J. of Supercritical Fluids 95 (2014) 17–23

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

journal homepage: www.elsevier.com/locate/supflu

Solubility of niflumic acid and celecoxib in supercritical carbon dioxide

Cheng-Chou Tsai, Ho-mu Lin, Ming-Jer Lee*

Department of Chemical Engineering, National Taiwan University of Science and Technology, 43 Keelung Road, Section 4, Taipei 106-07, Taiwan

ARTICLE INFO

Article history:
Received 2 May 2014
Received in revised form 31 July 2014
Accepted 31 July 2014
Available online 10 August 2014

Keywords:
Niflumic acid
Celecoxib
Carbon dioxide
Solubility

ABSTRACT

The solubility data of two fluorinated and non-steroidal anti-inflammatory drugs, niflumic acid (CAS No. 4394-00-7) and celecoxib (CAS No. 169590-42-5), 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. At the highest extraction temperature and pressure, the solubilities are 2.09×10^{-5} and 1.52×10^{-5} in mole fraction for niflumic acid and celecoxib, respectively. The saturated solubility data were correlated with the Chrastil model, the Mendez-Santiago–Teja equation, and the Peng–Robinson equation of state. The Chrastil model fitted the experimental data to about within the experimental uncertainty. The correlated results of the Mendez-Santiago–Teja model confirmed the consistency of the solubility data over the entire experimental conditions. Incorporating with two-parameter van der Waals one-fluid mixing rules, the Peng–Robinson equation of state represents satisfactorily the gas–solid equilibrium behavior of niflumic acid and celecoxib in supercritical carbon dioxide.

1. Introduction

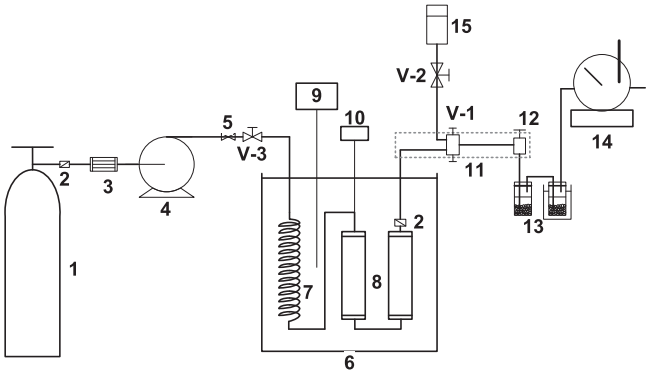
Since mid-1980 various supercritical fluid-assisted processing techniques have been applied to pharmaceutical industry such as extraction of active ingredients from natural resources [1], micronization and nanosization of pharmaceutical compounds [2], formation of microcapsules of medicines [3], production 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 an environmentally benign solvent and widely used in the practical applications because 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.

Fenamates are an important group of non-steroidal anti-inflammatory drugs (NSAIDs) with antipyretic, analgesic, and anti-inflammatory properties. Generally, fenamates have limited solubility in water and other common organic solvents, and thus the solubility is a key factor to govern their bioavailability [6]. Niflumic acid (NFA) is one of the widely used fenamates which is an analgesic and anti-inflammatory agent used in the treatment of rheumatoid arthritis [7]. Diverse pharmaceutical forms of NFA such as capsules, gels, ointments, and suppositories are available to allow peroral or transcutaneous applications. Celecoxib (CCB) belongs to the Coxib family, a class of NSAIDs, and is able to selectively inhibit cyclooxygenase-2 (COX-2) without affecting cyclooxygenase-1 (COX-1) activity [8]. For this reason, CCB has fewer gastrointestinal side effects, comparing with the conventional NSAIDs, and still has anti-inflammatory therapeutic efficacy. CCB is administered by oral mode in capsule form.

The solubility data of target compounds in supercritical fluids is the most important physical property for development of supercritical micronization processes. For example, the solubility should be sufficiently high in order to efficiently produce ultra-fine particles by using the rapid expansion of supercritical solutions (RESS) method. Otherwise, supercritical antisolvent (SAS) method may be more suitable. In the present study, the solubility data of NFA and CCB in supercritical carbon dioxide 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. No literature data are available for these two binary systems. These new solubility data were correlated with the Chrastil model [9], the Mendez-Santiago and Teja model [10], and the Peng–Robinson equation of state [11] over the entire experimental conditions.

* Corresponding author. Tel.: +886 2 2737 6626; fax: +886 2 2737 6644.
E-mail addresses: mjl@ch.ntust.edu.tw, mjlee@mail.ntust.edu.tw, mjl6626@gmail.com (M.-J. Lee).

http://dx.doi.org/10.1016/j.supflu.2014.07.026
0896-8446/



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.

2. Experimental method

2.1. Materials

Carbon dioxide (99.8+%) was supplied by Liu-Hsiang Gas Co. (Taiwan). Ethanol (HPLC grade) was purchased from Fisher Scientific (UK) and methanol (99.9+%, spectrophotometric grade) from Arco Organics (USA). NFA (98+%) was purchased from Sigma–Aldrich (USA) and CCB (99.95+%) from Aryl (AR). The basic information and physical properties of NFA and CCB are given in Tables 1 and 2, respectively. 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 gas–solid 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 ±0.1 K. A precision thermometer (**9**, Model 1560, Hart Scientific, USA) with a platinum resistance temperature detector (RTD) probe was used to measure the equilibrium temperature with an uncertainty of ±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 ±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 by a heating tape to prevent the precipitated solid from clogging 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 NFA and with methanol to dissolve the extracted CCB, and glass beads were also placed in the test tubes to promote the contact of sampling stream with the solvent. The second sampling tube was immersed in an ice bath to minimize the vaporization of solvent. A solvent reservoir (**15**), connected to the needle valve (**V-1**), 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 ±0.25%.

During the equilibrium measurements, the mass flow rate of carbon dioxide was regulated less than 0.0012 g/s for CO_2 + NFA system, and 0.0025 g/s for CO_2 + CCB system and the amount of packed drug in the equilibrium cells was about 2 g of NFA and about 1.5 g of CCB. Under these circumstances, the flow rates are sufficiently slow to ensure that carbon dioxide 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 contact times. At least three replicates were taken at each experimental condition. The solubility was obtained by averaging these replications. Generally, the uncertainty of the solubility data reported in the present study was estimated to be about ±10%.

2.3. Composition analysis

The concentrations of NFA and CCB in the collected samples were analyzed with an UV/visible spectrophotometer. The wavelength of the light source was set to 290 nm and 254 nm for the solutions containing NFA and CCB, respectively. Calibration was made with at least five standard samples over a concentration range of 0.1–30 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 contact times

The concentrations of the drugs in supercritical carbon dioxide were measured at 353.2 K and 31 MPa for NFA, and at 343.2 K and 30 MPa for CCB over a wide range of contact times. Fig. 2(a) and (b) illustrates the variations of NFA and CCB concentration in mole fraction (y_2) with contact time (τ), respectively. The definition of contact time is given by

$$\tau = \frac{W}{F} \tag{1}$$

where W (g) refers to the mass of drug packed in the extractors and F (g/s) represents the mass flow rate of carbon dioxide. It shows that equilibrium state was attained when the contact times are longer than 1600 s for NFA and 600 s for CCB in supercritical carbon dioxide. The microscopic images reveal that the mean particle size of NFA and CCB is about and 200 μm and 6 μm, respectively. Therefore, the smaller mean particle size of CCB providing the larger