Solubility of Diflunisal in Supercritical Carbon Dioxide

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The solubility of diflunisal, a nonsteroidal anti-inflammatory drug (NSAID), in supercritical carbon dioxide ($scCO_2$) was measured at (308.2, 318.2, and 328.2) K and in the pressure range from (9.0 up to 25.0) MPa. Results were obtained using a static analytical method. Experimental solubility was found to be between $0.54 \cdot 10^{-6}$ and $8.07 \cdot 10^{-6}$ (in terms of diflunisal mole fraction). Experimental data were satisfactorily correlated with an equation-of-state (EOS) model: the Peng−Robinson cubic equation of state (PR−EOS) together with the conventional van der Waals mixing and combining rules. Solid properties were estimated by different methods available in the literature. The solubilities of several NSAIDs in SCFs, namely in $scCO_2$, were obtained from the literature and plotted and represented as a function of the corresponding sublimation pressures and fusion temperatures.

Introduction

Aqueous solubility is one of the key factors affecting the "in vivo" bioavailability of any drug. However, nearly half of the substances which were identified as biologically active through the new paradigm of high-throughput screening are either insoluble or poorly soluble in water.[1] Therefore, the development of efficient formulations of poorly water-soluble compounds, aiming to increase in vivo drug bioavailability, represents nowadays one of the most frequent and greatest challenges for the pharmaceutical industry.

To improve the bioavailability of poorly water-soluble drugs as well as to avoid the occurrence of undesired systemic and nonsystemic side effects due to the use of formulations having high drug levels, various techniques have been recently proposed and developed, namely, particle size reduction,[2] surfactant−aid dispersion,[3] emulsions and microemulsions,[4] solid dispersions,[5] etc. But, and like many other traditional pharmaceutical processes, most of these techniques often require the use of toxic solvents, with all its negative implications, or the use of high processing temperatures which may degrade thermally labile drugs.

Supercritical fluid (SCF) technologies, and in particular supercritical carbon dioxide ($scCO_2$) based processes, are known to be new and interesting routes for pharmaceutical processing, avoiding most of the drawbacks of conventional methods, particularly those related with the use of toxic organic solvents.[6] Furthermore, SCFs present unique properties that may improve these processes as well as offer innovative possibilities for the development of new products, with better chemical, physical, morphological, and mechanical properties and, consequently, leading to novel and improved final pharmaceutical products. Micronization of drug particles,[7–9] drug−cyclodextrin complex formation,[10,11] and drug impregnation into polymeric matrixes[12,13] are some examples of current research strategies to improve bioavailability of poor water-soluble drugs using supercritical fluid based technology.

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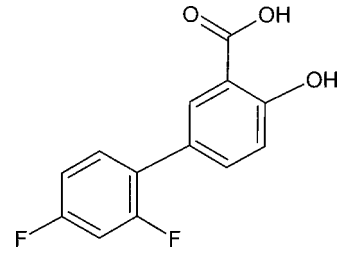

Figure 1. Chemical structure of diflunisal (5-(2,4-difluorophenyl)-2-hydroxy-benzoic acid).

Diflunisal (5-(2,4-difluorophenyl)-2-hydroxy-benzoic acid) (Figure 1) is a salicylate derivative possessing antipyretic, analgesic, and anti-inflammatory activities.[14] It belongs to the family of the nonsteroidal anti-inflammatory drugs (NSAIDs), and it is commonly used to relieve mild to moderate pain and inflammations caused by arthritis or other inflammatory conditions. Although NSAIDs are among the most frequently used drugs in the world, their oral administration is often limited because of their potential to cause adverse effects such as irritation and ulceration of the gastro-intestinal mucosa.[15] These problems are mainly caused because of the poor water solubility of these types of drugs. For this reason, considerable efforts have been made for the development of newer and better formulations for oral delivery systems of NSAIDs. Some of the present investigated strategies include also supercritical-based processes, namely in the field of particle generation using $scCO_2$ technologies, such as rapid expansion of supercritical solutions (RESS), supercritical anti-solvent (SAS), and particles from gas saturated solutions (PGSS).[7–9]

The accurate knowledge of equilibrium solubility of pharmaceutical products in the employed SCF, at different conditions of temperature and pressure, is indispensable for the design of any SCF-based process. This work continues our recent research activities regarding the preparation of polymeric drug delivery systems, namely by the use of a supercritical solvent impregnation technique[16–22] as well as our previous work on the experimental determination and correlation of the solubility of several drugs[23–26] and other solid compounds[27,28] in $scCO_2$. In

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Table 1. Experimental Solubility of Diflunisal in Supercritical Carbon Dioxide

$T = 308.2$ K		$T = 318.2$ K		$T = 328.2$ K	
P/MPa	$(y_2 \pm \mathrm{SD})\cdot 10^6$	P/MPa	$(y_2 \pm \mathrm{SD})\cdot 10^6$	P/MPa	$(y_2 \pm \mathrm{SD})\cdot 10^6$
9.4	1.845 ± 0.078	9.3	0.565 ± 0.045	9.1	0.544 ± 0.082
11.8	1.959 ± 0.283	11.6	1.212 ± 0.064	11.6	0.899 ± 0.087
14.2	2.060 ± 0.264	14.2	1.701 ± 0.186	14.2	1.730 ± 0.123
16.8	2.268 ± 0.242	17.0	3.143 ± 0.371	16.8	3.603 ± 0.042
19.5	2.675 ± 0.134	19.3	3.923 ± 0.320	19.3	4.593 ± 0.094
21.9	2.980 ± 0.192	21.9	4.497 ± 0.134	21.9	6.625 ± 0.177
24.6	3.892 ± 0.353	24.4	5.466 ± 0.260	24.4	8.072 ± 0.395

Table 2. Estimated Critical and Thermophysical Properties of Diflunisal

				$10^4\cdot P_2^{\mathrm{sub}}$/Pa		
T_c/K	P_c/MPa	ω	$10^6\cdot v_2$/m$^3\cdot$mol^{-1}	308.2 K	318.2 K	328.2 K
869.8[a]	3.211[a]	0.897[a]	125.5[b]	0.33[c]	1.42[c]	5.63[c]

[a] Estimated by the Constantinou−Gani (first order) method.[30] [b] Estimated by the Fedors method.[31] [c] Extrapolated from data presented by Perlovich et al.[32]

Table 3. Correlation Results Obtained with the PR−EOS Model

		PR-EOS		
T/K	mixing rule	k_{12}	l_{12}	AARD (%)
308.2	vdW1	0.173		19.2
	vdW2	0.140	−0.081	17.3
318.2	vdW1	0.169		20.5
	vdW2	0.194	0.070	20.6
328.2	vdW1	0.164		23.9
	vdW2	0.190	−0.071	23.3

the present work, we present the experimental solubility of diflunisal in $scCO_2$, at (308.2, 318.2, and 328.2) K and in a pressure range from (9.0 up to 25.0) MPa, using a static analytical method. We also present the correlation of the obtained experimental data by using the well-known Peng−Robinson cubic equation of state with the conventional van der Waals mixing and combining rules. The solubilities of several NSAIDs in SCFs, namely, in $scCO_2$, were obtained from literature and represented as a function of the corresponding sublimation pressures and fusion temperatures.

Experimental Section

Materials. Carbon dioxide (CAS 124-38-9, purity > 99.998 %) was purchased from Praxair; ethanol (CAS-64-17-5, purity > 99.5 %) was obtained from Panreac Quimica SA, and diflunisal (CAS 22494-42-4, 100 % pure) was obtained from Sigma-Aldrich.

Experimental Procedure. A static phase equilibrium apparatus was used to determine the experimental solubility of diflunisal in $scCO_2$. A detailed description of this apparatus and of its validation was given in previous works.[27,28] The typical experimental procedure is described below.

A high-pressure equilibrium cell, equipped with sapphire windows and with an internal volume of approximately 30 cm^3, is loaded with an excess amount of diflunisal and a magnetic stirrer. The cell is connected to the apparatus tubing lines and immersed in a water bath, equipped with a temperature controller which controls the operational temperature within ± 0.1 K. Carbon dioxide is liquefied in a cooling unit and compressed using a high-pressure liquid pump. When the water bath reaches the experiment temperature, the cell is pressurized with CO_2 until the desired experimental pressure is attained. Pressure is measured with a high-pressure transducer (Setra, model 204, (0 to 34.40) ± 0.04 MPa). After pressure and temperature stabilization, the magnetic stirring plate, positioned under the equilibrium cell, is switched on and the diflunisal + CO_2 mixture is left to stir for one hour (the period of time found to be necessary to attain equilibrium and complete fluid phase saturation), followed by a 20 min period, without stirring, to allow mixture stabilization. A homogeneous mixture sample is then removed from the cell, using a six-port sampling valve (Rheodyne, model 7060), into a sampling loop of 0.456 cm^3. This sample is then quickly depressurized and expanded into previously calibrated volumes, which are composed by a glass trap (15.9 cm^3), immersed in ice, and a stainless steel balloon (1735.05 cm^3), immersed in a water bath at room temperature and previously brought into subatmospheric pressure using a vacuum pump. The resulting pressure increase is then measured using a calibrated high-precision low-pressure transducer (Setra, model 204, (0 to 0.175) ± $1.9\cdot10^{-4}$ MPa). During expansion, the formerly dissolved solid precipitates in the glass trap. To recover all the precipitated solid, a cleaning solvent (ethanol) is injected through the sample loop and expansion lines and recollected in the glass trap. The lines are also cleaned with fresh CO_2 smoothly pressurized.

The amount of solubilized solid was determined by UV spectrophotometric analysis. Collected samples containing the solid are diluted to a convenient volume with ethanol, and the absorbance of the resulting solutions is measured at a fixed wavelength (254 nm) using a UV/vis spectrophotometer (JASCO V-530). A calibration curve was obtained by UV analysis of previously prepared standard solid samples. The amount of CO_2 in the sample loop is calculated using the Virial EOS (applied to pure CO_2) and considering the values of the precalibrated expansion volumes, the resulting subatmospheric pressure increase due to expansion, the temperature of the water bath where the expansion balloon is immersed, and the temperature of the ice-immersed glass trap (which is considered to be 273.15 K).

Each experimental solubility data point is the average of, at least, three replicate measurements. The relative standard deviation values were taken as an indication of replicate measurement reproducibility. The overall uncertainty, taking into consideration the random uncertainties (statistical, associated to Beer−Lambert's calibration curve and to the average of the experimental solubility measurements) and the systematic uncertainties (uncertainties due to the preparation of standard calibration solutions and to pressure and temperature measurements), was found to be less than $1.1\cdot10^{-6}$ (in terms of diflunisal mole fraction).

EOS Correlation of Experimental Solubility Data. Usually, in solid-SCF phase equilibria, the supercritical phase is treated as a compressed gas phase, and the solid solubility is then given

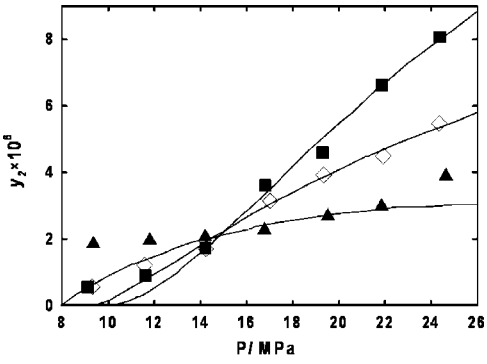

Figure 2. Solubility of diflunisal in $scCO_2$. Experimental: ▲, 308.2 K; ◇, 318.2 K; and ■, 328.2 K. —, Correlated with the PR-vdW2 model.

by an expression derived from the thermodynamic equilibrium conditions between the solid phase and that high-pressure gas phase.

Thus, the solubility of a solid solute (y_2), in equilibrium with a high-pressure fluid, can be calculated using the following general expression[26]

$$y_2 = \frac{P_2^{sub}}{P}\frac{1}{\varphi_2^{SCF}}\exp\left[\frac{v_2(P - P_2^{sub})}{RT}\right] \quad (1)$$

This equation is derived from the equifugacity condition between the solid and the fluid phase, under the assumptions that the solubility of the solvent ($scCO_2$) in the solid phase is negligible, that the solid is incompressible, and that the saturated vapor of the pure solid solute at sublimation behaves like an ideal gas. In eq 1, P is the pressure; P_2^{sub} is the sublimation pressure of the pure solid (at temperature T); v_2 is the molar volume of the solid; and φ_2^{SCF}, is the solid fugacity coefficient in the high-pressure fluid phase, which expresses the nonideality of the fluid phase. This parameter is usually evaluated by an EOS, and cubic EOSs are the most widely used models to evaluate the fugacity coefficients of solids in compressed fluid phases. In this work, the well-known Peng−Robinson cubic equation of state[29] (PR−EOS) was employed to evaluate the fugacity coefficient of the solid in the compressed fluid phase

$$P = \frac{RT}{v - b} - \frac{a}{v(v + b) + b(v - b)} \quad (2)$$

$$a = 0.45724\left(\frac{R^2T_c^2}{P_c}\right)\left\{1 + n\left[1 - \left(\frac{T}{T_c}\right)^{0.5}\right]\right\}^2 \quad (3)$$

$$n = 0.37464 + 1.54226\omega - 0.26992\omega^2 \quad (4)$$

$$b = 0.07780\frac{RT_c}{P_c} \quad (5)$$

To apply the above EOS model for a binary solid + $scCO_2$ system, we employed the classical van der Waals (vdW) mixing and combining rules, with one or with two adjustable parameters, k_{ij} and l_{ij}

$$a = \sum_i \sum_j y_i y_j a_{ij} \quad (6)$$

$$b = \sum_i \sum_j y_i y_j b_{ij} \quad (7)$$

$$a_{ij} = (a_{ii}a_{jj})^{0.5}(1 - k_{ij}) \quad (8)$$

$$b_{ij} = \left(\frac{b_{ii} + b_{jj}}{2}\right)(1 - l_{ij}) \quad (9)$$

The optimal binary interaction parameters, k_{ij} and l_{ij}, for each temperature must be obtained by the correlation of experimental data, through the minimization of the objective function average absolute relative deviation (AARD), defined as

$$\mathrm{AARD}(\%) = \frac{100}{N}\sum_n \frac{|y^{calcd} - y^{exptl}|}{y^{exptl}} \quad (10)$$

In this equation, N is the number of experimental data points for each temperature; y^{calcd} corresponds to the calculated solubilities; and y^{exptl} corresponds to the experimental solubility data points.

As can be seen, the PR−EOS model always need information concerning the critical properties and the Pitzer's acentric factors of all involved compounds as well as the molar volume and the sublimation pressure of the studied solid. However, and for most organic solids (like NSAIDs and other common drugs), these properties are usually unknown and difficult, or even impossible, to obtain. This represents a well-known disadvantage for the application of cubic EOS correlation models. Thus, the required solid properties are normally obtained using group contribution estimation methods or other estimation methods that can be found in the literature. For practical reasons, the majority of these estimation methods was developed based on the behavior of pure components that are gases or liquids at normal temperature and pressure (which is not the case in most situations). An excellent review on the most important estimation methods for these properties can be found in the recent book by Poling, Prausnitz, and O'Connell[30] as well as on its previous editions. On previous works, we already discussed the applicability of several of these property estimation methods[26,28] and referred that these should be selected and employed very carefully. Furthermore, and without any reliable experimental sublimation pressure data, special attention should be paid to this property because it is recognized to be a key property to achieve successful EOS-based correlation results.[28]

In this work, diflunisal critical properties and acentric factors were estimated using the Constantinou−Gani (first order) method.[30] Solid molar volume was estimated using the Fedors method.[31] Diflunisal sublimation pressures, at (308.2, 318.2, and 328.2) K, were extrapolated from the Clausius−Clapeyron equation presented by Perlovich et al.,[32] which was derived from experimental sublimation pressures measured between (349 and 410) K.

Results and Discussion

The experimental mole fraction solubilities of diflunisal in $scCO_2$ were obtained at (308.2, 318.2, and 328.2) K, in a pressure range from (9.0 up to 25.0) MPa, and are reported in Table 1. The obtained diflunisal solubility values (y_2) varied between $0.54 \cdot 10^{-6}$ and $8.07 \cdot 10^{-6}$ and, as referred to in the Experimental Section, each reported data point is the average of at least three replicate experimental measurements.

The relative standard deviation (RSD) values were taken as an indication of replicate measurement reproducibility and varied between 15.1 % (T = 328.2 K, P = 9.1 MPa) and 2 % (T = 328.2 K, P = 19.3 MPa). In general terms and as usually found in the literature for this type of measurements, the experimental points presenting higher values of RSD were those obtained at lower experimental pressures, which correspond to the lower solid solubility values.

The values of the required critical and thermophysical properties for the PR−EOS correlation of diflunisal solubility in $scCO_2$ are presented in Table 2.

The optimal fitted binary interaction parameters and the corresponding AARD values, which were obtained by the correlation of experimental solubility data with the PR−EOS model and using the set of properties indicated in Table 2, are presented in Table 3. The vdW mixing and combining rules with one adjustable parameter (PR-vdW1) or with two adjustable parameters (PR-vdW2) were employed.

As can be seen, the applied models were able to correlate the experimental data, however yielding AARD values around 20 %. Notably, the model with only one fitted parameter (PR-vdW1) demonstrated a similar capacity to correlate the obtained experimental data as the model with two fitted parameters (PR-vdW2). From our previous experience[25–28] in the correlation of solid/$scCO_2$ solubility data with cubic

Table 4. Fusion Temperature, Sublimation Pressure, and Experimental Solubility in $scCO_2$ of Some NSAIDs

				solubility in $scCO_2$		
drug	formula	T_f (°C)	P^a (Pa)	T (°C)	P (MPa)	y_2
ACET	$C_8H_9NO_2$	168 to 172	Exp[34.3 to 14010/T(K)][a]	40	10 to 25	(0.4 to 1.8)·10^{-6}[g]
ASAL Ac	$C_9H_8O_4$	138 to 140	Exp[38.2 to 13190/T(K)][b]	45	12 to 25	(0.7 to 2.6)·10^{-4}[h]
DIF	$C_{13}H_8F_2O_3$	219 to 220	Exp[36.4 to 14400/T(K)][c]	45	10 to 25	(0.6 to 5.5)·10^{-6}[i]
FLU	$C_{15}H_{13}O_2$	110 to 112	Exp[33.8 to 13040/T(K)][c]	40	10 to 24	(0.2 to 1.5)·10^{-4}[j]
IBU	$C_{13}H_{18}O_2$	73 to 76	Exp[40.4 to 13927/T(K)][d]	40	10 to 22	(0.5 to 6.4)·10^{-3}[k]
KET	$C_{16}H_{14}O_3$	93 to 94	Exp[33.0 to 13250/T(K)][e]	40	9 to 25	(0.4 to 9.2)·10^{-5}[l]
NAP	$C_{14}H_{14}O_3$	153 to 154	Exp[39.7 to 15431/T(K)][f]	40	9 to 19	(0.2 to 2.4)·10^{-5}[m]

[a] Ref 37. [b] Ref 38. [c] Ref 32. [d] Ref 39. [e] Ref 40. [f] Ref 41. [g] Ref 42. [h] Ref 43. [i] This work. [j] Ref 23. [k] Ref 44. [l] Ref 45. [m] Ref 46. Ibuprofen (IBU), acetylsalicylic acid (ASAL Ac), flurbiprofen (FLU), ketoprofen (KET), naproxen (NAP), diflunisal (DIF), acetaminophen (ACET).

equations of state, like the PR−EOS and the Soave−Redlich−Kwong (SRK) EOS, and using the vdW mixing and combining rules, we found that usually a model with two adjustable parameters is required to successfully fit experimental solubility points in the whole pressure range, especially at higher pressures, the model with only one adjustable parameter being unable to do that.

In these works, we also noticed that the solid sublimation pressure plays, among all the input properties, a dominant role in the ability of a cubic EOS model to correlate experimental solubility data, especially when only one adjustable parameter is used. Previously, other authors reached the same conclusion.[33,34] Unfortunately, and for the majority of low volatile solids, this property is usually unknown and is often calculated by empirical correlations or by extrapolation of experimental data at different pressure and temperature conditions which, in some cases, may lead to doubtful estimations. Moreover, and mainly for this reason, a different strategy which considers the sublimation pressure as an adjustable parameter, together with the binary interaction parameters, can also be employed.[26,35,36]

In this work, the employed values of diflunisal sublimation pressure were obtained based on diflunisal experimental sublimation pressure data, and this fact can explain the observed good fitting results achieved even with the one adjustable parameter model (PR-vdW1). Once again, this evidences the importance of having reasonably accurate sublimation pressure values when using these types of EOS models for the correlation of solid solubility experimental data.

In Figure 2, the experimental solubility of diflunisal in $scCO_2$ is represented as a function of pressure, for the three studied isotherms. The corresponding correlation curves (obtained with the PR-vdW2 model) are also shown. As can be seen, higher deviations are observed for lower pressures and for lower isotherms. Furthermore, for the results at 308.2 K, the correlation curve is far from fitting the experimental points. The typical retrograde solubility behavior of the solid is also present at this system. This phenomenon is well-known for most solid + SCFs systems, and it is caused by the opposite effect of temperature on the density of the SCF and on the solid sublimation pressure. For this system, the so-called cross-over region, where one can observe the intersection of the solubility isotherms and where below this point an isobaric increase in temperature corresponds to a solubility decrease, is located around 15.0 MPa.

Due to their widely spread use, NSAIDs have been the subject of many research works, namely on the field of pharmaceutical formulations, in which scientists face the challenge of developing better and safer formulations for these inherently poor water-soluble class of drugs. And, as mentioned, the use of supercritical processes to overcome

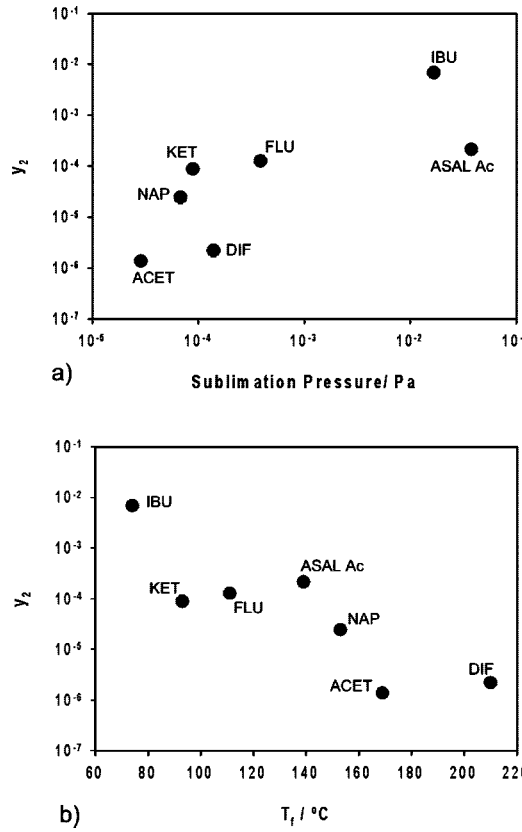

Figure 3. Solubility of several NSAIDs in $scCO_2$, at (40 to 45) °C and at approximately 20 MPa, plotted against: (a) sublimation pressure; (b) fusion temperature (T_f). Ibuprofen (IBU), acetylsalicylic acid (ASAL Ac), flurbiprofen (FLU), ketoprofen (KET), naproxen (NAP), diflunisal (DIF), and acetaminophen (ACET).

these issues has also been under intense investigation. Therefore, the solubility of many of these drugs in SCFs, namely in $scCO_2$, has been quite studied. Table 4 displays a collection of the experimental solubilities (in $scCO_2$) of some of the most important NSAIDs. Solubility is expressed in terms of mole fraction solubilities of these drugs. The experimental values of the corresponding fusion temperatures (T_f) and of sublimation pressures (P^{sub}) are also presented in this table. All these experimental values were obtained from the literature.

In Figure 3, the logarithms of the solubilities of these drugs (at approximately 20 MPa and at (40 to 45) °C) are plotted against the corresponding sublimation pressures (Figure 3a) and against fusion temperatures (Figure 3b).

As can be seen in Figure 3a, the logarithms of the solubilities of these NSAIDs present an increasing tendency with the matching sublimation pressures. On the other hand, in Figure 3b, it is also possible to observe an overall decreasing trend

between the NSAID logarithms of solubilities and their fusion temperatures. These general trends were expected since it is well established that the solubility of a solid in a pure SCF, like CO_2, is mainly determined by the SCF density and the by the volatility of the solid which is always dependent on properties such as solid sublimation pressure and solid fusion temperature.

Conclusions

The experimental solubility of diflunisal in $scCO_2$ was measured at (308.2, 318.2, and 328.2) K and in a pressure range from (9.0 up to 25.0) MPa, using a static analytical method. The obtained experimental solubility data were successfully correlated by the Peng−Robinson cubic EOS and using the classical van der Waals mixing rules, with one or with two adjustable parameters.

The solubilities of several NSAIDs in SCFs, namely in $scCO_2$, were obtained from the literature and plotted and represented as a function of the corresponding sublimation pressures and fusion temperatures.

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