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Measurement and correlation for the solid solubility of non-steroidal anti-inflammatory drugs (NSAIDs) in supercritical carbon dioxide

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Abstract

The solubilities for three non-steroidal anti-inflammatory drugs (NSAIDs) of nabumetone, phenylbutazone and salicylamide in supercritical carbon dioxide were measured in this study using a semi-flow type apparatus. The experimental data were taken at 308.2, 318.2 and 328.2 K, over the pressure range from 10 to 22 MPa. The measured results were then correlated using semi-empirical equation presented by Chrastil, and that presented by Mendez-Santiago and Teja. With optimally fitted parameters, these two equations yielded satisfactory results where the average absolute relative deviation (AARD) was below 7%. Furthermore, the solid solubilities of these three compounds and seven other NSAIDs in supercritical carbon dioxide were correlated by applying the regular solution model coupled with a Flory–Huggins term. The solution model, which has fewer parameters than the semi-empirical equations, yielded comparable correlation results. The parameters in the solution model could be generalized for the specific group of NSAIDs. Finally, the predicted solubilities of 10 NSAIDs in supercritical carbon dioxide were demonstrated to be reliable.

Keywords: Solid solubility; Supercritical carbon dioxide; Experiment; Correlation

1. Introduction

Supercritical fluid (SCF) technology, recognized as a green process, is applied in diversified fields of extraction, reaction, particle formation and material processing [1,2]. Carbon dioxide has been widely employed for the formation of micronized pharmaceutical compounds [3–6]. Various physical properties such as diffusion coefficient or solubility for supercritical fluid mixtures are crucial to the efficient design of industrial processes. Experimental solid solubility data in supercritical CO_2 have been reviewed by several authors [7–9]. It is observed that more experimental data are still required for specialty chemicals and there is a need for generalized correlation models.

We have previously measured the solid solubilities of aromatic compounds in supercritical CO_2 [10]. In this study, we used the similar semi-flow apparatus to measure the solid solubilities of nabumetone, phenylbutazone and salicylamide in supercritical CO_2 at temperatures of 308.2, 318.2 and 328.2 K, over the pressure range from 10 to 22 MPa. These three compounds are non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties and are used to treat fever, headache and pain associated with colds, influenza and arthritis. No solid solubility data for these compounds in supercritical CO_2 seem to have been reported in literature. The results of this study thus supply new data for further engineering design and theoretical modeling. The measured solid solubility data were firstly correlated using the three-parameter semi-empirical equation presented by Chrastil [11], or that presented by Mendez-Santiago and Teja. [9]. Solid solubility data in supercritical fluids have also been correlated by solution models [12]. Our recent studies applied the regular solution model coupled with a Flory–Huggins term to correlate the solubilities of biological and pharmaceutical systems with satisfactory accuracy [13,14]. One advantage of the solution model approach is that the parameters might be able to be generalized and that prediction of solid solubilities might be possible. It was pointed out [14] that, rather than using a single set of universally correlated parameters, the generalized parameters in the solution model could be presented for different groups of compounds with specific chemical structures. The grouping of generalized parameters would effectively improve the prediction accuracy. The measured solid solubilities of three pharmaceutical compounds in

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this study, together with those data from literature for seven other NSAIDs, were correlated using the generalized solution model. It was intended to demonstrate that the solution model approach provides a feasible way for predicting the solubilities of complex compounds in supercritical CO_2.

2. Experimental

2.1. Chemicals

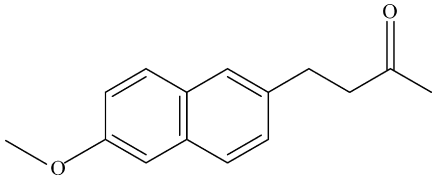
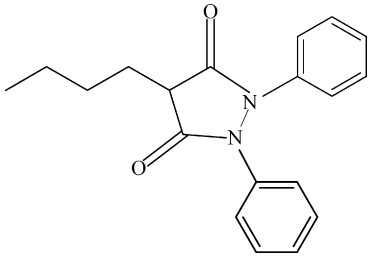
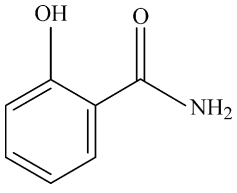
Carbon dioxide was purchased from Liu-Hsiang Gas Co. (Taiwan) with a minimum purity of 99.8%. Nabumetone ($C_{15}H_{16}O_2$), phenylbutazone ($C_{19}H_{20}N_2O_2$), salicylamide ($C_7H_7NO_2$) and salicylic acid ($C_7H_6O_3$) were purchased from Sigma–Aldrich Co. with a minimum purity of 99%. These chemicals were used without further purification. The chemical structure and physical properties of nabumetone, phenylbutazone and salicylamide are listed in Table 1.

2.2. Experimental apparatus and procedures

A semi-flow type apparatus used in this study for measuring solid solubility in supercritical CO_2 is shown in Fig. 1. The experimental system included three parts: (I) the feed of supercritical CO_2, (II) the equilibrium between the solid and the supercritical phases and (III) the analysis of experimental results. Pure CO_2 was liquefied to 273.2 K by a cooler and then was compressed to the desired pressure by a HPLC pump (Thermo Separation Product). The pressure was regulated by a back pressure regulator. The high pressure CO_2 passed through the pre-heating coil, which was immersed in a water bath. It was then charged into the pre-equilibrium and equilibrium cells. Both cells had a volume of 75 cm^3 where 10 g drug sample was packed with glass beads. The cells were plugged at their ends with glass wool or filter to avoid any physical entrainment. The temperature and pressure were measured using a calibrated thermocouple and a Druck pressure transducer (PTX 610), respectively. The resolutions for temperature and pressure measurements were ±0.1 K and ±0.01 MPa, respectively.

After the equilibrium cell, supercritical CO_2 was expanded to atmospheric pressure through a needle valve wrapped with heating tape. The temperature of the heating tape was kept in the temperature range of 10–20 K above the melting point of the drug solid in order to avoid precipitation and blockage in the line. After the expansion, solid was separated from the gas phase and was dissolved into a flask with organic solvent. Residual solute in the line was recovered by further delivery of organic solvent. The sampling line was then purged by air to remove organic solvent. The total volume of CO_2 flow was measured by a wet test meter (Ritter TG05). A HPLC system equipped with UV–VIS detector (Jasco UV-975) was used to analyze the concentration of the organic solution in the flask. In this study, ethyl acetate was chosen as the solvent. A sharp absorption peak in the UV–VIS detector for nabumetone, phenylbutazone and salicylamide was observed at the band of 263, 249 and 305 nm, respectively. Calibrations for the UV analyses were made before the experiments using standard solutions of known concentrations. In each experiment, at least four measurements were taken at a given temperature and pressure. Repeated measurements were taken at various effluent CO_2 flow rates between 3 and 10 L/h at atmospheric conditions. These flow rates had no effect on solid solubility

Table 1
Physical properties of nabumetone, phenylbutazone and salicylamide

Compound	Structure	Formula	Molecular weight (kg/mol)	T_m (K)	Purity (%)
Nabumetone		$C_{15}H_{16}O_2$	0.2283	353.15 [22]	>99
Phenylbutazone		$C_{19}H_{20}N_2O_2$	0.3083	378.58 [22,23]	>99
Salicylamide		$C_7H_7NO_2$	0.1371	413.58 [22,23]	>99

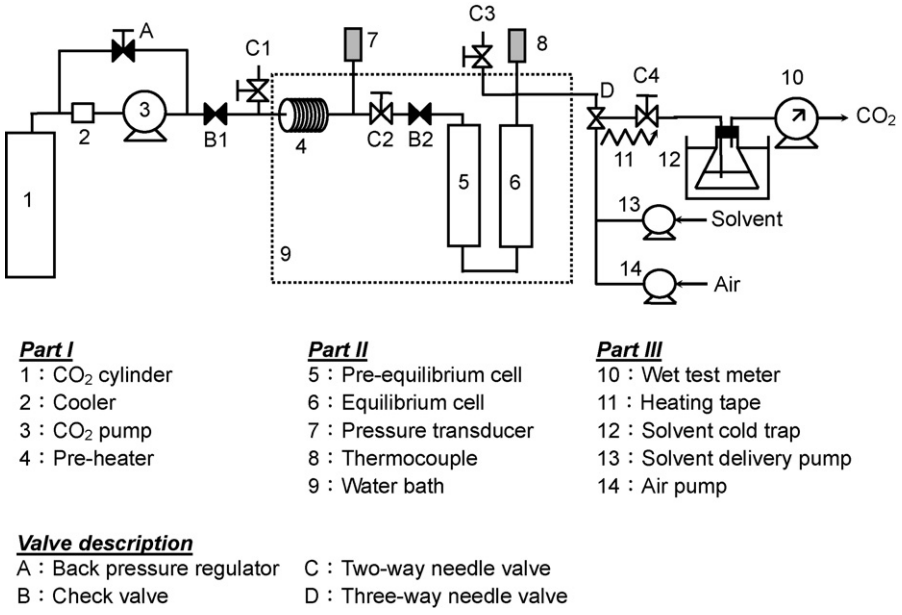


Fig. 1. Schematic diagram of the experimental apparatus.

measurements, and the experimental results were confirmed as equilibrium data.

3. Results and discussion

3.1. Experimental results

The reliability of the experimental apparatus and procedures were preliminarily confirmed by measuring the solubility of salicylic acid in supercritical carbon dioxide and comparing with literature data [15–17]. The results are shown in Fig. 2 where satisfactory agreement between various measurements was observed.

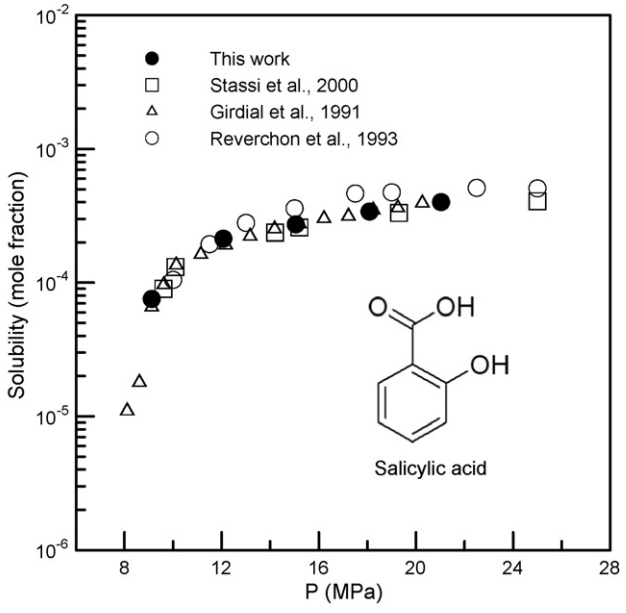


Fig. 2. Comparison of solubility data of salicylic acid in supercritical carbon dioxide at 313 K.

The isothermal solid solubility data (308.2, 318.2 and 328.2 K) of three NSAIDs (nabumetone, phenylbutazone and salicylamide) in supercritical carbon dioxide were measured over the pressure range from 10 to 22 MPa. The equilibrium mole fractions of these solid compounds in the supercritical phase are listed in Tables 2–4, respectively. Repeated measurements at various CO_2 flow rates had been carried out in this study. The reported equilibrium solubilities showed satisfactory reproducibility. It was observed that the solubility increases

Table 2
Solubilities of nabumetone (2) in supercritical carbon dioxide (1)

T (K)	P (MPa)	y_2	S.D.
308.2	10.0	5.56E-04	9.2E-06
	12.0	7.93E-04	1.5E-05
	14.0	9.84E-04	1.6E-05
	16.0	1.14E-03	2.8E-05
	18.0	1.31E-03	3.5E-05
	20.1	1.46E-03	2.8E-05
	22.0	1.60E-03	4.0E-05
318.2	10.1	2.34E-04	5.2E-06
	12.1	6.64E-04	1.4E-05
	14.0	9.77E-04	2.5E-05
	16.1	1.32E-03	2.1E-05
	18.0	1.61E-03	3.4E-05
	20.1	1.91E-03	2.9E-05
	22.0	2.14E-03	6.0E-05
328.2	10.1	3.93E-05	7.6E-07
	12.1	3.37E-04	9.0E-06
	14.0	8.20E-04	1.3E-05
	16.1	1.39E-03	3.8E-05
	18.0	1.87E-03	4.1E-05
	20.0	2.34E-03	4.2E-05
	22.0	2.68E-03	6.4E-05

Standard deviation; S.D. $= \sqrt{1/(N-1)\sum_{i=1}^{N}(y_i - y_{avg})^2}$, N: number of repeated experiments.

Table 3
Solubilities of phenylbutazone (3) in supercritical carbon dioxide (1)

T (K)	P (MPa)	y_3	S.D.
308.2	10.0	5.51 E-04	1.4 E-05
	12.0	8.20 E-04	9.7 E-06
	14.0	1.10 E-03	9.9 E-06
	16.1	1.39 E-03	2.2 E-05
	18.0	1.54 E-03	2.0 E-05
	20.0	1.77 E-03	4.5 E-05
	22.0	1.94 E-03	5.3 E-05
318.2	10.0	1.60 E-04	1.7 E-06
	12.0	5.69 E-04	1.7 E-05
	14.0	9.67 E-04	2.0 E-05
	16.0	1.36 E-03	9.8 E-06
	18.0	1.69 E-03	1.6 E-05
	20.0	1.95 E-03	3.5 E-05
	22.0	2.23 E-03	4.7 E-05
328.2	10.0	1.99 E-05	4.6 E-07
	12.0	2.47 E-04	6.3 E-06
	14.0	6.50 E-04	1.4 E-05
	16.1	1.22 E-03	3.2 E-05
	18.1	1.75 E-03	2.5 E-05
	20.0	2.20 E-03	5.1 E-05
	22.0	2.65 E-03	3.2 E-05

Standard deviation; S.D. $= \sqrt{1/(N-1)\sum_{i=1}^{N}(y_i - y_{avg})^2}$, N: number of repeated experiments.

with increasing pressure along an isotherm for each solid compound. Nabumetone and phenylbutazone had similar solubility range from 10^{-4} to 10^{-3}. Salicylamide showed lower solid solubility owing to its relatively higher melting temperature. The standard deviations (S.D.) for all data points were very small

Table 4
Solubilities of salicylamide (4) in supercritical carbon dioxide (1)

T (K)	P (MPa)	y_4	S.D.
308.2	10.2	5.57 E-05	1.6 E-06
	12.0	6.76 E-05	1.4 E-06
	14.1	7.48 E-05	1.9 E-06
	16.1	8.59 E-05	1.8 E-06
	18.1	9.64 E-05	1.7 E-06
	20.1	1.09 E-04	2.8 E-06
	22.0	1.16 E-04	2.3 E-06
318.2	10.1	2.84 E-05	4.1 E-07
	12.0	6.45 E-05	4.4 E-07
	14.1	8.45 E-05	9.4 E-07
	16.0	1.08 E-04	1.9 E-06
	18.0	1.23 E-04	2.7 E-06
	20.0	1.42 E-04	3.1 E-06
	22.0	1.59 E-04	3.4 E-06
328.2	10.0	8.45 E-06	2.1 E-07
	12.0	4.24 E-05	1.0 E-06
	14.1	8.78 E-05	2.4 E-06
	16.0	1.25 E-04	2.1 E-06
	18.0	1.54 E-04	2.6 E-06
	20.0	1.80 E-04	1.7 E-06
	22.0	2.10 E-04	6.0 E-06

Standard deviation; S.D. $= \sqrt{1/(N-1)\sum_{i=1}^{N}(y_i - y_{avg})^2}$, N: number of repeated experiments.

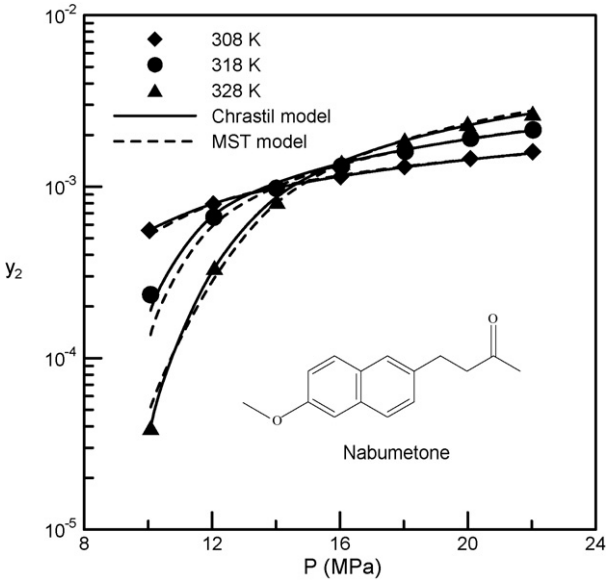


Fig. 3. Solubility for nabumetone (2) in supercritical carbon dioxide (1).

(Tables 2–4). The coefficient of variance, defined as (standard deviation/mean value), for the solid solubility measurements was below 3%. These results indicated the repeatability of our experimental measurements. Graphical presentations are shown in Figs. 3–5, respectively. Temperature effect on the solid solubility was demonstrated by the presence of crossover points shown in these figures. The crossover pressures for nabumetone, phenylbutazone and salicylamide were determined at 15, 17 and 13 MPa, respectively.

Two semi-empirical equations presented by Chrastil [11], and Mendez-Santiago and Teja [9] are commonly employed to correlate the solid solubility in supercritical CO_2. The Chrastil model is expressed by a linear relationship between the logarithm of the solid solubility and the logarithm of the density of the pure

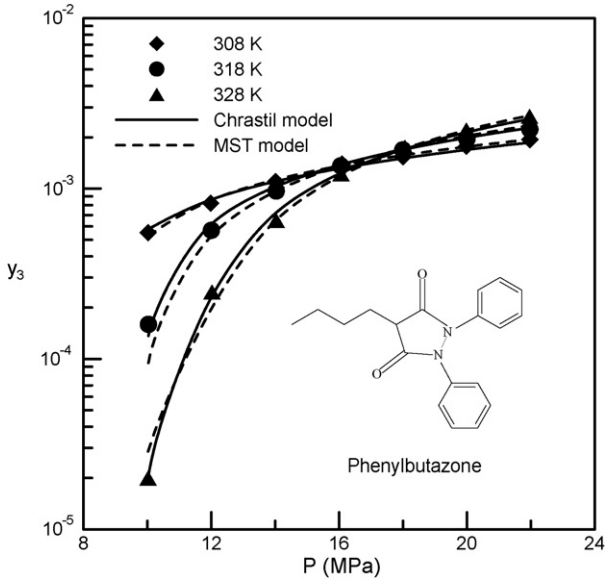


Fig. 4. Solubility for phenylbutazone (3) in supercritical carbon dioxide (1).

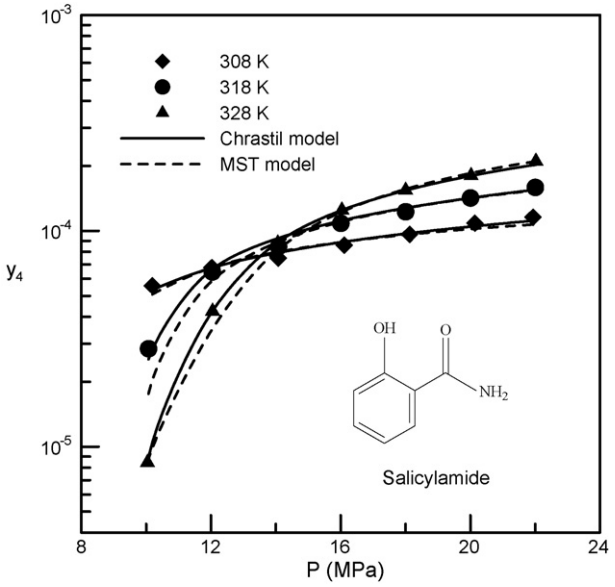


Fig. 5. Solubility for salicylamide (4) in supercritical carbon dioxide (1).

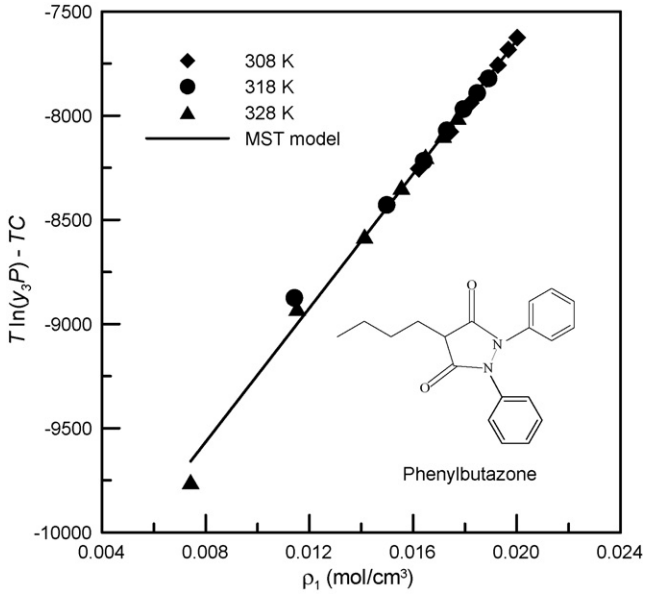


Fig. 6. Test of consistence for solubility data of phenylbutazone using Mendez-Santiago and Teja (MST) model.

CO_2 (component 1):

$$\ln c_j = k \ln \rho_1 + \frac{a}{T} + b \tag{1}$$

where c_j is the concentration of solute j in supercritical fluid (kg/m^3) and ρ_1 is the density of pure CO_2 (kg/m^3). The association number k and the other two constants a and b were taken as three empirically fitted model parameters. These optimal parameters were determined by minimizing the following objective function in data regression:

$$\text{Obj.} = \frac{100}{n} \sum_{k=1}^{n} \frac{|y_{j,k}^{\text{exp}} - y_{j,k}^{\text{cal}}|}{y_{j,k}^{\text{exp}}} \tag{2}$$

where the subscript k denotes the kth experimental data point for solid solute j.

Mendez-Santiago and Teja [9] developed another semi-empirical equation, also with three parameters:

$$T \ln(y_j P) = A + B\rho_1 + CT \tag{3}$$

The parameters (A, B and C) in Eq. (3) were optimally fitted in this study using the measured solid solubility data by minimizing the same objective function shown in Eq. (2).

The correlation results and optimally fitted parameters from these two semi-empirical equations are presented in Table 5. With the optimally fitted parameters, satisfactory accuracy for the calculated solid solubilities was observed from either equation with average absolute relative deviation below 7%. The correlated results from the Chrastil equation and Mendez-Santiago and Teja equation (MST model) are graphically presented in Figs. 3–5. It was stated [9] that a self-consistency test can be examined for the experimental data using the MST model. A typical example is shown in Fig. 6 for phenylbutazone. The plot of $T \ln(y_3 P) - TC$ against the density of supercritical CO_2 is observed as a straight line. This result demonstrates that the parameters correlated using the MST model can be extrapolated to other temperatures. The similar results are observed for the other two solid compounds, and also for the Chrastil model.

Table 5
Correlated results of solid solubility data in supercritical carbon dioxide

Model	Parameters	ARDY (%)
CO_2 (1) + nabumetone (2)		
Chrastil	$k = 5.9$, $a = -5.7374 \times 10^3$, $b = -19.6$	2.5
Mendenz-Santiago and Teja	$A = -1.1382 \times 10^4$, $B = 1.5308 \times 10^5$, $C = 25.9$	5.9
CO_2 (1) + phenylbutazone (3)		
Chrastil	$k = 6.6$, $a = -5.0503 \times 10^3$, $b = -26.6$	4.2
Mendenz-Santiago and Teja	$A = -1.1032 \times 10^4$, $B = 1.6958 \times 10^5$, $C = 23.9$	6.8
CO_2 (1) + salicylamide (4)		
Chrastil	$k = 4.7$, $a = -5.2633 \times 10^3$, $b = -15.8$	2.9
Mendenz-Santiago and Teja	$A = -1.0450 \times 10^4$, $B = 1.2748 \times 10^5$, $C = 21.9$	5.9

ARDY(%) $= (100/n) \sum_{k=1}^{n} \frac{|y_{j,k}^{\text{exp}} - y_{j,k}^{\text{cal}}|}{y_{j,k}^{\text{exp}}}$, the summation is over all kth experimental points for each solid j.

Table 6
Data reference and physical properties for NSAIDs in this study

Component	Formula	Mw (kg/mol)	T range (K)	P range (MPa)	Data points	T_m (K)	ΔH^f (kJ/mol)	$\Delta U^{vap,298.15\,K}$ (kJ/mol)	Reference
Aspirin	$C_9H_8O_4$	0.1802	308–328	12–25	24	407.36	23.01	82.24	[24]
Flurbiprofen	$C_{15}H_{13}FO_2$	0.2443	303–323	8–25	27	383.90	21.68	105.29	[25]
Ibuprofen	$C_{13}H_{18}O_2$	0.2063	308–318	8–22	29	349.15	19.72	85.46	[26]
Ketoprofen	$C_{16}H_{14}O_3$	0.2543	313–332	9–25	25	367.15	20.74	116.96	[27,28]
Nabumetone	$C_{15}H_{16}O_2$	0.2283	308–328	10–22	21	353.15	19.95	93.55	[a]
Naproxen	$C_{14}H_{14}O_3$	0.2303	308–348	9–36	58	427.24	31.50	97.36	[29,30]
Nimesulide	$C_{13}H_{12}N_2O_5S$	0.3083	313–332	13–22	8	421.65	23.82	116.46	[28]
Phenylbutazone	$C_{19}H_{20}N_2O_2$	0.3084	308–328	10–22	21	378.58	21.38	130.94	[a]
Piroxicam	$C_{15}H_{13}N_3O_4S$	0.3314	313–332	10–22	9	469.15	26.51	167.84	[28]
Salicylamide	$C_7H_7NO_2$	0.1371	308–328	10–22	21	413.58	23.42	91.63	[a]

[a] Solubility data measured in this study.

3.2. Correlation of solubility for NSAIDs using the solution model approach

Correlation of the solid solubility data for NSAIDs was also performed in this study using the solution model approach [12–14]. The supercritical fluid was assumed as a liquid where the nonideal behavior between the NSAID solute and CO_2 was represented by an activity coefficient. The equilibrium solubility of solid solute (component j) in supercritical CO_2 (component l) is expressed as

$$y_j = \frac{f_j^s}{\gamma_j^\infty f_j^l} \tag{4}$$

where γ_j^∞ is the infinite dilution activity coefficient of the solid solute j at its low solubility in the supercritical phase. f_j^s and f_j^l are the fugacities of pure solute j in the solid and supercritical phases, respectively. The ratio for these fugacities can be commonly approximated by:

$$\ln \frac{f_j^s}{f_j^l} = \frac{\Delta H_j^f}{R}\left(\frac{1}{T_{j,m}} - \frac{1}{T}\right) \tag{5}$$

where ΔH^f is the molar heat of fusion and T_m is the melting temperature. The infinite dilution activity coefficient was expressed by the modified regular solution model coupled with a Flory–Huggins term by Iwai et al. [12] and our previous studies [13,14]:

$$\ln \gamma_j^\infty = \left(\frac{v_j}{RT}\right)(\delta_1 - \delta_j)^2 + 1 - \left(\frac{v_j}{v_1}\right) + \ln\left(\frac{v_j}{v_1}\right) \tag{6}$$

where δ is the solubility parameter and v is the molar volume. Incorporating Eqs. (5) and (6), the solubility of a solid solute in the supercritical phase was:

$$\ln y_j = \frac{\Delta H_j^f}{R}\left(\frac{1}{T_{j,m}} - \frac{1}{T}\right) - \left(\frac{v_j}{RT}\right)(\delta_1 - \delta_j)^2 - 1 + \left(\frac{v_j}{v_1}\right) - \ln\left(\frac{v_j}{v_1}\right) \tag{7}$$

The melting temperature of solute, $T_{j,m}$, in Eq. (7) was taken from literature. The value of δ_1 was evaluated using the Peng–Robinson equation of state [18]. δ_j was calculated using the molar volume of the solute (v_j) and the molar internal energy change of vaporization (ΔU_j^{vap}). The latter was estimated by group contribution method developed by Fedor [19]. The molar heat of fusion, ΔH_j^f, was either taken from literature or estimated by the method of Yalkowsky [20]. The molar volume of supercritical carbon dioxide (v_1) was estimated from the Jacobsen and Stewart equation of state with 32 constants regressed by Ely et al. [21]. Physical properties required for correlating the solubility data of NSAIDs in this study are listed in Table 6. The adjustable parameter v_j was observed as a function of the density of CO_2 in previous literatures [12–14]:

$$\ln v_j = \alpha \ln \rho_1 + \beta \tag{8}$$

where ρ_1 was density of CO_2, and α, β were two temperature-independent adjustable parameters for each solid solute j. The optimal values of these two parameters were evaluated by minimizing the objective function shown in Eq. (2).

Incorporating Eq. (8) with Eq. (7), correlation of solid solubilities was denoted as the two-parameter model. Table 7 presents the optimally fitted parameters (α and β) of the two-parameter model. The calculated average absolute relative deviation in solid solubility (ARDY) for 10 NSAIDs was 13.9%. This

Table 7
Calculation results for the solubilities of NSAIDs in supercritical carbon dioxide using the two-parameter and one-parameter models

Component	Two-parameter model, Eq. (8)			One-parameter model ($\beta = -13.03$)	
	α	β	ARDY (%)	α	ARDY (%)
Aspirin	−1.25	−13.71	11.5	−1.08	17.6
Flurbiprofen	−1.17	−13.14	21.0	−1.15	21.5
Ibuprofen	−1.03	−12.60	16.7	−1.13	32.6
Ketoprofen	−1.16	−12.98	19.9	−1.17	20.5
Nabumetone	−1.16	−13.09	11.0	−1.15	11.2
Naproxen	−1.17	−13.22	14.5	−1.13	16.9
Nimesulide	−1.12	−12.75	20.0	−1.18	24.9
Phenylbutazone	−1.18	−12.70	6.7	−1.26	29.7
Piroxicam	−1.20	−12.58	8.1	−1.31	33.6
Salicylamide	−1.23	−13.49	5.7	−1.12	18.2
Overall			13.9		21.3

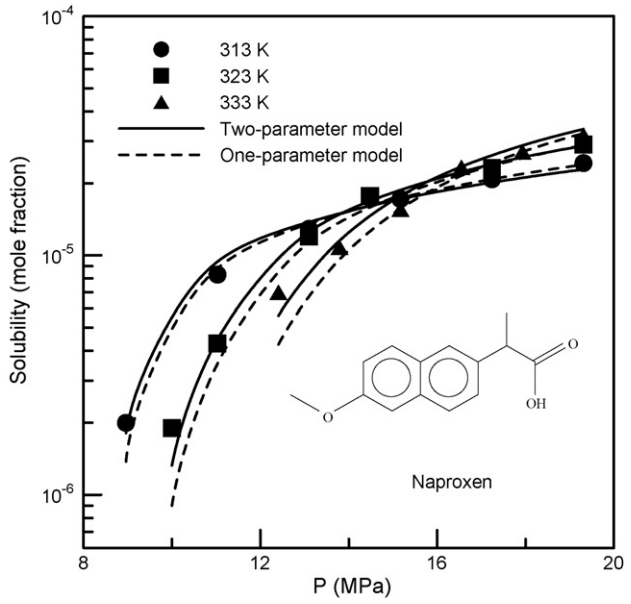


Fig. 7. Comparison of the experimental and calculated solid solubilities of naproxen in supercritical CO_2 at various temperatures.

Table 8
Prediction of solid solubilities of NSAIDs in supercritical carbon dioxide using various models

Component	Predictive model[a]			
	I	II	III	IV
	ARDY (%)	ARDY (%)	ARDY (%)	ARDY (%)
Aspirin	424.7	21.3	36.3	18.6
Flurbiprofen	241.4	100.9	23.1	28.6
Ibuprofen	38.4	84.9	82.9	59.7
Ketoprofen	159.3	158.0	22.0	27.6
Nabumetone	28.3	74.1	80.3	15.2
Naproxen	232.7	55.2	17.2	24.3
Nimesulide	35.1	30.8	49.7	29.0
Phenylbutazone	94.8	92.2	97.2	30.1
Piroxicam	55.3	26.7	37.3	33.6
Salicylamide	166.5	21.9	29.6	19.7
Overall	173.5	71.2	43.3	28.6

[a] Models, I: $\beta = -13.26$; $\alpha = -0.9517 - 0.002173\Delta U_j^{vap}$ [13], II: $\beta = -12.89$; $\alpha = 0.3579 - 0.3185 \ln \Delta U_j^{vap}$ [14], III: $\beta = -13.03$; $\alpha = -0.8712 - 0.002616\Delta U_j^{vap}$ (this study), IV: $\beta = -13.03$; α was calculated using one experimental data point at the lowest T and P.

calculation error was within the range of experimental accuracy. A further simplification for the model parameters was attempted as presented in our previous study [13,14] by reducing one model parameter. An average value of $\beta = -13.03$ was employed for 10 NSAIDs compounds in this study, and α was left as a single adjustable parameter. The results are shown in Table 7 as the one-parameter model with an ARDY of 21.3%. Using only one parameter, it was observed that 70% of the calculated solid solubilities had ARDY less than 25%. This calculated deviation can be considered as acceptable for these complex molecules. Fig. 7 shows the calculated solid solubility of naproxen using either the two- or one-parameter solution model in this study. The ARDY were 14.5% and 16.9% from each model, respectively. The results in Fig. 7 show that the solution model, with temperature-independent parameters, was feasible in correlating the experimental solubility data at various temperatures.

The single parameter α was further generalized in this study to make the solid solubility calculations predictable. A comparison of various predictive methods is shown in Table 8. In our previous studies, generalization of parameter α had been suggested. Cheng et al. [13] proposed a generalized equation that includes aromatic and biological compounds, and is cited as model I in Table 8. Su and Chen modified the generalized correlation of Cheng et al. [13], and presented an improved equation for α over 60 pharmaceutical solids. The equation recently demonstrated by Su and Chen [14] is taken as model II in Table 8. Applying either model I or model II for 10 NASIDs gave unsatisfactory results with high ARDY. Model II showed better results than model I because model II was obtained specifically for pharmaceutical compounds. Su and Chen [14] suggested that further correlation for α could be investigated for various groups of compounds with specific functions. For the NSAIDs, we tried a new correlation of α. Fig. 8 shows a plot of the best-fitted α values for each NSAID in the one-parameter model against the physical properties ΔU_j^{vap}. A nearly linear relationship was observed:

$$\alpha = -0.8712 - 0.002616\,\Delta U_j^{vap} \quad (9)$$

The correlation Eq. (9) is cited as model III in Table 8. The predicted results from model III had an ARDY of 43.3% that was significantly improved over models I and II. The distribution of calculated errors from model III was also satisfactory. Over 70% of the predicted solid solubilities had ARDY less than 50%. Prediction and comparison for solid solubility of salicylamide in supercritical CO_2 is shown in Fig. 9. The ARDY for

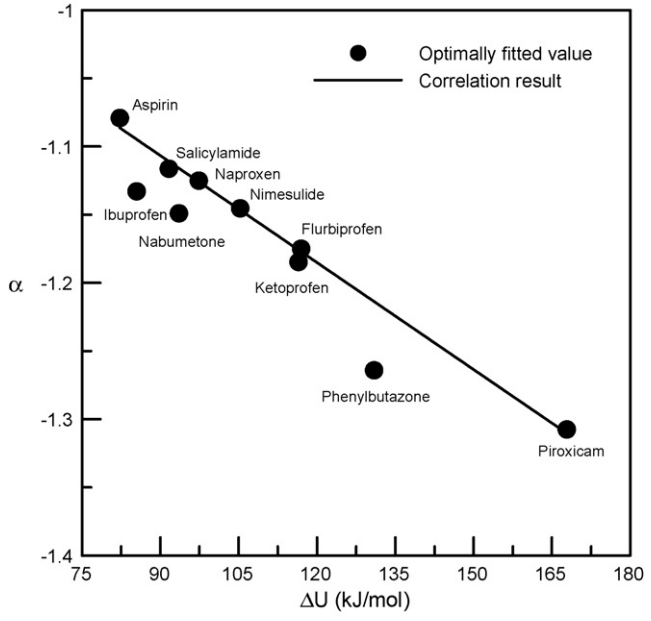


Fig. 8. Plot of the optimally fitted α values against the internal energy change of vaporization for various NSAIDs.

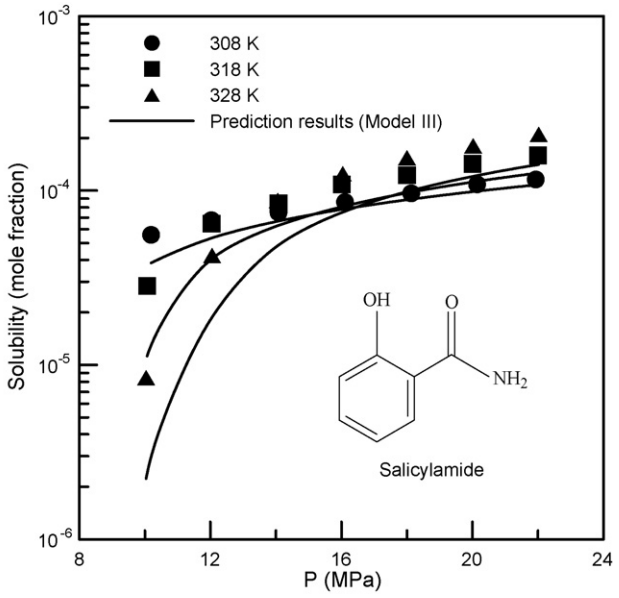


Fig. 9. Predicted solid solubility of salicylamide in supercritical CO_2 using the generalized correlation of α in this study.

this system was 29.6% over three temperatures. The predicted solid solubility showed larger deviation at the low-pressure end. The solubilities at high pressures were predicted with acceptable accuracy.

Three NSAIDs of ibuprofen, nabumetone and phenylbutazone showed ARDY higher than 80% from model III in Table 8. This indicates that further improvement of model III can be investigated. It is suggested to apply the one-parameter model but the α parameter was determined using only one experimental data point. This approach is cited as model IV in Table 8, in which the α parameter was evaluated by one experimental data point at the lowest temperature and pressure for each solid compound. It is presented in Table 8 that the overall ARDY from model IV was 28.6%, and was comparable to that from the correlative one-parameter model. As shown in Table 8, the calculated ARDY of phenylbutazone decreased from 97.2% in model III to 30.1% in model IV. Fig. 10 shows graphically the improvement for nabumetone. It depicts that using the solution model and only limited experimental information, the solid solubilities in supercritical CO_2 can be predicted over extended temperatures and pressures with acceptable accuracy.

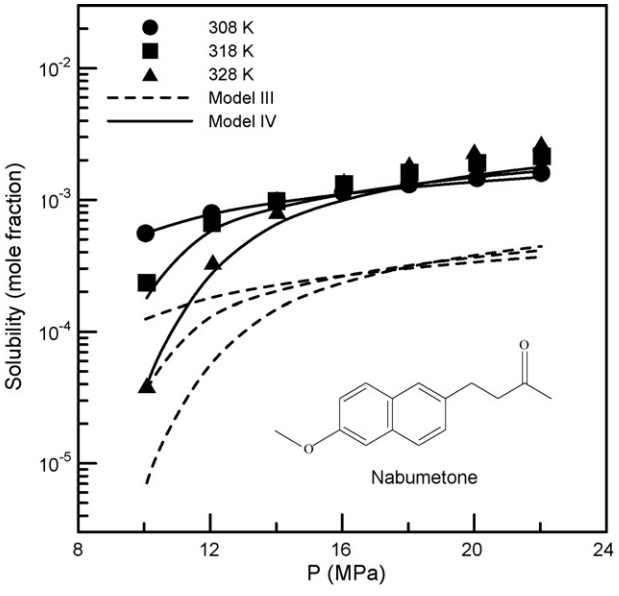


Fig. 10. Comparison for the predicted solid solubility of nabumetone in supercritical CO_2 using two predictive models.

4. Conclusion

New solid solubility data for three NSAIDs of nabumetone, phenylbutazone and salicylamide in supercritical CO_2 are presented in this study at 308.2, 318.2 and 328.2 K over the pressure range from 10 to 22 MPa. Nabumetone and phenylbutazone had similar solubility range of 10^{-4} to 10^{-3}. Salicylamide showed lower solid solubility owing to its relatively higher melting temperature. Satisfactory correlation results for solid solubilities were observed using the Chrastail or Mendez-Santiago and Teja semi-empirical equations where the average absolute relative deviation in solid solubility (ARDY) was below 7%. The solution model was applied to correlate the solid solubilities of these three compounds and seven other NSAIDs. With two temperature-independent parameters for each system, the calculated ARDY was 13.9%. These parameters were further generalized and the overall predicted error was 43.3% (model III). It was finally demonstrated that with only one experimental data, the solution model parameters were satisfactorily adjusted (model IV). Model IV yielded an ARDY of 28.6% for 10 NSAIDs over extended temperature and pressure ranges.

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