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APPLICATION OF PC-SAFT AND CUBIC EQUATIONS OF STATE FOR THE CORRELATION OF SOLUBILITY OF SOME PHARMACEUTICAL AND STATIN DRUGS IN SC-CO₂

In this work, the solubilities of some anti-inflammatory (nabumetone, phenylbutazone and salicylamide) and statin drugs (fluvastatin, atorvastatin, lovastatin, simvastatin and rosuvastatin) were correlated using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) with one-parameter mixing rule and commonly used cubic equations of state Peng-Robinson (PR) and Soave-Redlich-Kwong (SRK) combining with van der Waals 1-parameter (VDW1) and van der Waals 2-parameter (VDW2) mixing rules. The experimental data for the studied compounds were taken from literature at temperature and pressure in ranges of 308–348 K and 100–360 bar, respectively. The critical properties required for the correlation with PR and SRK were estimated using Gani and Noonanol contribution group methods whereas, PC-SAFT pure-component parameters: segment number (m), segment diameter (σ) and energy parameter (ϵ/k) have been estimated by Tihic's group contribution method for nabumetone. For phenylbutazone and salicylamide those parameters were determined using a linear correlation. For statin drugs, PC-SAFT parameters were fitted to solubility data, and binary interaction parameters (k_{ij} and l_{ij}) were obtained by fitting the experimental data. The results were found to be in good agreement with the experimental data and showed that the PC-SAFT approach can be used to model solid-SCF equilibrium with better correlation accuracy than cubic equations of state.

Keywords: solid solubility, cubic equation of state, PC-SAFT, anti-inflammatory, supercritical carbon dioxide, correlation.

The chemical industry conducts constant research in new technologies where the main objective is to satisfy the customer expectations by offering high-efficiency products and to comply with international standards, which are becoming more and more severe in terms of hygiene and environment protection.

Super critical fluids are one of the most interesting technologies that became the target of several research studies in recent years. Such importance is related to the development of new cheap-priced pro-

ducts without pollution constraints related to the environment. One of their major trumps is to be a plausible alternative to the organic solvents. In many cases, they offer some solutions that cannot be provided by traditional techniques in terms of efficient operation, non-toxicity, availability, low-cost and the easiness of separation compared to classic process. Thus, many works have been published on the application of this technology [1-3].

Carbon dioxide is the most commonly used supercritical fluid because of its ability to replace organic solvents with more advantages (its availability, inertness, non-toxicity, low critical temperature and pressure).

Modelling of solubility of solids in supercritical fluids is needed for the separation process design, development and optimization. Undoubtedly, the most used models are the cubic equations of state, such as

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Peng-Robinson (PR) [4] and Soave-Redlich-Kwong (SRK) [5]. Although those models are the basic tools for supercritical fluid-solid equilibrium calculations, their application is associated with some drawbacks, mainly the non-availability of the solids properties for pharmaceutical compounds, polymers and bio-molecules (critical properties, molar volume and sublimation pressure). For this reason, and in order to perform the estimation of those parameters, several studies [6-7] have been carried out based on the so-called group contribution techniques, but their prediction ability is limited to classes of components with simple structures. Therefore, the sensitivity of solubility correlations to solids' properties can add a factor of uncertainty to the approach. For example, Coimbra [8] and Valderrama and Zavaleta [9] found that the variations of 10% in the sublimation pressure estimation of solute might produce deviations between 5 and 19% in solubility calculations. To surpass this problem, more accurate methods were developed, such as the Marrero and Gani [10] and Nannoolal method [11].

More theoretical equations of state were developed based on Werthiem's perturbation theory [12-14] such as Statistical Associating Fluid Theory (SAFT) [15-17], Lennard-Jones (SAFT-LJ) [18-19], soft-SAFT [20-21], Variable Range (SAFT-VR) [22-23], Hard-Sphere (SAFT-HS) [24-26], and Perturbed-Chain (PC-SAFT) [27-28], and recently SAFT + Cubic equation of state [29], etc. In the last decade, attempts were carried out in order to model the phase equilibrium with the latter SAFT-EOS where numerous applications were reported in the literature and have been recently reviewed by McCabe and Galindo [30].

SAFT models require five pure associating-component parameters and three parameters for non-associating fluids: the segment number (m), the interaction energy (ϵ/k) and the segment diameter (σ). The application of PC-SAFT-EOS for modeling of solid compounds-SCF phase equilibrium is limited because of the non-availability of pure component parameters for multifunctional molecules. Several works treating this subject can be found in the literature [31-33].

The purpose of this work is the application of both PC-SAFT equation of state, Peng-Robinson (PR) and Soave-Redlich-Kwong (SRK) cubic equations of state for correlating the solubility of some anti-inflammatory drugs (compounds that are non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties and are used to treat fever, headache and pain associated with cold influenza and arthritis) and statin drugs in supercritical CO₂ (components are used to reduce cholesterol and risk of heart attack [34]). The chemical structures of the studied solid drugs are shown in Figure 1.

THERMODYNAMIC MODELS

In this work, the PC-SAFT, PR and SRK equations of state were used for correlating of solid drugs in the supercritical carbon dioxide.

The PR and SRK equation of state

The PR equation of state

The explicit form of PR equation of state for mixture can be written as:

$$P = \frac{RT}{(v - b_m)} - \frac{a_m(T)}{v(v + b_m) + b_m(v - b_m)} \quad (1)$$

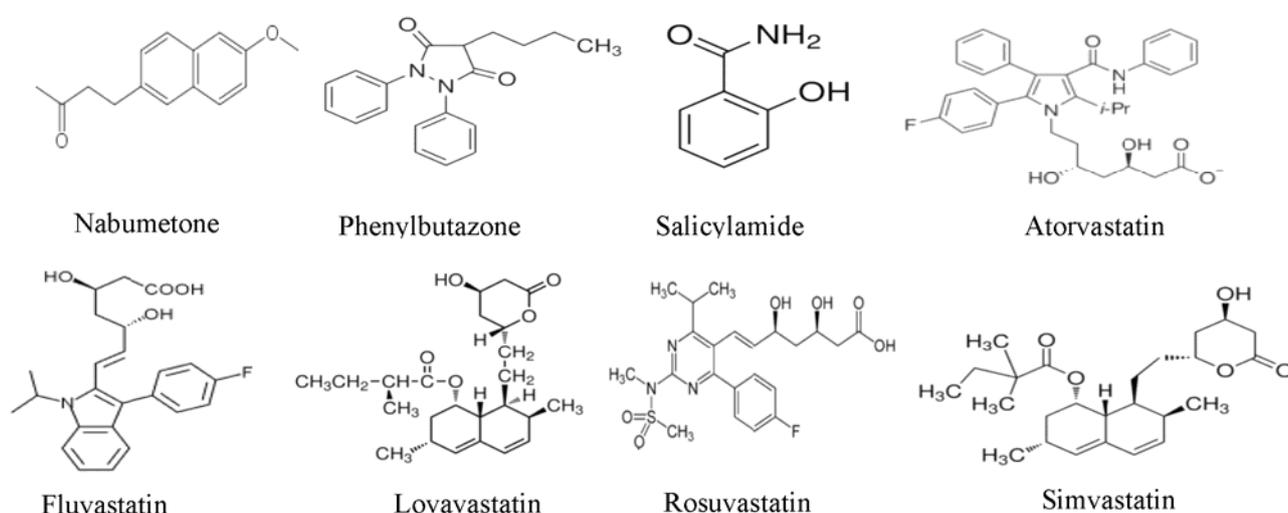


Figure 1. Chemical structures of the studied drugs.

where P is the pressure, T is the temperature, R is the gas constant, v is the molar volume of the component, and a_m and b_m are van der Waals energy and volume parameters for mixture, respectively. The latter parameters can be obtained using mixing rules. In this work, the van der Waals 1-parameter (VDW1) and van der Waals 2-parameter (VDW2) rules were applied:

VDW1 mixing rule:

$$a_m = \sum_i \sum_j y_i y_j \sqrt{a_i a_j} (1 - k_{ij}) \quad (2)$$

$$b_m = \sum_i y_i b_i \quad (3)$$

VDW2 mixing rule:

$$a_m = \sum_i \sum_j y_i y_j \sqrt{a_i a_j} (1 - k_{ij}) \quad (4)$$

$$b_m = \sum_i \sum_j y_i y_j b_{ij} \quad (5)$$

$$b_{ij} = \left(\frac{b_i + b_j}{2} \right) (1 - l_{ij}) \quad (6)$$

where k_{ij} and l_{ij} are the binary interaction parameters; a_i and b_j are energy and volume parameters for pure components defined as:

$$a_i = 0.45724 \frac{R^2 T_c^2}{P_c} \alpha(T_r, \omega) \quad (7)$$

with $\alpha(T_r, \omega)$ being a temperature-dependent function in the attractive parameter of EOS defined as:

$$\alpha(T_r, \omega) = \left[1 + (0.37464 + 1.5422\omega - 0.26992\omega^2) \times (1 - T_r^{0.5}) \right]^2 \quad (8)$$

$$b_i = 0.077796 \frac{RT_c}{P_c} \quad (9)$$

where ω is the acentric factor, T_c and P_c are the critical constants, and T_r is the reduced temperature.

The expression for the fugacity coefficient for a mixture can be written as:

$$\ln \varphi_i = \frac{b_i}{b_m} (Z - 1) - \ln(Z - B) - \frac{A}{2\sqrt{2}B} \left(\frac{2 \sum_{j=1}^n y_j a_{ij}}{a_m} - \frac{b_i}{b_m} \right) \ln \left(\frac{Z + (1 + \sqrt{2})B}{Z + (1 - \sqrt{2})B} \right) \quad (10)$$

The SRK equation of state

SRK cubic equation of state for mixture is given by the following expression:

$$P = \frac{RT}{(v - b_m)} - \frac{a_m(T)}{v(v + b_m)} \quad (11)$$

For pure components, a_i and b_j are expressed as follows:

$$a(T) = 0.42747 \frac{R^2 T_c^2}{P_c} \alpha(T_r, \omega) \quad (12)$$

with:

$$\alpha(T_r, \omega) = \left[1 + (0.480 + 1.574\omega - 0.176\omega^2) \times (1 - T_r^{0.5}) \right]^2 \quad (13)$$

$$b = 0.08664 \frac{RT_c}{P_c} \quad (14)$$

It should be mentioned that a_m and b_m for SRK-EOS can be obtained using the van der Waals 1-parameter (VDW1) and 2-parameter (VDW2) rules cited in the PR-EOS section.

The expression of fugacity coefficient is given by:

$$\ln \varphi_i = \frac{b_i}{b_m} (Z - 1) - \ln(Z - B) - \frac{A}{B} \left(2 \frac{\sqrt{a_i}}{\sqrt{a_m}} - \frac{b_i}{b_m} \right) \ln \left(1 + \frac{B}{Z} \right) \quad (15)$$

The PC-SAFT equation of state

The Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) is an equation of state that is expressed in terms of Helmholtz energy for mixtures of non-associating molecules:

$$\check{a} = A / NkT = \check{a}^{id} + \check{a}^{hc} + \check{a}^{disp} \quad (16)$$

where \check{a}^{id} is the ideal gas contribution that is considered as unit, \check{a}^{hc} is the contribution of hard sphere chain reference system and \check{a}^{disp} is the contribution of dispersion force.

As it can be seen, this equation consists of the hard-chain reference contribution and the dispersion contribution, and it can be expressed in terms of Helmholtz energy for N -component of non-associating chains as:

$$\check{a}^{es} = \check{a}^{hc} + \check{a}^{disp} \quad (17)$$

The hard-chain reference contribution is given by:

$$\tilde{a}^{\text{hc}} = \bar{m}\tilde{a}^{\text{hs}} - \sum_{i=1}^N y_i(m_i - 1) \ln g_{ii}^{\text{hs}}(\sigma_{ii}) \quad (18)$$

where \bar{m} is the mean segment number in the mixture:

$$\bar{m} = \sum_{i=1}^N y_i m_i \quad (19)$$

where y_i is the mole fraction of chains of component i , m_i is the number of segments in a chain of component i .

Dispersion contribution

$$\begin{aligned} \tilde{a}^{\text{disp}} = & -2\pi\rho \left[l_{1,xk} \overline{m^2 \varepsilon \sigma^3} + l_1 (\overline{m^2 \varepsilon \sigma^3})_{xk} \right] - \\ & -\pi\rho \left\{ [m_k C_1 l_2 + \bar{m} C_{1,xk} l_2 + \bar{m} C_1 l_{2,xk}] \times \right. \\ & \left. \times \overline{m^2 \varepsilon^2 \sigma^3} + \bar{m} C_1 l_2 (\overline{m^2 \varepsilon^2 \sigma^3})_{xk} \right\} \end{aligned} \quad (20)$$

Pairs of unlike segments are obtained by using conventional combining rules:

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad (21)$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j} (1 - k_{ij}) \quad (22)$$

where k_{ij} is a binary interaction parameter that is introduced to correct the segment-segment interactions of unlike chains.

The density to a given system pressure, P^{sys} , is determined iteratively by adjusting the reduced density of molecules, η , until $P^{\text{calc}} = P^{\text{sys}}$. For a converged value of η , the number density of molecules, ρ (\AA^{-3}), is calculated from:

$$\rho = \frac{6}{\pi} \eta \left(\sum_{i=1}^N y_i m_i d_i^3 \right)^{-1} \quad (23)$$

Equation for the compressibility factor is derived from the relation:

$$Z = 1 + \eta \left(\frac{\partial \tilde{a}^{\text{res}}}{\partial \eta} \right)_{T,x_i} = 1 + Z^{\text{hc}} + Z^{\text{disp}} \quad (24)$$

The pressure can be calculated in units of Pa by applying the relation:

$$P = ZkT\rho \left(10^{10} \frac{\text{\AA}}{\text{m}} \right)^3 \quad (25)$$

The expression for the fugacity coefficient is given by:

$$\ln \phi_k = \frac{\mu_k^{\text{res}}(T, V)}{kT} - \ln Z \quad (26)$$

The chemical potential can be obtained from:

$$\begin{aligned} \frac{\mu_k^{\text{res}}(T, V)}{kT} = & \tilde{a}^{\text{res}} + (Z - 1) + \left(\frac{\partial \tilde{a}^{\text{res}}}{\partial x_k} \right)_{T, V, x_j \neq k} - \\ & - \sum \left[y_i \left(\frac{\partial \tilde{a}^{\text{res}}}{\partial x} \right)_{T, V, x_i \neq j} \right] \end{aligned} \quad (27)$$

Modeling solid-SCF phase equilibrium

The solubility of a non-volatile pure solid (2) in a supercritical fluid (1), y_2 , is determined from standard thermodynamic relationships by equating fugacities in the solid phase and in the supercritical phase for each component (the isofugacity condition):

$$f_2^{\text{solid}} = f_2^{\text{SCF}} \quad (28)$$

The fugacity of component (2) in the supercritical phase is expressed by:

$$f_2^{\text{solid}} = y_2 \phi_2^{\text{SCF}} P \quad (29)$$

The solubility can be expressed as the solute mole fraction:

$$y_2 = \left(\frac{P_2^{\text{sub}}}{P} \right) E \quad (30)$$

where E is the enhancement factor defined as:

$$E = \frac{\phi_2^{\text{sub}} \exp \left[\frac{V_2^{\text{s}}}{RT} (P - P^{\text{sub}}) \right]}{\phi_2^{\text{SCF}}} \quad (31)$$

where P is the equilibrium pressure, T is the equilibrium temperature, V_2^{s} is the molar volume of the pure solid, ϕ_2^{sub} is the fugacity coefficient of pure solid at its sublimation pressure, and ϕ_2^{SCF} is the fugacity coefficient of pure solid in the supercritical phase.

Physical properties

The Pitzer acentric factor and the molar volume of solutes have been estimated by the Lee-Kesler correlation using PE software [35] and the Fedors method [36], respectively. Values of the required physical properties for all compounds used in the calculation and estimation methods are displayed in the Tables 1 and 2.

PC-SAFT pure-component parameters

PC-SAFT pure-component parameters for nabumetone have been estimated by the Tihic group contribution method. For the other compounds (phenylbutazone, salicylamide and statin drugs), it is shown that this method cannot be applied for missing functional groups (*i.e.*, this method does not offer the values of contributions for all group-assignments of those compounds). The solution was the use of a

Table 1. Required physicals properties of anti-inflammatory drugs used

Compound	T_c^a / K	P_c^a / bar	w	$V_S^b / \text{cm}^3 \text{mol}^{-1}$	P^{sub} / bar^c		
					308.2 K	318.2 K	328.2 K
Carbon dioxide	304.2	73.76	0.225	-	-	-	-
Nabumetone	843.93	23.68	0.602 ^d	195.8	1.462×10^{-7}	4.586×10^{-7}	1.313×10^{-6}
Phenylbutazone	984.71	13.39	0.412 ^d	266.9	9.2×10^{-10}	3.488×10^{-9}	1.357×10^{-8}
Salicylamide	796.95	56.03	1.348 ^d	79.9	5.833×10^{-8}	2×10^{-7}	6.216×10^{-7}

^aEstimated by Gani Method [10]; ^bestimated by Fedors method [36]; ^cestimated by Nannoolal method [11]; ^destimated by Lee-Kesler correlation [35]

Table 2. Required physicals properties of statin drugs used

Compound	T_c / K	P_c / bar	w	$V_S / \text{cm}^3 \text{mol}^{-1}$	P^{sub} / bar				
					308 K	318 K	328 K	338 K	348 K
Atorvastatine	1028.89 ^a	12.08 ^a	1.1616	368.9	2.00×10^{-16b}	1.73×10^{-15b}	1.29×10^{-15b}	8.35×10^{-14b}	4.77×10^{-13b}
Lovastatine	901.80 ^a	13.49 ^a	1.295	335.4	5.90×10^{-8b}	1.71×10^{-7b}	4.61×10^{-7b}	1.16×10^{-6b}	2.74×10^{-6b}
Rosuvastatine	1065.21 ^c	18.92 ^c	0.7648	293.3	4.24×10^{-13b}	2.31×10^{-12b}	1.11×10^{-11b}	4.86×10^{-11b}	1.92×10^{-10b}
Simvastatine	878.52 ^a	13.01 ^a	1.2803	350.7	1.19×10^{-11a}	6.54×10^{-11a}	3.12×10^{-10a}	1.31×10^{-9a}	4.94×10^{-9a}
Fluvastatine	921.70 ^a	15.40 ^a	1.4726	288.1	8.41×10^{-16b}	7.83×10^{-15b}	6.21×10^{-14b}	4.25×10^{-13b}	2.55×10^{-12}

^aEstimated by Nannoolal method [11]; ^bestimated by Ambrose-Walton corresponding method [7]; ^cestimated by Gani Method [10]

linear correlation developed by Tihic *et al.* [37] for estimating phenylbutazone and salicylamide parameters. While for statin drugs, PC-SAFT-parameters were considered adjustable parameters and were fitted to solubility data (Table 3). This is because the Tihic's linear correlations gave very large values for the segment number (m) and the segment diameter (σ), and small values for the segment energy parameter (ϵ/k) that lead to an overestimate of the solubility. Such a result is expected because the statin molecules are characterized by multiple functional groups (aromatic nitrogen, alcohol and acid functions, fluorine, sulfone, etc.) which makes it difficult to have a good representation with those correlations or the right classification into families that have been adopted by Tihic and his co-workers [37].

Table 3. PC-SAFT pure component parameters for all compounds used

Compound	m	$\sigma / \text{\AA}$	$\epsilon/k, \text{K}$
Carbon dioxide ^a	2.07	2.78	169.21
Nabumetone	6.29	3.66	319.18
Phenylbutazone	6.86	4.14	312.05
Salicylamide	3.39	3.86	334.30
Atorvastatine	9.40	4.20	309.10
Lovastatine	5.60	4.10	233.10
Rosuvastatine	7.70	4.20	299.90
Simvastatine	6.40	4.17	299.60
Fluvastatine	8.90	4.19	342.00

^aPure component parameters for CO₂ is taken from literature [27]

RESULTS AND DISCUSSION

In this work, the solubilities of three anti-inflammatory and five statin drugs in sc-CO₂ were correlated. The experimental data were taken from literature [38,39]. The correlation was performed by minimizing the objective function, which is the absolute average relative deviation (*AARD*) usually defined as:

$$OF = AARD(\%) = \frac{100}{N} \sum_1^n \frac{|y^{calc} - y^{exp}|}{y^{exp}} \quad (32)$$

The absolute average relative deviation (*AARD*, %) values along with values of regressed binary interaction parameters for studied equations of state for CO₂ + nabumetone, CO₂ + phenylbutazone and CO₂ + salicylamide are shown in Table 4 at various temperatures.

This table shows that *AARD* values obtained with PR-VDW1 model varied from 4.7% at 308.2 K for the nabumetone-CO₂ system to 34.3% at 328.2 K for the salicylamide-CO₂ system, whereas with the PR-VDW2 model the *AARD* values varied from 4.5 to 32.3% for the same binary system at the same temperatures, respectively. Also, the application of SRK-VDW1 model gave deviations that range from 3.8% at 328.2 K for nabumetone-CO₂ system to 32.2% found at 328.2 K for the salicylamide-CO₂ system. Meanwhile, with SRK-VDW2 model the deviation varied from 3.4 to 32.1% for the same binary systems at the same temperatures, respectively. For PC-SAFT, the deviation varied between 1.4% obtained for nabumetone-CO₂ system at 318.2 K to 22% found in correlating of salicylamide-CO₂ system at 328.2 K. It is also

Table 4. Correlation results for solubility of nabumetone, phenylbutazone and salicylamide in *sc*-CO₂ with PR, SRK EoS's using VDW1 and VDW2 and PC-SAFT with BR1 mixing rules at various temperatures

Model	Parameter	T = 308.2 K			T = 318.2 K			T = 328.2 K		
		Nabu- metone	Phenyl- butazone	Salicyl- amide	Nabu- metone	Phenyl- butazone	Salicyl- amide	Nabu- metone	Phenyl- butazone	Salicyl- amide
PR-vdw1	k_{12}	0.1076	0.0154	0.1501	0.1017	0.0123	0.1331	0.095	0.0101	0.1098
	AARD / %	4.7	6.6	21.2	7.1	11.62	8.6	5.1	15.0	32.3
PR-vdw2	k_{12}	0.1057	0.013	0.15	0.098	0.0068	0.133	0.101	-0.002	0.1095
	l_{12}	-0.65	-0.50	-0.3868	-0.717	-0.70	-0.2911	0.81	-0.72	-0.45
	AARD / %	4.5	6.2	21.2	6.8	10.7	28.6	5.0	10.7	32.3
SRK-vdw1	k_{12}	0.1191	0.0269	0.0174	0.1124	0.0222	0.1559	0.1024	0.0188	0.1323
	AARD / %	6.3	8.8	20.7	7.7	12.0	27.9	3.8	14.4	32.2
SRK-vdw2	k_{12}	0.1169	0.024	0.1738	0.11	0.0173	0.1558	0.11	0.11	0.1319
	l_{12}	-0.59	-0.54	-0.12	-0.47	-0.69	-0.70	0.80	-0.70	-0.67
	AARD / %	6.1	8.5	20.7	7.6	11.3	27.9	3.4	13.1	32.1
PC-SAFT	k_{12}	0.1123	0.0921	0.0048	0.095	0.0871	-6.53.10 ⁻⁴	0.0996	0.083	0.0109
	AARD / %	1.6	3.9	8.8	1.4	6.4	14.9	1.9	16.0	22.0

worth mentioning that the values of AARD increased with the increase of temperature. For example, AARD values obtained with PR-VDW1 for salicylamide-CO₂ system at 308.2 K (21.2%) were higher for the same system at 328.2 K (32.3%).

The correlation results for five statin drugs (Tables 5 and 6) confirm the superiority of PC-SAFT in predicting of the solubility compared to cubic equation of state.

AARD values obtained with the PC-SAFT model ranged between 2.9 and 27.3%. However, very important deviations were observed by applying the cubic equations of state. For example, the values of AARD obtained with PR-VDW1 varied from 10.3% at 308 K for RV-CO₂ system to 74.7% found at 328 K for LV-CO₂ system, whereas with SRK-VDW1 model the devi-

ations ranged from 16.2 to 75% for the same binary system at the same temperatures, respectively.

Fitting the experimental solubility data provided best-fit values to the binary interaction parameter k_{12} that is introduced to correct energetic interaction between the solute-SCF (it ranges between -0.0091 obtained in (FV + CO₂) system with PR-VDW2 at 348 K to 0.437 obtained in (LV + CO₂) system with SRK-VDW2 model). However, high and negative values for interaction parameter, l_{12} , were obtained, the highest one being for the (AV + CO₂) system at 348 K with SRK-VDW2 model. Such results are not surprising since l_{12} is introduced in the b_m parameter to correct the volumetric interaction between the solute and solvent. An analysis of the treated binary systems shows that they consist of small solvent molecules (molar

Table 5. Correlation results for solubility of statin (AV, LV and RV) in *sc*-CO₂ with PR, SRK EoS's using VDW1 and VDW2 and PC-SAFT with BR1 mixing rules at various temperatures

Model	Parameter	308 K			318 K			328 K			338 K			348 K		
		AV	LV	RV	AV	LV	RV	AV	LV	RV	AV	LV	RV	AV	LV	RV
PR-vdw1	k_{12}	0.0537	0.353	0.1014	0.0418	0.3627	0.0975	0.03	0.3802	0.0932	0.0146	0.3977	0.0885	0.0017	0.4115	0.081
	AARD / %	44.6	64.7	10.3	35.4	70.3	11.9	30.6	74.7	12.2	28.9	72.9	18.1	24.4	68.4	23.9
PR-vdw2	k_{12}	0.053	0.353	0.1016	0.0424	0.3628	0.098	0.031	0.3804	0.093	0.0269	0.3977	0.0882	0.0058	0.4115	0.0817
	l_{12}	-0.79	-0.493	-0.793	0.856	-0.85	0.97	0.9	-0.77	-0.545	0.88	-0.745	-0.63	0.88	-0.788	0.88
	AARD / %	44.7	64.6	10.3	35.3	70.1	12.0	29.9	74.7	12.2	27.5	72.4	18.0	22.5	68.3	23.6
SRK-vdw1	k_{12}	0.0807	0.3861	0.1187	0.0774	0.395	0.1135	0.063	0.411	0.1079	0.0499	0.426	0.1006	0.029	0.4368	0.09
	AARD / %	51.4	68.2	16.2	42.6	72.9	14.8	36.7	75.0	14.4	34.0	72.0	18.3	27.7	66.8	21.9
SRK-vdw2	k_{12}	0.086	0.3864	0.1186	0.0757	0.395	0.1131	0.0625	0.4112	0.1076	0.045	0.426	0.1011	0.031	0.437	0.0911
	l_{12}	-0.1574	-0.88	-0.778	0.852	-0.75	-0.80	0.89	-0.80	-0.796	0.88	-0.79	0.88	0.90	-0.79	-0.79
	AARD / %	51.4	68.3	16.2	42.7	72.9	14.8	35.8	75.6	14.4	31.5	72.1	18.4	24.6	66.8	21.9
PC-SAFT	k_{12}	0.0377	0.0785	0.0558	0.0293	0.0784	0.055	0.02	0.3977	0.046	0.0113	0.085	0.0405	0.023	0.0878	0.0345
	AARD / %	11.6	4.9	9.0	9.4	4.1	8.5	13.4	4.2	8.3	20.0	6.6	15.1	28.0	7.4	20.5

Table 6: Correlation results for solubility of Statin (FV and SV) in *sc*-CO₂ with PR, SRK EoS's using VDW1 and VDW2 and PC-SAFT with BR1 mixing rules at various temperatures

Model	Parameter	308 K		318 K		328 K		338 K		348 K	
		SV	FV	SV	FV	SV	FV	SV	FV	SV	FV
PR-vdw1	k_{12}	0.1485	0.0355	0.1537	0.0263	0.1592	0.0165	0.165	0.006	0.1758	-0.0062
	AARD / %	49.5	14.3	51.8	20.8	56.5	24.4	55.8	29.2	55.4	36.3
PR-vdw2	k_{12}	0.148	0.0357	0.1533	0.0263	0.1592	0.0157	0.1653	0.0044	0.1743	-0.0091
	l_{12}	-0.88	0.4553	-0.80	0.0978	0.0313	-0.769	0.894	-0.789	0.74	-0.875
	AARD / %	49.2	14.3	51.7	20.8	56.5	24.3	55.7	28.7	55.4	34.7
SRK-vdw1	k_{12}	0.1824	0.0745	0.1865	0.0645	0.1908	0.0518	0.1949	0.0408	0.1948	0.0274
	AARD / %	56.5	15.5	57.9	20.0	60.4	23.7	56.2	28.0	56.9	33.8
SRK-vdw2	k_{12}	0.1845	0.0746	0.1834	0.0643	0.1908	0.051	0.195	0.0404	0.1961	0.0247
	l_{12}	-0.80	0.1922	-0.79	-0.3895	0.238	-0.87	0.90	-0.228	0.89	-0.736
	AARD / %	56.7	15.5	57.9	20.0	60.4	23.6	56.0	28.1	56.7	32.3
PC-SAFT	k_{12}	0.0526	0.0783	0.0529	0.0727	0.0508	0.0667	0.0485	0.06	0.0473	0.054
	AARD / %	9.5	13.7	7.9	15.2	5.0	19.9	2.9	24.3	19.4	27.3

weight of carbon dioxide is 44 g/mol) and very large solute molecules (molar weight values vary between 137 for salicylamide to 540 g/mol for AV) providing highly asymmetric systems. In this case, large values of l_{12} are expected for well representing the complex forming as a result of the association of solute-solvent. Despite these large values, there is no remarkable influence on AARD values when the two-parameter mixing rule VDW2 was used instead of the one-parameter mixing rule VDW1. This can be explained by the following:

1. The binary interaction parameter, l_{12} , is related to the volumetric interaction between supercritical fluid (CO₂) and solid solute. Such correction has a small effect on the correlation of the solubility of solid in SCF since the concentration of solid in the solvent

is usually close to zero (mole fraction, y_2), and that of the solvent is usually on the order of 0.999. Consequently, the behaviour of solid-SCF is governed by the energetic interaction (due to the nature of atoms and liaisons formed the complex) more than the relative number of solute molecules in *sc*-CO₂.

2. Some important deviations for both cubic equation of state and PC-SAFT models may be the result of either the formation of aggregates that need to be taken into account in the application of any model with more experimental studies about this phenomenon for correlating solubility, or the fluctuation of the density of solvent close to the critical region.

Figures 2 and 3 show the solubility curves of nabumetone and phenylbutazone in *sc*-CO₂. These include a comparison between experimental data and

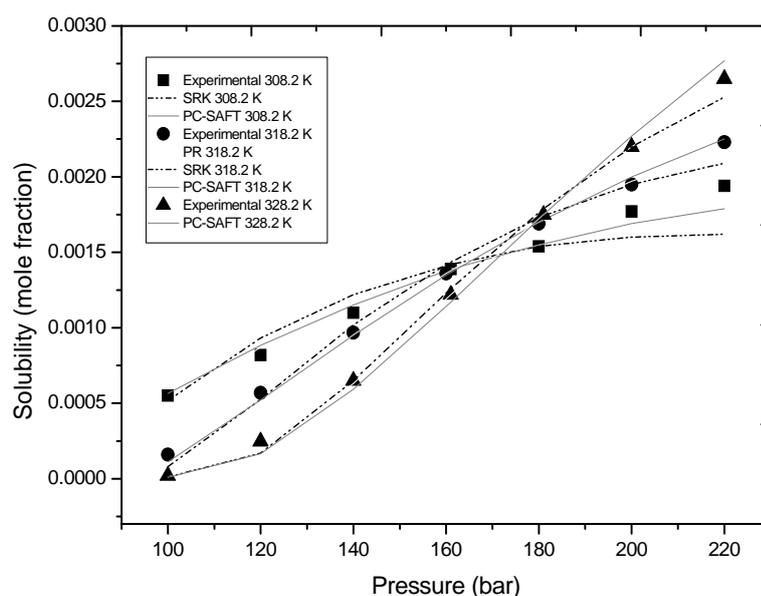


Figure 2. Experimental solubility in *sc*-CO₂ of nabumetone and correlation results obtained by PC-SAFT and PR-VDW2 at various temperatures.

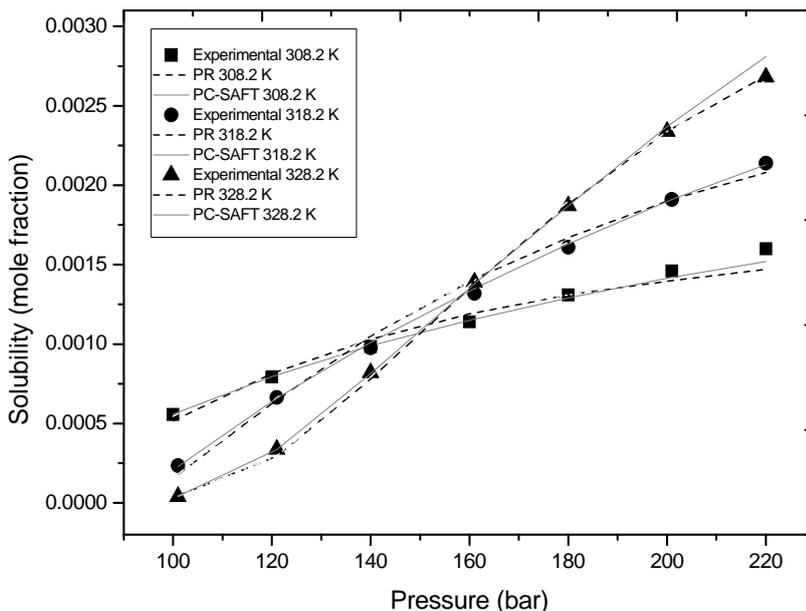


Figure 3. Experimental solubility in *sc*-CO₂ of phenylbutazone and correlation results obtained by PC-SAFT and SRK-VDW2 at various temperatures.

solubility predicted by PC-SAFT, PR and SRK equations.

For the three experimental temperatures, the figures show an excellent agreement between experimental literature data (shown as circles, squares and upward-triangles), and the solubility estimated by PC-SAFT more than those estimated by cubic-EOS (shown as solid and dashed lines, respectively).

For the correlation results of lovastatin and rosuvastatin, it is clear from the graphical analysis considered in Figures 4 and 5 that the solubility predicted

by PC-SAFT (shown as lines) follows the trend of the experimental data (shown as circles, triangles and squares), which suggests a good predictive ability of this equation at various temperatures.

CONCLUSION

In this work, PC-SAFT EOS were used with conventional combining rule to evaluate the capability of this approach for modeling the solubility of solid solutes in SCFs and the commonly used PR and SRK

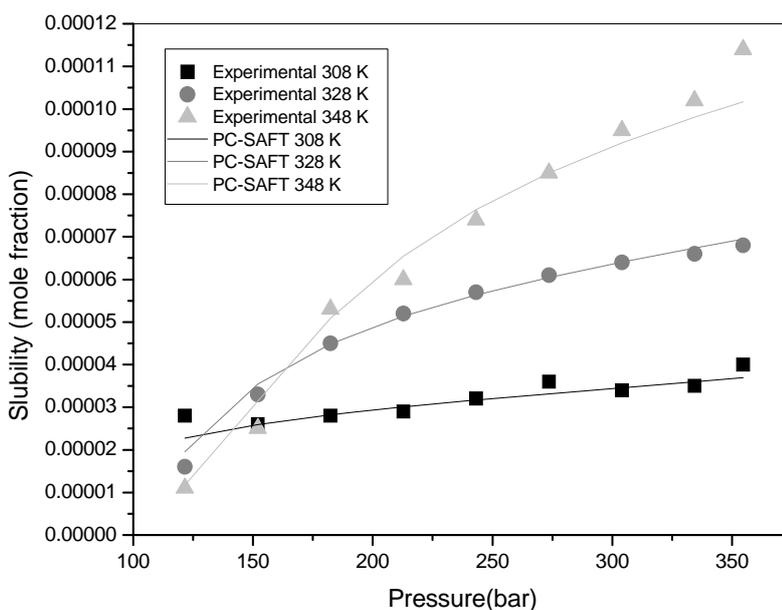


Figure 4. Experimental solubility in *sc*-CO₂ of lovastatin and correlation results obtained by PC-SAFT.

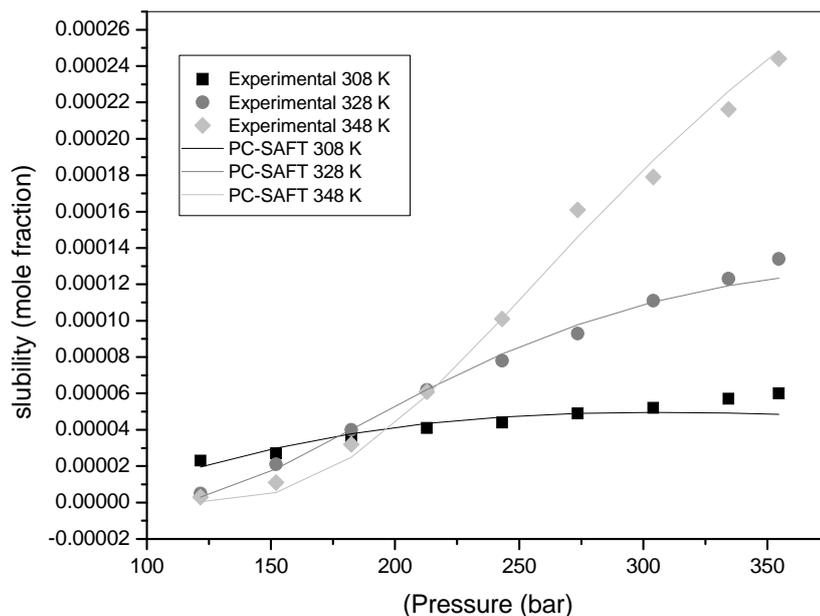


Figure 5. Experimental solubility in *sc*-CO₂ of rosuvastatin and correlation results obtained by PC-SAFT.

cubic equations of state along with VDW1 and VDW2 mixing rules for correlating the solubility of NSAIDs and statin drugs in supercritical carbon dioxide. The obtained results show that PC-SAFT has an advantage over cubic EOS and gives a good correlative accuracy than the cubic-EOS. Also, it should be mentioned that the use of the VDW2 (two binary interaction parameters, k_{ij} and l_{ij}) mixing rule does not substantially improve the results of the modeling obtained with the VDW1 (one binary interaction parameter, k_{ij}) mixing rule for both the SRK and PR equations of state.

The accurate values of physical properties are very important to the success of the correlation of solubility data using equation of state, mainly the sublimation pressure. One of the most critical factors that can influence the ability of estimation is the complexity of the molecules' structure, including poly-functional groups and several cycles and aromatic cores. It can be the origin of an important deviation in its estimating as well as in the calculated solubility (case of statin drugs) as it has been confirmed in previous works [40].

Special attention was paid to the estimation of PC-SAFT pure component parameters for non-associating substances because of the non-availability and the complexity of structure. Tihic's method used for estimating PC-SAFT parameters for nabumetone gave good correlation results of solubility in terms of relative deviations, *AARD*. The Tihic linear correlation for polyaromatic family used for calculating phenylbutazone and salicylamide gave accurate values and

could describe well the PC-SAFT component parameters, as well as the solubility estimate, compared to those found using cubic-EOS. More complicated systems were treated (CO₂ (1) + statins (2)) where the results obtained by PC-SAFT were obviously more accurate than cubic EOSs. The PC-SAFT pure component parameters were determined by fitting the solubility data, as it was done by Spyriouni *et al.* [41]. Despite the complexity of their structures, the non-availability of parameters and the limitation of the available estimation techniques, this approach can represent the experimental data of solubility of solid drugs in supercritical fluid with more accuracy than the other models.

Nomenclature

<i>AARD</i>	average absolute relative deviation
<i>a</i>	attractive term in PR and SRK-EOS
\check{a}	Helmoltz free energy
AV	atorvastatin
a_m, b_m	EOS mixture parameter
EOS	equation of State
FV	fluvastatin
<i>k</i>	Boltzmann constant, J/K
k_{ij}	binary interaction parameter
l_{ij}	binary interaction parameter
LV	lovastatin
NC	number of compounds
NSAID	non steroidal anti-inflammatory drug
OF	objective Function
<i>P</i>	pressure (bar)
P_c	critical pressure

P^{sub}	sublimation pressure (bar)
PC-SAFT	perturbed chain statistical associated fluid theory
PR	Peng-Robinson
RV	rosuvastatin
SAFT	statistical associated fluid theory
SCF	super-critical fluid
SRK	Soave-Redlich-Kwong
SV	simvastatin
T	equilibrium temperature (K)
T_c	critical temperature (K)
VDW1	Van-der-Waals mixing rule with one adjustable parameter
VDW2	Van-der-Waals mixing rule with two adjustable parameters
V	volume
v_2^s	molar volume of solid
y_2	mole fraction solubility of the solid, in super-critical phase
Z	compressibility factor

Greek letters

ϵ	depth of pair potential, J
η	packing fraction
ρ	total number density of molecules
σ	segment diameter, Å
Φ_i	fugacity coefficient of component i
ω	Pitzer's acentric factor

Superscripts

calc	calculated property
disp	contribution due to dispersive attraction
exp	experimental property
hc	residual contribution of hard-chain system
hs	residual contribution of hard-sphere system
id	ideal gas contribution
s	solid
sub	sublimation

Subscripts

2	solute (solid)
c	critical property
i, j	components i, j
m	constant for mixtures

REFERENCES

- [1] N. Elvassor, I. Kikic, G. Vetter, High Pressure Process Technology: Fundamentals and Application, Elsevier Science, Amsterdam, 2001, pp. 612-625
- [2] Z. Knez, E. A. Weidner, G. Vetter, in High pressure process technology: fundamentals and applications, A. Bertucco, G. Vetter Eds., Elsevier, Amsterdam, 2001, pp. 587-611
- [3] J. Jung, M. J. Perrut, Particle design using supercritical fluids: literature and patent survey, J. Supercrit. Fluid. **20** (2001) 179-219
- [4] D.Y. Peng, D.B. Robinson, A new two constant equation of state, Ind. Eng. Chem. Fundam. **15** (1976) 59-64
- [5] G. Soave, Equilibrium constant from a Modified Redlich-Kwong equation of state, Chem. Eng. Sci. **56** (1972) 1197-1203
- [6] K.G. Joback, R.C. Reid, Estimation of Pure-Component Properties from Group- Contributions, Chem. Eng. Commun. **57** (1987) 233-243
- [7] W.J. Lyman, W.F. Reehl, D.H. Rosenblatt, Handbook of Chemical Property Estimation Methods, J Am. Chem. Soc., Washington DC, 1990
- [8] P. Coimbra, C.M. Duarte, H.C. de Sousa, Cubic equation-of-state correlation of the solubility of some anti-inflammatory drugs in supercritical carbon dioxide, Fluid Phase Equilib. **239** (2006) 188-199
- [9] J.O. Valderrama, R. Zavaleta, Sublimation pressure calculated from High-Pressure Gas-Solid Equilibrium Data Using Genetic Algorithms, Ind. Eng. Chem. Res. **44** (2005) 4824-4833
- [10] J. Marrero, R. Gani, Group-contribution based estimation of pure component properties, Fluid Phase Equilib. **183-184** (2001) 183-208
- [11] Y. Nannoolal, J. Rarey, D. Ramjugernath, Estimation of pure component properties: Part3. Estimation of the vapour pressure of non-electrolyte organic compounds via group contribution and group interactions, Fluid Phase Equilib. **269** (2008) 117-133
- [12] M.S. Wertheim, Fluids with highly Ddirectional attractive forces I. Statistical thermodynamics, J. Stat. Phys. **35** (1984) 19-34
- [13] M.S. Wertheim, Fluids with highly directional attractive forces: II. Thermodynamic perturbation theory and integral equations J. Stat. Phys. **35** (1984) 35-47
- [14] M.S. Wertheim, Fluids with highly directional attractive forces. III. Multiple attraction sites, J. Stat. Phys. **42** (1986) 459-476
- [15] W.G. Chapman, K.E. Gubbins, G. Jackson, M. Radosz, SAFT: Equation of state solution model for associating fluid, Fluid Phase Equilib. **52** (1989) 31-38
- [16] W.G. Chapman, K.E. Gubbins, G. Jackson, M. Radosz, New reference equation of state for associating liquids, Ind. Eng. Chem. Res. **29** (1990) 1709-1721
- [17] S.H. Huang, M. Radosz, Equation of State for Small, Large, polydisperse, and associating molecules, Ind. Eng. Chem. Res. **29** (1990) 2284-2294
- [18] T. Kraska, K.E. Gubbins, Phase Equilibria calculations with a Modified SAFT Equation of state. 1. Pure Alkanes, Alkanols, and Water, Ind. Eng. Chem. Res. **35** (1996) 4727-4737
- [19] T. Kraska, K.E. Gubbins, Phase equilibria calculations with a modified SAFT equation of state. 2. Binary mixtures of n -alkanes, 1-alkanols, and water, Ind. Eng. Chem. Res. **35** (1996) 4738-4746

- [20] F.J. Blas, L.F. Vega, Prediction of binary and ternary diagrams using the Statistical Associating Fluid Theory (SAFT) Equation of State, *Ind. Phys. Chem. Res.* **37** (1998) 660-674
- [21] F.J. Blas, L.F. Vega, Thermodynamic behaviour of homonuclear Lennard-Jones chains with association sites from simulation and theory, *Mol. Phys.* **92** (1997) 135-150
- [22] A. Gil-Villegas, A. Galindo, P.J. Whitehead, S.J. Mills, G. Jackson, A.N. Burgess, Statistical Associating Fluid Theory for chain molecules with attractive potentials of variable range, *J. Chem. Phys.* **106** (1997) 4168-4186
- [23] A. Galindo, L. A. Davies, A. Gil-Villegas, G. Jackson, The thermodynamics of mixtures and the corresponding mixing rules in the SAFT-VR approach for potentials of variable range, *Mol. Phys.* **93** (1998) 241-252
- [24] A. Galindo, P.J. Whitehead, G. Jackson, A.B. Burgess, Predicting the phase equilibria of mixtures of hydrogen-fluoride with water, difluoromethane (HFC-32) and 1,1,1,2-tetrafluoromethane (HFC-134a) using a simplified SAFT approach, *J. Phys. Chem.* **10** (1997) 2082-2091
- [25] A. Galindo, P.J. Whitehead, G. Jackson, Predicting the high-pressure phase equilibria of binary aqueous solutions of 1-butanol, n-butoxyethanol and n-decyl-pentaoxyethylene ether (C10E5) using the SAFT-HS approach, *J. Phys. Chem.* **100** (1996) 6781-6792
- [26] W.G. Chapman, G. Jackson, K.E. Gubbins, Phase Equilibria of Associating Fluid Chain Molecules with Multiple Bonding Sites, *Mol. Phys.* **65** (1988) 1057-1079
- [27] J. Gross, G. Sadowski, Perturbed-Chain SAFT: An Equation of State Based on a Perturbation Theory for Chain Molecules, *Ind. Eng. Chem. Res.* **40** (2001) 1244-1260
- [28] J. Gross, G. Sadowski, Application of perturbation theory to a hard-chain reference fluid: an equation of state for square-well chains, *Fluid Phase Equilibria* **168** (2000) 183-199
- [29] I. Polishuk, Generalization of SAFT + Cubic equation of state for predicting and correlating thermodynamic properties of heavy organic substances, *J. supercrit. Fluid.* **67** (2012) 94-107
- [30] C. McCabe, A. Galindo, SAFT associating fluids and fluid mixtures, in: A.R.H. Goodwin, J.V. Sengers, C.J. Peters, Eds., *Applied Thermodynamics of Fluids*, RSC Publishing, Cambridge, 2010
- [31] A. Tihic, G.M. Kontogeorgis, N. Von Solms, M.L. Michelsen, A Predictive Group-Contribution Simplified PC-SAFT Equation of State: Application to Polymer Systems, *Ind. Eng. Chem. Res.* **47** (2008) 5092-5101
- [32] S. Skjold-Jorgensen, Gas solubility calculations. II. Application of a new group-contribution equation of state, *Fluid Phase Equilib.* **16** (1984) 317-351
- [33] H.P. Gros, E.A. Bottini, A group contribution equation of state for associating mixtures, *Fluid Phase Equilib.* **116** (1996) 537-544
- [34] W. Palinski, Immunomodulation: a new role for statins, *Nat. Med.* **2** (2000) 1311-1312
- [35] O. Pfohl, S. Petkov, G. Brunner, High pressure fluid-phase equilibria containing supercritical fluids, In 8th International Conference on properties and Phase Equilibria for Product and Process Design, Noordwijkerhout, 1998
- [36] R. Fedors, A method for estimating both the solubility parameters and molar volumes of liquids, *Polym. Eng. Sci.* **14**(2) (1974) 147-154
- [37] A. Tihic, G.M. Kontogeorgis, N. Von Solms, M.L. Michelsen, Application of the simplified perturbed-chain SAFT equation of state using an extended parameter table, *Fluid Phase Equilib.* **248** (2006) 29-43
- [38] C.S. Su, Y.P. Chen, Measurement and correlation for the solubility of non-steroidal anti-inflammatory drugs in supercritical carbon dioxide, *J. supercrit. Fluids.* **43** (2008) 438-446
- [39] M. Hojjati, Y. Yamini, M. Khajeh, A. Vatanara, Solubility of some statin drugs in supercritical carbon dioxide and representing the solubility data with several density-based correlations, *J. Supercrit. Fluids.* **41** (2007) 187-194
- [40] I. Ashour, R. Almehaideb, S.E. Fateen, G. Aly, Representation of solid-supercritical fluid phase equilibria using cubic equation of state, *Fluid Phase Equilib.* **167** (2000) 41-61
- [41] T. Spyriouni, X. Krokidis, I.G. Economou, Thermodynamics of pharmaceuticals: Prediction of solubility in pure and mixed solvents with PC-SAFT, *Fluid Phase Equilib.* **302** (2011) 331-337.

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NAUČNI RAD

PRIMENA PC-SAFT I KUBNE JEDNAČINE STANJA ZA KOERELISANJE RASTVORLJIVOSTI NEKIH FARMACEUTSKIH I STATINSKIH AKTIVNIH SUPSTANCI U SUPEKRITIČNOM CO₂

U ovom radu su rastvorljivosti nekih antiinflamatornih (nabumeton, phenilbutazon i salicilamid) i statinskih (fluvastatin, atorvastatin, lovastatin, simvastatin i rosuvastatin) aktivnih supstanci korelisani PC-SAFT (sa jednoparametarskim pravilom mešanja) i uobičajenim kubnim jednačinama Peng-Robinson-a (PR) i Soave-Redlich-Kwong-a (SRK) kombinovanim sa van-der Waals-ovim jedno- i dvo-parametarskim pravilima mešanja (VDW1 i VDW2). Eksperimentalni podaci za ispitivana jedinjenja u opsegu temperature 308-348 K i pritiska 100-360 bar su uzeti iz literature. Krična svojstva potrebna za korelisanje pomoću PR i SRK jednačina su izračunate Gani-Noonanol-ovom metodom doprinosa grupa, dok su u slučaju nabumetona parametri PC-SAFT jednačine za čiste komponente (segmentni broj, segmentni prečnik i energetski parameter, ϵ/k) izračunati metodom doprinosa grupa. U slučaju fenilbutazona i salicilamida, ovi parametri su određeni linearnom korelacijom. PC-SAFT parametri statinskih jedinjenja su određeni iz podataka za rastvorljivost, a parametri binarne interakcije su dobijeni fitovanjem eksperimentalnih podataka. Dobijeni rezultat je bio u saglasnosti sa eksperimentalnim podacima. Pokazano je da se PC-SAFT jednačina može upotrebiti za modelovanje ravnoteže čvrsto-superkritični fluid boljom korelacijom tačnošću od kubnih jednačina stanja.

Ključne reči: rastvorljivost čvrstih jedinjenja, kubna jednačina stanja, PC-SAFT, antiinflamatoran, supekritičan CO₂, korelacija.