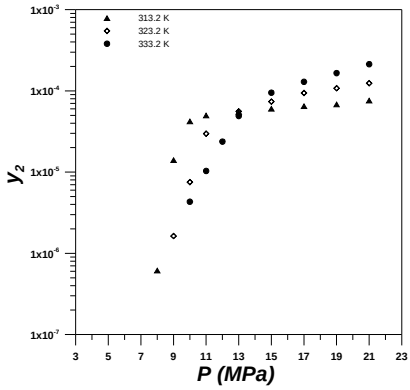

Fig. 4. Equilibrium solubilities (y_2) of flufenamic acid in supercritical carbon dioxide.

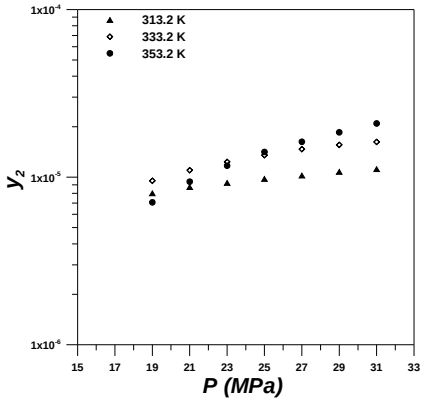

Fig. 5. Equilibrium solubilities (y_2) of niflumic acid in supercritical carbon dioxide.

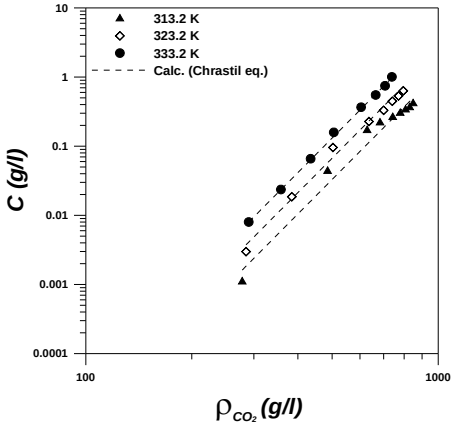

Fig. 6. Comparison of the correlated results from the Chrastil equation with experimental values for CO_2 (1) + flufenamic acid (2) system.

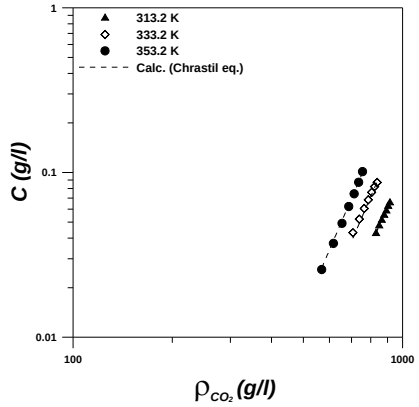

Fig. 7. Comparison of the correlated results from the Chrastil equation with experimental values for CO_2 (1) + niflumic acid (2) system.

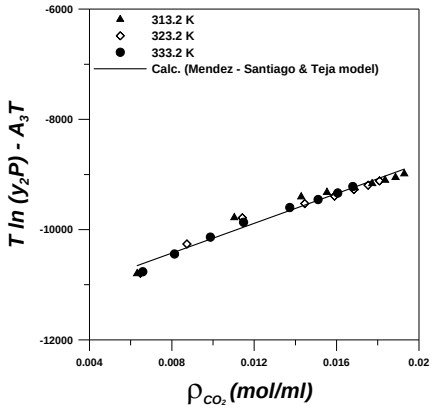

Fig. 8. Comparison of the correlated results from the Mendez-Santiago and Teja model with experimental values for CO_2 (1) + flufenamic acid (2) system.

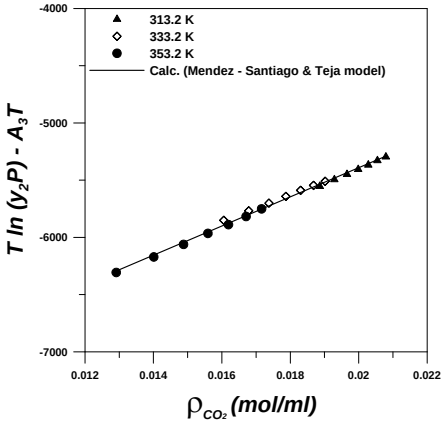

Fig. 9. Comparison of the correlated results from the Mendez-Santiago and Teja model with experimental values for CO_2 (1) + niflumic acid (2) system