Solubility of Anti-Inflammatory Drugs in Supercritical Carbon Dioxide

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Supercritical fluid extraction is a potential technique for the purification of pharmaceutical products containing residual solvents. The solubilities of the drugs in supercritical carbon dioxide are being measured as part of a program in which the potential applications of this technology are being investigated. The solubilities of three inhibitors of inflammatory activity, Ketoprofen, Piroxicam, and Nimesulide, in supercritical CO_2, measured using a dynamic saturation technique, are reported at pressures between 100 bar and 220 bar and at two temperatures: 312.5 K and 331.5 K. These chemicals have relatively high solubilities with values ranging from 4×10^{-6} to 15×10^{-4} mole fraction. The solubilities exhibit a clear dependence on the solvent density, and this has been used to provide a simple and precise correlation of the data.

Introduction

As a consequence of two decades of development of supercritical fluid extraction (SFE) in food industries, there is at the moment a widespread interest in the application of supercritical fluids also in pharmaceutical industries.

Supercritical fluid extraction of active molecules from medicinal plants (such as alkaloids, steroids, taxanes, vitamins), extraction from dilute media for metabolite recovery (i.e. cyclosporin), enzymatic reactions (an example is the hydrolysis or transesterification of glycerides), recrystallization through gas antisolvent, precipitation, micronization, and impregnation are some of the areas of application under investigation and development.

One advantage of SFE (mainly when carbon dioxide is used as a supercritical fluid) is that it permits one to process materials at ambient temperature and under relatively high pressures (from 8 to 20 MPa); moreover the products obtained by extraction are of far better quality than those obtained by organic solvent extraction.

The solubility of the active principles in the supercritical fluids is therefore a very important property since it defines the performance of the extraction.

Dealing with natural products, irregular and complex structure molecules are involved. Often there is very little physical and chemical property data known about them, and existing techniques for estimating these properties, such as group contribution methods, are not normally reliable for such molecules, so that an evaluation of the performance of the extraction cannot be made a priori.

Many drugs fall into this category and therefore the solubilities of three nonsteroidal inhibitors of inflammatory activity, Ketoprofen, Nimesulide, and Piroxicam, have been measured in supercritical CO_2.

Experimental Section

Apparatus and Procedures. The solubilities of the drugs in pure CO_2 were measured using a continuous flow apparatus similar to that described previously (Yun et al., 1991; Gurdial and Foster, 1991, Macnaughton et al., 1995) and is shown schematically in Figure 1.

Liquid carbon dioxide (food grade, 99.8% minimum purity) was fed through a 2 μm filter to an ISCO 260D high-pressure syringe pump. The CO_2 was compressed and pumped into a preheating coil contained in a temperature-controlled water bath. The fluid passed into an equilibrium cell which was packed with solute and plugged at each end with glass wool to eliminate entrainment. The fluid was then flashed to atmospheric pressure through a regulating valve, resulting in the precipitation of solute within both the valve and a 0.5 μm filter attached immediately downstream of the valve. The gas released through the regulating valve was passed through a water saturator and a wet test meter for the volume determination.

During each experiment, the system pressure was maintained to within ±0.2% of the desired value by adjusting the regulating valve and the pump flow rate. The system temperature was controlled to within ±0.1 K using an immersion circulator (Haake N3). The determination of solubility was based on the mass of solute trapped in the valve and filter and the corresponding volume of CO_2. The gas volume was measured with a precision of ±0.01 L using a wet test meter (SIM Brunt calibrated to an accuracy of ±0.4%). The mass of solute was determined to be ±0.2 mg using a Mettler H31 balance. The typical mass of solute that was collected in each experiment was greater than 100 mg, giving a potential error due to weighing of 0.2%. The system temperature was measured using a RTD platinum probe accurate to ±0.1 K, and the system pressure was measured using a Druck pressure transducer (DPI 260) accurate to ±0.1%.

The reliability and efficiency of this solubility measuring technique have been previously established by measuring the solubility of salicylic acid in supercritical CO_2 and compared with literature data: there is excellent agreement with the data of Gurdial and Foster (1991), Stahl et al. (1978), and Reverchon et al. (1994), as reported in a previous work (Macnaughton et al., 1995).

Materials. The source and purities of the chemicals used in this study are listed in Table 1; there is a significant

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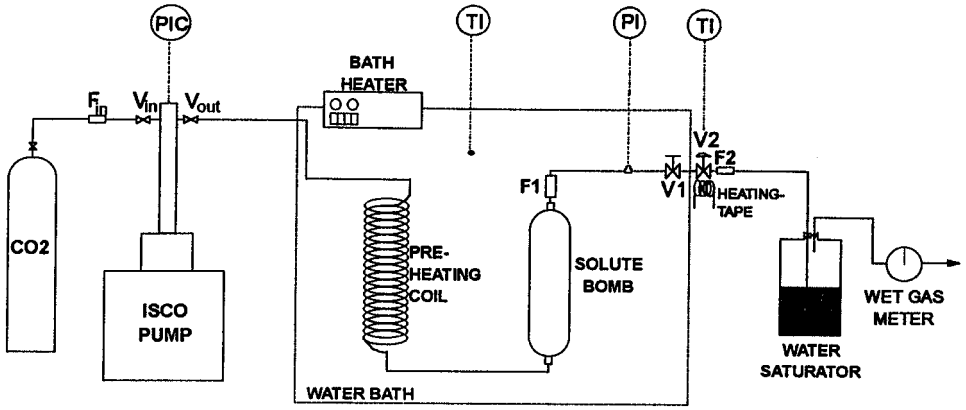
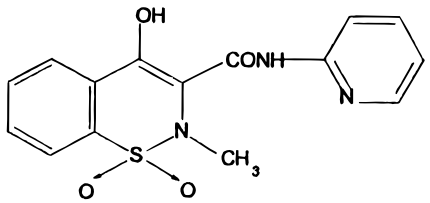
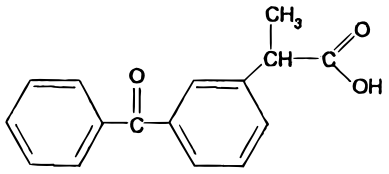


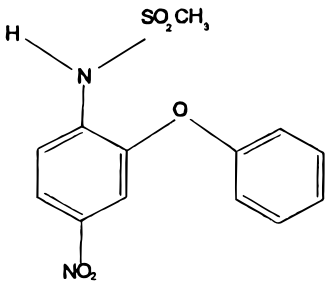
Figure 1. Experimental apparatus.



Piroxicam



Ketoprofen



Nimesulide

Figure 2. Structures of the studied drugs.

Table 1. Source and Purity of the Materials Used

material	source	purity/%
CO_2	SIAD	99.98
Ketoprofen	Farmitalia C. Erba	99.42
Piroxicam	Chiesi Farmaceutica	99.35
Nimesulide	Helsinn	99.0

Table 2. Melting Point T_m, Solid Density d (298 K), and Molar Mass M for the Drugs

compound	T_m/K	d/g dm^{-3}	M/g mol^{-1}
Ketoprofen	367.65	1224	254.29
Piroxicam	469.15	1497	331.30
Nimesulide	421.65	1414	308.31

lack of physical and chemical property data for the compounds used in this study: some of the available data are listed in Table 2. In Figure 2 the structures of the drugs are shown.

Ketoprofen (3-benzoyl-α-methylbenzeneacetic acid) is weakly acidic, it has two polymorphic forms: one is glassy and metastable; the other has a regular and stable crystalline form (this form has been used in this work). The compound must be protected from humidity and from light; it is soluble in many solvents.

Piroxicam (4-hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2 benzothiazine-3-carboxamide 1,1-dioxide) has two different crystalline polymorphic forms: the one used in this work has a melting point of 196.0 °C, it has a dipole moment of 3.68 (Mihalic et al, 1986), and it is soluble in polar organic solvents.

Nimesulide is *N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide, it is weakly acidic (pK = 6.5) and differs from other steroids in that its chemical structure contains a sulfonamide moeity as the acidic group.

The purity of the drugs was higher than 99% mass and no purification was made before use. However in the process of measuring the solubilities, small quantities of volatile impurities were extracted. These impurities were only present during the extraction of the first 2 to 4% of the material charged in the extraction vessel. Solubility measurements were only commenced after there was no longer any evidence of impurities in the extract. The extractions on which the measurements were based yielded homogeneous and uniformly colored crystals.

Table 3. Experimental Solubility for the Drugs in Supercritical CO_2

		10^5y		
T/K	P/bar	Ketoprofen	Piroxicam	Nimesulide[a]
312.5	100	1.33	0.45	
	130	2.90	1.21	1.89
	160	5.14	1.92	3.18
	190	7.20	2.92	5.11
	220	7.98	4.33	7.42
331.5	115.6	0.78		
	130	1.63	0.37	0.85
	160	5.50	1.26	3.80
	190	10.5	2.31	7.08
	220	15.5	3.89	9.85

[a] The data for Nimesulide are determined at 313.1 K and 333.1 K, respectively.

Results and Discussion

The solubilities of the three drugs along with the temperature, pressure, and density of CO_2 that corresponded to each measurement are listed in Table 3. The results represent the average of at least three separate measurements. The maximum deviation between the measurements was ±3% and gives a good indication of the expected accuracy of the results. Since the overall error (i.e. pressure, temperature, mass and volume) connected to the individual equipment errors is significantly below this level, the deviation is due to random experimental

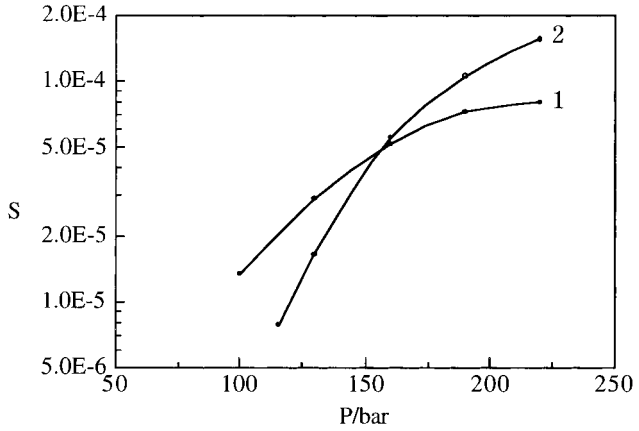


Figure 3. Mole fraction solubilitiy *S* of Ketoprofen as a function of pressure *P* in supercritical carbon dioxide at 312.5 K (●, 1) and 331.5 K (○, 2).

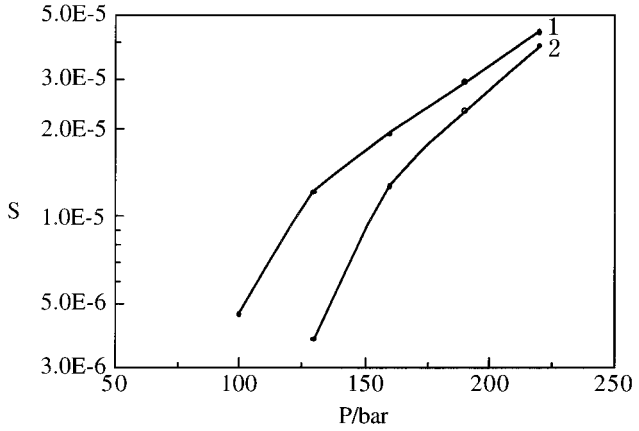


Figure 4. Molar fraction solubility *S* of Piroxicam as a function of pressure *P* in supercritical carbon dioxide at 312.5 K (●, 1) and 331.5 K (○, 2).

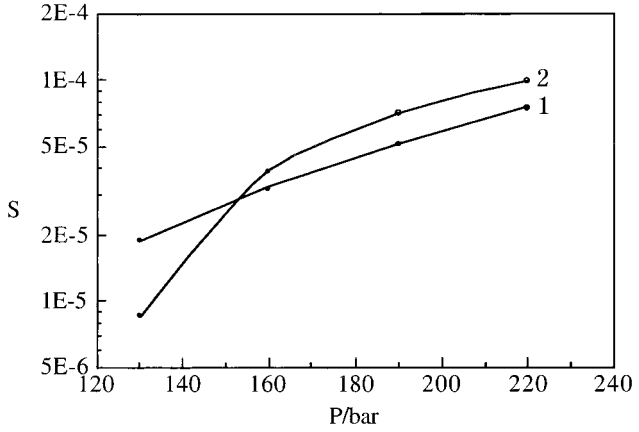


Figure 5. Molar fraction solubility *S* of Nimesulide as a function of pressure *P* in supercritical carbon dioxide at 313.1 K (●, 1) and 333.1 K (○, 2).

errors associated with the difficulties of working with high-pressure supercritical fluids and with the problems connected with the continuous flow technique used, such as partial clogging of the regulating valve with consequently possible fluctuations of flow rate.

The solubilities for each system as a function of pressure are given in Figures 3−5. These results show trends that are similar to those observed for other solids in previous studies (Macnaughton and Foster, 1994; Foster et al., 1991).

For these particular compounds having complex and different structures but at the same time being all three

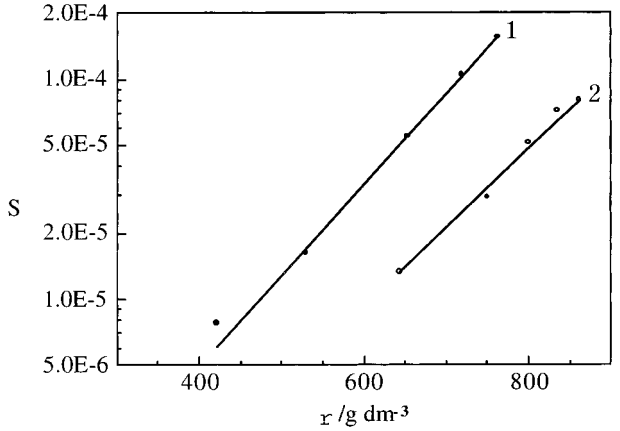


Figure 6. Molar fraction solubility *S* of Ketoprofen in supercritical carbon dioxide as a function of the carbon dioxide density ρ at 312.5 K (●, 1) and 331.5 K (○, 2). Lines represent regression fits of the data.

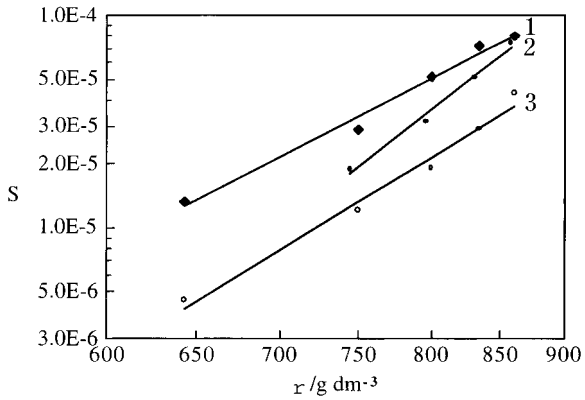


Figure 7. Mole fraction solubility *S* of three drugs in supercritical carbon dioxide as a function of carbon dioxide density ρ. Lines represent regression fits of the data. (◆, 1) Ketoprofen at 312.5 K; (●, 2) Nimesulide at 313.1 K; (○, 3) Piroxicam at 312.5 K.

weakly acidic, the solubilities parallel the order of the relative melting point or the molecular weight: the higher the melting point or the molecular weight, the lower the solubility.

The crossover pressure is clearly defined where the two isotherms intersect: for Ketoprofen the crossover pressure is around 165 bar, for Nimesulide it is around 160 bar, and for Piroxicam we should expect a crossover pressure above 220 bar but it was not determined due to the limitation in pressure of the instrumentation used in this work.

Below the crossover pressure the solubility decreases with increases in temperature, and above this value the reverse is the case. Supercritical solubility is strongly influenced by the system temperature and the density of the solvent. The influences of these two variables are shown in Figure 6 which presents the solubility of Ketoprofen as a function of CO_2 density. The isothermal dependence of solubility on density can be clearly seen. The solubility also increases with temperature at constant density due primarily to the associated increase in vapor pressure. Similar behavior is shown by the other compounds. In Figure 7 the solubilities of the drugs at 313.1 K are shown as a function of density.

A rigorous thermodynamic modeling of solubility is difficult due to an almost complete lack of knowledge of the physical properties for these compounds necessary for the evaluation of pure component parameters requested for an equation of state; moreover the estimation methods for irregular molecules are in general unreliable.

Table 4. Correlation of the Density Dependence of Solubility

drug	T/K	a_1	a_2	AARD/%
Ketoprofen	312.5	6.4	−52.5	5.26
	331.5	5.1	−42.8	14.5
Piroxicam	312.5	7.5	−60.9	8.61
	331.5	6.3	−51.8	6.26
Nimesulide	313.1	9.5	−74.0	4.74
	333.1	6.2	−50.3	3.13

The solubilities y from this study were correlated with density ρ (g dm^{-3}) according to

$$\ln(y) = a_1 \ln(\rho) + a_2$$

where a_1 and a_2 are two empirical constants that should be determined by fitting experimental data.

This formulation has been utilized previously (Stahl et al., 1978; Kumar and Johnston, 1988) although the density dependence of ln(y) can be linear or logarithmic in nature. Regression analysis confirmed that this equation is the most applicable to these results and the regression coefficients are given in Table 4. The constants a_1 and a_2 were allowed to vary for each compound and at each temperature. In all cases the correlation is good and the overall error from the regression has a magnitude similar to that of the expected experimental error (±3%).

Conclusion

The solubilities of three drugs have been measured in supercritical CO_2 at pressures between 100 bar and 220 bar and at temperatures of 313.1 K and 333.1 K. The experimental error is estimated to be less than 3% on the basis of the average of three separate measurements for each reported solubility. The results exhibit trends that are typical of the solubility of nonvolatile organic molecules in supercritical CO_2. Correlating the solubility with the density of the CO_2 was successful with regression errors that matched the magnitude of the experimental errors.

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