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# Temperature independent mixing rules to correlate the solubilities of antibiotics and anti-inflammatory drugs in $SCCO_2$

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ABSTRACT

The accurate experimental determination of the solubilities of antibiotics and anti-inflammatory drugs in supercritical fluids (SCFs) and correlations are essential for the development of supercritical technologies for the pharmaceuticals industry. In this work, the solubilities of penicillinG, penicillinV, flurbiprofen, ketoprofen, naproxen, ibuprofen, aspirin and diflunisal in supercritical carbon dioxide ($SCCO_2$) were correlated using Peng–Robinson equation of state (PR EOS) with the modified Kwak and Mansoori mixing rules (mKM) and with Bartle model. The ability of mKM rules was compared against the conventional mixing rules of van der Waals in correlating the solubilities. In the present model, vapor pressure was considered as an adjustable parameter along with binary interactions parameters. In the proposed model, the constants used in the mixing rule, and vapor pressure expression coefficients are temperature independent. The optimization of these constants with experimental data gives binary interaction parameters along with vapor pressure correlations. Sublimation enthalpies were estimated with both the models compared with literature reported experimental values.



## 1. Introduction

Traditional pharmaceutical processes make use of conventional solvents for product processing. These solvents cause environmental pollution as well as react with the pharmaceutical product. These issues can be effectively handled using supercritical fluid technologies (SFTs). Supercritical fluids (SCFs) have a high diffusivity that is comparable to that of a gas and a solvent capacity that is comparable to that of liquids making them good solvents for the extraction processes. In particular, supercritical carbon dioxide ($SCCO_2$) has a moderate critical pressure, high critical density and critical temperature close to ambient temperature making it ideal for separation processes and reactions and in the food and pharmaceutical industry [1–3].

The antibiotics and anti-inflammatory drugs are the most frequently used drugs in the world. The accurate experimental determination of antibiotics and anti-inflammatory drugs in supercritical fluids (SCFs) and their correlations are important to the development of SFTs for the pharmaceuticals industry [4]. Equations of state (EOS) correlations are quite useful in solid-SCF phase equilibria [5]. In this work, the solubilities of antibiotics namely penicillinG [6], penicillinV [7] and anti-inflammatory drugs namely flurbiprofen [8], ketoprofen [9,10], naproxen [11], ibuprofen [12], aspirin [13] and diflunisal [14] in $SCCO_2$ were correlated using Peng–Robinson equation of state (PR EOS) with the modified Kwak and Mansoori (mKM) mixing rules [15–18] with temperature independent constants.

## 2. Modeling of solubilities in supercritical fluids

Previous thermodynamic studies [4,6,7,9,19] have reported correlation constants for the antibiotics and anti-inflammatory drugs that are temperature dependent. Temperature independent correlation constants are useful for the better prediction of solubilities in supercritical fluids. Therefore, a thermodynamic model based on the PR EOS with mKM [15–18] was considered for the study.

### 2.1. Thermodynamic model

The EOS approach is often used in modeling SCF phase equilibria [1,5,15–18]. The molar solubility of the solid solute in the supercritical fluid, $y_2$, is [1]

$$y_2 = \frac{p_2^{sub}\phi_2^{sat}}{p\hat{\phi}_2^{SCF}} \exp\left(\frac{(p - p_2^{sub})V_2^s}{RT}\right) \quad (1)$$

where $p_2^{sub}$ is the sublimation vapor pressure of the pure solid solute at system temperature $T$, $p$ is the system pressure and $R$ is the universal gas constant. $\hat{\phi}_2^{sat}$ is the fugacity coefficient of the solid at saturation and is assumed to be unity. The molar volume of the solid solute, $V_2^s$ is assumed to be constant. In this work, the PREOS in

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combination with Valderrama modification of Kwak and Mansoori mixing rules (mKM) [15–18] was used to determine the fugacity of the solute/solid in supercritical fluid, $\hat{\phi}_2^{SCF}$.

*2.1.1. mKM mixing rule*

PREOS consistent with statistical-mechanical basis of van der Waals mixing rules [15–18] is

$$Z = \frac{v}{v-b} - \frac{(a/RT)+c-2\sqrt{ac/RT}}{(v+b)+(b/v)(v-b)} \quad (2)$$

where $a = a(T_c)(1+\kappa)^2$; $c = a(T_c)\kappa^2/RT_c$; $a(T_c) = 0.45724R^2T_c^2/p_c$; $\kappa = 0.37464 + 1.54226\varpi - 0.26992 \times \varpi^2$; $a$, $b$ and $c$ are independent constants with the following mixing rules

$$a = \sum_i^n \sum_i^n x_i x_j a_{ij} \quad (3)$$

$$b = \sum_i^n \sum_i^n x_i x_j b_{ij} \quad (4)$$

$$c = \sum_i^n \sum_i^n x_i x_j c_{ij} \quad (5)$$

The combining rules are

$$a_{ij} = (1-k_{ij})\sqrt{a_{ii}a_{jj}} \quad (6)$$

$$b_{ij} = \frac{(b_{ii}+b_{jj}\times(1-l_{ij}))}{2} \quad (7)$$

$$c_{ij} = \frac{(c_{ii}+c_{jj}\times(1-m_{ij}))}{2} \quad (8)$$

where $v$ is the molar volume of the supercritical phase, $T_c$ is the critical temperature, $p_c$ is the critical pressure and $\varpi$ is the acentric factor. $k_{ij}$, $l_{ij}$, and $m_{ij}$ are adjustable binary interaction parameters which are temperature independent constants. In contrast to conventional mixing rules, for parameters $b_{ij}$, $c_{ij}$ the values of $l_{ij}$ and $m_{ij}$ apply to $b_{ij}$ and $c_{ij}$ only. The fugacity coefficient of the solute in the supercritical phase $\hat{\phi}_2^{SCF}$ is calculated using cubic equation of state along with mKM. The fundamental expression used for calculation $\hat{\phi}_2^{SCF}$ is [5]

$$\ln(\hat{\phi}_2^{SCF}) = \frac{1}{RT}\int_v^\infty \left( \left( \frac{\partial p}{\partial N_i} \right)_{T,V,N_j} - \frac{RT}{v} \right) dv - \ln Z \quad (9)$$

For the PREOS with the mKm mixing and combining rules Eq. (9) assumes the following form [18]

**Table 1**
Critical and physical properties of drugs investigated in this study.

| Substance | Formula | $T_c$ (K) | $P_c$ (MPa) | $\omega$ | $V^s$ ($m^3$/kg mol) | Ref. |
|---|---|---|---|---|---|---|
| PenicillinG | $C_{16}H_{18}N_2O_4S$ | 902.78 | 2.355 | 1.3249 | 0.2261 | [6] |
| PenicillinV | $C_{16}H_{18}N_2O_5S$ | 921.70 | 1.720 | 1.1676 | 0.2317 | [7] |
| Ibuprofen | $C_{13}H_{18}O_2$ | 891.20 | 2.250 | 0.7880 | 0.1821 | [4,10] |
| Ketoprofen | $C_{16}H_{14}O_3$ | 1090.70 | 2.584 | 0.9140 | 0.1956 | [9] |
| Naproxen | $C_{14}H_{14}O_3$ | 807.00 | 2.452 | 0.9040 | 0.1790 | [10] |
| Diflunisal | $C_{13}H_8F_2O_3$ | 869.80 | 3.211 | 0.8970 | 0.1255 | [14] |
| Aspirin | $C_9H_8O_4$ | 762.90 | 3.280 | 0.8170 | 0.1290 | [13] |
| Flurbiprofen | $C_{15}H_{13}FO_2$ | 690.5[a] | 2.918[b] | 1.2400[c] | 0.1899[d] | [26–28] |

[a] Estimated by the Fedors method [27].
[b] Estimated by the Joback modification of Lydersen's method [26,27].
[c] Estimated by the Lee-Kesler method [27].
[d] Estimated by the additivity method of Immirzi and Pirini [28].

**Table 2**
Details on the phase equilibrium data for the eight drugs considered in this study.

| System | $N$ | $T$ (K) | $P$ (MPa) range | $y_2$ ($\times 10^6$) range | Ref. |
|---|---|---|---|---|---|
| PenicillinG | 18 | 313.15 | 10.00–35.00 | 535.0–1980.0 | [6] |
| | | 323.15 | 10.00–35.00 | 462.0–4620.0 | |
| | | 333.15 | 10.00–35.00 | 420.0–6330.0 | |
| PenicillinV | 24 | 314.85 | 8.07–28.04 | 62.30–432.0 | [7] |
| | | 324.85 | 7.98–27.96 | 58.70–501.0 | |
| | | 334.85 | 8.01–28.01 | 54.50–576.0 | |
| Ibuprofen | 29 | 308.15 | 8.00–22.00 | 0.53–44.10 | [11] |
| | | 313.15 | 9.50–22.00 | 5.85–64.90 | |
| | | 318.15 | 8.50–17.00 | 0.30–58.40 | |
| Ketoprofen | 15 | 313 | 9.00–25.00 | 3.90–91.50 | [9] |
| | | 318 | 11.00–25.00 | 3.30–188.00 | |
| Naproxen | 18 | 313.1 | 8.90–19.31 | 2.00–24.30 | [10] |
| | | 323.1 | 10.00–19.31 | 1.90–29.10 | |
| | | 333.1 | 12.41–19.31 | 7.00–31.80 | |
| Diflunisal | 21 | 308.2 | 9.40–24.60 | 1.845–3.89 | [14] |
| | | 318.2 | 9.40–24.60 | 0.565–5.46 | |
| | | 328.2 | 9.40–24.60 | 0.544–8.07 | |
| Aspirin | 24 | 308.15 | 12.00–25.00 | 89.00–151.0 | [13] |
| | | 318.15 | 12.00–25.00 | 72.00–258.0 | |
| | | 328.15 | 12.00–25.00 | 63.0–347.0 | |
| Flurbiprofen | 27 | 303 | 8.90–24.50 | 21.70–83.37 | [8] |
| | | 313 | 9.80–24.20 | 16.72–149.50 | |
| | | 323 | 11.20–23.40 | 26.30–196.83 | |

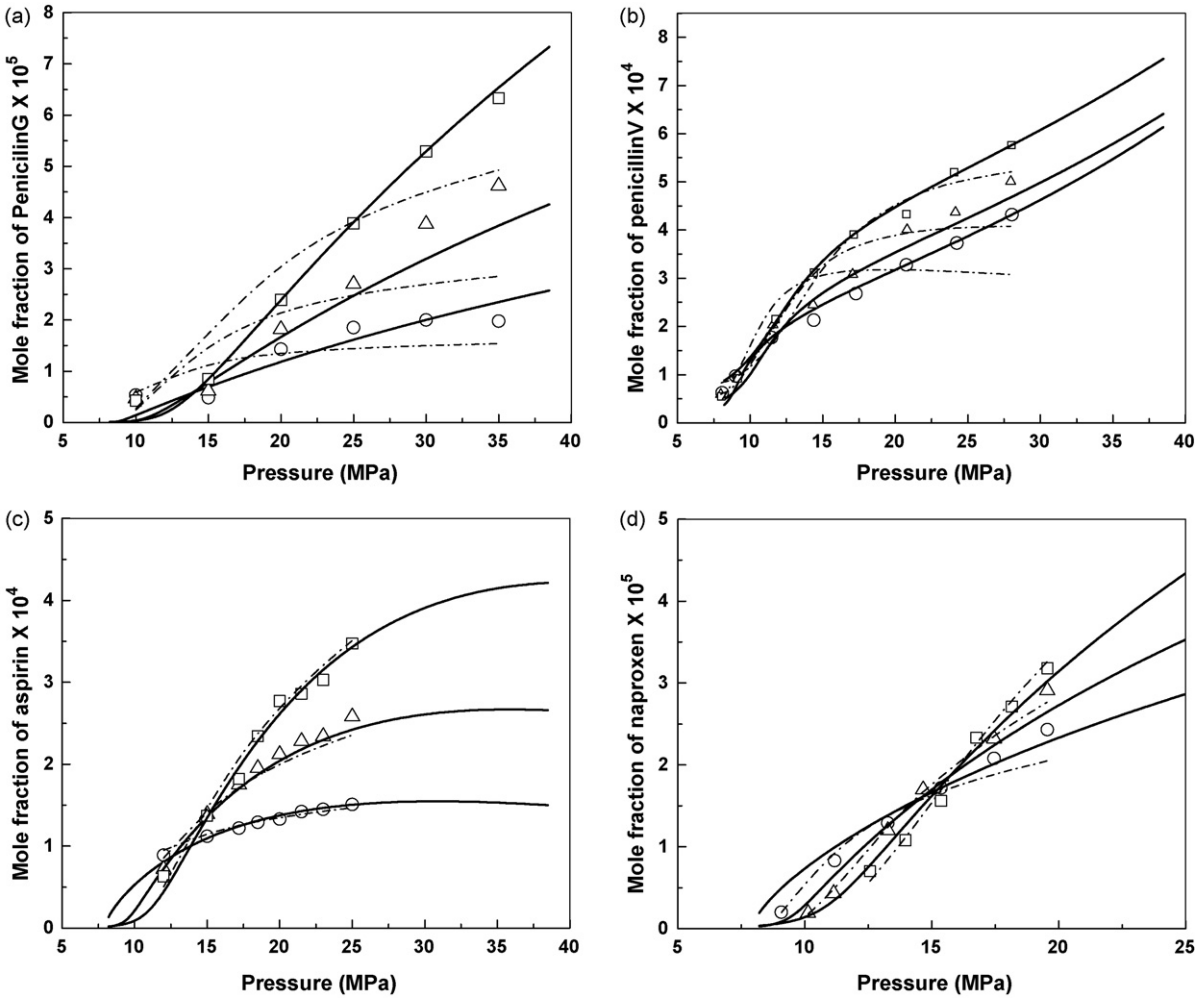


**Fig. 1.** Variation of mole fraction with pressure for (a) PenicillinG + $SCCO_2$ at (○) 313.15 K; (△) 323.15 K; (□) 333.15 K. Experimental data from Gordillo et al. [6]. (b) PenicillinV + $SCCO_2$ at (○) 314.85 K; (△) 324.85 K; (□) 334.85 K. Experimental data from Ko et al. [7]. (c) Aspirin + $SCCO_2$ at (○) 308.15 K; (△) 318.15 K; (□) 328.15 K. Experimental data from Huang et al. [13]. (d) Naproxen + $SCCO_2$ at (○) 313.15 K; (△) 323.15 K; (□) 333.15 K. Experimental data from Ting et al. [11]. The solid lines are model predictions based on the PR EOS with modified Kwak and Mansoori mixing rules and respective model parameters are given in Table 3. The dash dot lines are model predictions based on Bartle model and respective model parameters are given in Table 5.

$$\ln(\hat{\phi}_2^{SCF}) = \left(\frac{2\hat{B}}{b} - 1\right)(Z-1) - \ln\left(Z\left(1-\frac{b}{v}\right)\right) - \left[\frac{\Delta}{\sqrt{2}RTb}\right] \times \ln\left(\frac{1+(1+\sqrt{2})b/v}{1+(1-\sqrt{2})b/v}\right) \quad (10)$$

where

$$\Delta = \left[\frac{G}{2} - \frac{G\hat{B}}{b} + \hat{A}\left(1-\sqrt{\frac{RT_c}{a}}\right) + \hat{C}\left(RT - \sqrt{\frac{RT_a}{c}}\right)\right]$$

$$G = a + cRT - 2\sqrt{acRT}$$

$$\hat{A} = \sum x_i a_{ij}$$

$$\hat{B} = \sum x_i b_{ij} \quad \text{and} \quad \hat{C} = \sum x_i c_{ij}$$

These are used in Eq. (1) to determine the solubility by the model and compared with the experimental data. The required drug solute critical properties are estimated with group contribution

**Table 3**
Fitted parameters and corresponding AARD (%) values for the correlated eight drug-$SCCO_2$ systems. Correlations were performed using the PR EOS with the mKM mixing rules.

| System | $k_{ij}$ | $l_{ij}$ | $m_{ij}$ | $A/R$ | $B/R$ | $\Delta_{sub}C_p/R$ | AARD % |
|---|---|---|---|---|---|---|---|
| $SCCO_2$-penicillinG | 0.092531 | 0.17340 | 0.70703 | −9.6087 | −827.96 | 54.546 | 23.95 |
| $SCCO_2$-penicillinV | 0.14346 | 0.63798 | 0.62625 | −32.372 | 9608.3 | 66.315 | 11.03 |
| $SCCO_2$-ibuprofen | −0.063363 | 0.1369 | 0.53236 | −3.5040 | −1147.1 | 46.309 | 10.76 |
| $SCCO_2$-ketoprofen | −0.13945 | −0.10114 | 0.50936 | −8.189 | −1718.6 | 52.609 | 10.93 |
| $SCCO_2$-naproxen | 0.0024805 | 0.25974 | 0.54035 | 41.099 | −14556.0 | −3.3030 | 2.97 |
| $SCCO_2$-diflunisal | 0.23094 | 0.81048 | 0.47184 | 0.77397 | −1588.50 | 33.451 | 15.82 |
| $SCCO_2$-aspirin | 0.27485 | −0.14421 | 0.88612 | 100.4 | −31755.0 | −60.925 | 3.77 |
| $SCCO_2$-flurbiprofen | 0.51101 | 0.15364 | 0.98163 | −39.372 | 10128.0 | 70.377 | 4.90 |

methods [4,6–13]. It has been shown in various investigations that the sublimation pressure of solute plays an important role in the thermodynamic modeling of solid solubilities in supercritical fluids [4,6,7,9,10,19]. In this work, the sublimation pressure was used as an adjustable parameter together with the binary interaction parameters. These parameters were estimated by minimizing the absolute value of average relative deviation (AARD %) between experimental and predicted solubility data. The expression used for the sublimation pressure is that suggested by [20] to determine vapor pressure and enthalpies of phase transition,

$$R\ln(p^s) = A + \frac{B}{T} + \Delta_{sub}C_p \ln\left(\frac{T}{T_0}\right) \quad (11)$$

where $T_0$ is an arbitrary reference temperature and 298.15 K has been used in this work. Because the coefficients of the Eq. (11) are pressure independent it can be used for solid-SCF studies. The optimization procedure reduces the averaged absolute relative deviation percentage, AARD (%). It is defined as $(100/N_i)\sum_{i=1}^{N_i}|y_2^{cal} - y_2^{exp}|/y_2^{exp}$ where $N_i$ is number of data points, $y_2$ represents the molar solubility of the solute and the superscripts *cal* and *exp* denotes the calculated and experimental values, respectively.The optimization procedure directly gives the binary interaction parameters along with sublimation pressure expression coefficients ($A/R$, $B/R$ and $\Delta_{sub}C_p/R$). From these coefficients, the vapor pressure and enthalpy of sublimation ($\Delta_{sub}H$) is estimated. The enthalpy at the temperature $T$ is given by

$$\Delta_{sub}H = -B + \Delta_{sub}C_pT. \quad (12)$$

### 2.2. Bartle et al. model and sublimation enthalpy from solubilities

The Bartle et al. empirical model [21,22,23] was based on the concept of an enhancement factor proposed by Johnston et al. [24]

$$\ln\left(\frac{xP}{P_{ref}}\right) = M + K(\rho - \rho_{ref}) \quad (13)$$

where $x$ is the solubility in mole fraction, $P$ is the pressure, $P_{ref}$ is reference pressure of 1 bar, $\rho$ is $SCCO_2$ density, $\rho_{ref}$ is reference $SCCO_2$ density (700 kg/m$^3$) and $M$ and $K$ are constants. The reason for using a value of $\rho_{ref}$ of 700 kg/m$^3$ is to make constant $M$ much less sensitive to experimental errors in solubility data when extrapolated to zero density [21]. The value of $K$ is assumed to remain constant over the entire temperature range [22] and $M$ is assumed to obey the linear relation with temperature as $M = I + J/T$. Therefore, Eq. (13) will result in

$$\ln\left(\frac{xP}{P_{ref}}\right) = I + \frac{J}{T} + K(\rho - \rho_{ref}) \quad (14)$$

The density of $SCCO_2$, $\rho$ was calculated from the 27 parameter equation of state [25]. In Eq. (14) parameter $J$ is related to the enthalpy of vaporization of the solid, $\Delta_{sub}H$ by [22]

$$\Delta_{sub}H = -JR \quad (15)$$

where $R$ is the universal gas constant. The validity of Eq. (15) relies on the assumption that the vapor pressure in the enhancement factor is independent of temperature [22].

## 3. Results and discussion

In this work, the solubility of penicillinG (at 313.15, 323.15 and 333.15 K), penicillinV (at 314.85, 324.85 and 334.85 K), ketoprofen (at 313 and 318 K), naproxen (at 313.1, 323.1 and 333.1 K), ibuprofen (at 308.15, 313.15 and 318.15 K), aspirin (at 308.15, 318.15 and 328.15 K), flurbiprofen (at 303, 313 and 323 K) and diflunisal (at 308.2, 318.2 and 328.2 K) are correlated with PREOS with mKM. The correlation computational program was developed in MATLAB 6.1®, using a minimization algorithm, *fminsearch* (Nelder-Mead Simplex Algorithm). In this algorithm, the least squares solution minimizes the AARD (%). Tables 1 and 2 show the basic physiochemical properties of the drug compounds along with details on the original phase equilibrium data. The experimental solubilities were taken from literature and model predictions for the solubilities of penicillinG, penicillinV, aspirin and naproxen in supercritical carbon dioxide are shown in Fig. 1a–d, respectively. In Table 3, the values of $k_{ij}$, $l_{ij}$, and $m_{ij}$ for antibiotics and anti-inflammatory drugs along with AARD (%) are reported. In Table 4, the values of binary interaction parameter reported in the literature with conventional van der Waals mixing rule are reported. Tables 3 and 4 show that the temperature independent mixing rule results in lower AARD (%). So, the present temperature independent mixing rule used in this model gives better correlations than the conventional van der Waals mixing rule.

**Table 4**
Literature values for fitted interaction parameters and corresponding AARD (%). Correlations were performed using the PREOS with the conventional van der Waals mixing rules.

| System | $T$ (K) | $k_{ij}$ | $l_{ij}$ | AARD (%) | Ref. |
|---|---|---|---|---|---|
| PenicillinV | 314.85 | 0.318 | | 36.23 | [7] |
| | 324.85 | 0.205 | | 40.25 | |
| | 334.85 | 0.272 | | 41.30 | |
| Ibuprofen | 308.15 | 0.211 | | 27.30 | [11] |
| | 313.15 | 0.205 | | 19.20 | |
| | 318.15 | 0.229 | | 43.60 | |
| Ketoprofen | 313 | 0.232 | | 9.50 | [9] |
| | 318 | 0.251 | | 10.40 | |
| Naproxen | 313.1 | 0.223 | | 13.90 | [10] |
| | 323.1 | 0.223 | | 13.70 | |
| | 333.1 | 0.229 | | 9.40 | |
| Diflunisal | 308.2 | 0.14 | −0.081 | 17.30 | [14] |
| | 318.2 | 0.194 | 0.07 | 20.60 | |
| | 328.2 | 0.19 | −0.071 | 23.30 | |
| Aspirin | 308.15 | 0.2088 | | 2.24 | [13] |
| | 318.15 | 0.2056 | | 8.19 | |
| | 328.15 | 0.2062 | | 7.45 | |
| Flurbiprofen | 303 | 0.0863 | | 6.06 | [8] |
| | 313 | 0.0774 | | 11.08 | |
| | 323 | 0.1556 | | 7.66 | |

From the experimental data, each isotherm was fitted using Eq. (13) to obtained values of $M$ and $K$. The values of $K$ were then averaged for each drug and the values are reported in Table 5. Then the isotherms were refitted to obtained new values of $M$ using the averaged values of $K$. These values were plotted against $1/T$ for each drug and values for $I$ and $J$ were obtained from $M = I + J/T$, which are also reported in Table 5.

The observation that temperature independent mixing rules used in this model gives better correlations than the conventional van der Waals mixing rules are in general agreement with that of the Valderrama and Alvarez [18]. The advantage of the present model is the vapor pressure correlations for the drugs involved and their enthalpy of sublimation ($\Delta_{sub}H$) are also obtained from the correlation. For many drugs, this information is not reported. The vapor pressure is one of the fundamental properties that determine the solubility of the drug in the SCFs [4,6,7,9,19]. Thus the model proposed in this study gives the vapor pressure correlations as well as the sublimation enthalpy based on the solubility data. The correlation results of the Bartle model are reported in Table 5. From Tables 3 and 5, it is clear the temperature independent mixing rule results in lower AARD (%) than the Bartle model. In Table 6, the estimated sublimation enthalpies from the EOS model and Bartle model are compared with *experimental values* reported in the literature. From Table 6, it is clearly evident that the present EOS model is able to predict the sublimation enthalpies of the drug compounds

**Table 5**
Fitted parameters and corresponding AARD (%) values for the correlated eight drug-$SCCO_2$ systems. Correlations were performed with the density-based Bartle et al. model.

| System | $I$ | $J$ (K) | $K$ ($m^3$ $kg^{-1}$) | AARD % |
|---|---|---|---|---|
| $SCCO_2$-penicillinG | 21.343 | −8850.7 | 0.007244 | 41.05 |
| $SCCO_2$-penicillinV | 12.541 | −5022.1 | 0.004996 | 16.58 |
| $SCCO_2$-ibuprofen | 36.408 | −10890 | 0.012224 | 12.26 |
| $SCCO_2$-ketoprofen | 21.479 | −8512.7 | 0.012029 | 12.52 |
| $SCCO_2$-naproxen | 19.362 | −8162.6 | 0.008777 | 6.56 |
| $SCCO_2$-diflunisal | 13.731 | −6908.0 | 0.006900 | 23.94 |
| $SCCO_2$-aspirin | 22.309 | −8440.2 | 0.0088015 | 6.54 |
| $SCCO_2$-flurbiprofen | 29.152 | −10830 | 0.0114691 | 13.25 |

**Table 6**
Experimental and estimated sublimation enthalpies of drugs (in kJ $mol^{-1}$).

| Drug | Temperature | Experimental sublimation enthalpies | Estimated sublimation enthalpies | |
|---|---|---|---|---|
| | $T$ (K) | $\Delta_{sub}H$ | Eq. (12) | Eq. (15) |
| PenicillinG | 298.00 | | 142.03 | 73.59 |
| PenicillinV | 298.00 | | 84.42 | 41.76 |
| Ibuprofen | 298.00 | 115.80[a] | 124.27 | 90.54 |
| Ketoprofen | 298.00 | 110.10[b] | 144.60 | 70.77 |
| Naproxen | 298.00 | 128.30[c] | 112.84 | 67.86 |
| Diflunisal | 377.65 | 119.30[d] | 118.19 | 57.43 |
| Aspirin | 298.00 | 109.70[e] | 113.07 | 70.17 |
| Flurbiprofen | 341.65 | 108.40[d] | 115.70 | 90.04 |

[a] Ref. [29].
[b] Ref. [30].
[c] Ref. [31].
[d] Ref. [32].
[e] Ref. [33].

better than the Bartle model. Thus the model proposed in this study gives reliable vapor pressure correlations as well as the sublimation enthalpies based on the solubility data.

## 4. Conclusions

The determination of the solubilities of various drugs in supercritical fluids is essential for the development of technologies involving reactions and extractions in the pharmaceutical industries. In this work, the solubilities of various drugs in supercritical carbon dioxide were correlated using the Peng–Robinson equation of state (PR EOS) with the temperature independent Kwak and Mansoori mixing rules (mKM) and compared to the correlations obtained with the conventional mixing rules and with the Bartle model. Based on the results and discussion presented in the study, it was shown that the temperature independent mixing rules exhibit better correlations than both the conventional van der Waals mixing rules and Bartle model. The present study also gives reliable vapor pressure correlations and enthalpy of phase transition for the systems studied, which are valuable information needed for the development of supercritical fluid technologies.

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