A thermodynamic approach for correlating the solubility of drug compounds in supercritical CO₂ based on Peng–Robinson and Soave–Redlich–Kwong equations of state coupled with van der Waals mixing rules

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(Received 5 November 2018, revised 27 April, accepted 6 May 2019)

Abstract: In the present study, the effect of equations of state and mixing rules in a thermodynamic approach has been investigated for the correlation of the solubility of four new solid pharmaceutical compounds, namely, benzamide, cetirizine, metaxalone and niflumic acid in supercritical CO₂ at different temperatures and pressures. Two equations of state, the Peng–Robinson (PR) and Soave–Redlich–Kwong (SRK), coupled with mixing rules of one-parameter van der Waals (vdW1) and two-parameter van der Waals (vdW2) were used, where the binary interaction parameters for these sets of equations were evaluated. The approach correlations and the robustness of the numerical technique were validated with the experimental data previously reported for these compounds at different temperatures and pressures. The calculated average absolute relative deviations (AARD) were 7.51 and 5.31 % for PR/vdW1 and PR/vdW2 couples, and 11.05 and 10.24 % for SRK/vdW1 and SRK/vdW2 couples, respectively. It was also found that the PR equation of state results in modeling performance better than the SRK equation, and the vdW2 mixing rule better than the vdW1 one. These results obviously demonstrate that the combined approach used in this study is applicable for correlation of solid solubilities of some pharmaceutical compounds in supercritical CO₂. Additionally, a semi-empirical correlation is proposed for estimating the solubility of drug solids in supercritical CO₂ as a function of pressure and temperature.

Keywords: solid pharmaceutical compounds, SRK, PR, equations of state, mixing rules.

INTRODUCTION

New extraction technologies that are cost effective and comply with both environmental pressures and consumer preference are becoming more popular. Supercritical fluid extraction is one of the most efficient methodologies that has
found a great variety of applications in recent years. Supercritical fluids (SCFs) are increasingly replacing the organic solvents that are used in industrial purification operations because of regulatory control. Applications of SCF include recovery of organics from oil shale, bioseparation, petroleum recovery, crude deasphalting and dewaxing, coal processing, selective extraction of fragrances, oils and impurities from agriculturals, essential oils, food products, cosmetics, pharmaceutical, chemical and perfumes industries, pollution control, combustion and many other applications.

Various solid compounds are used for making drugs in the pharmaceutical industry. Many of these compounds are extracted from herbs using different technologies, including supercritical fluid extraction. Determination of the solubility of these solid compounds is of great importance in the drug industry. Despite all of the benefits of SCF technology, the experimental procedure of determining solid solubility in a supercritical fluid can be time consuming and expensive. Consequently, studies were made to model and correlate the solubility of a solid solute in a supercritical fluid. Hitherto, researches that performed on solubility modeling of drug compounds are rare.

Benzamide is used for making trimethobenzamide that treats nausea and vomiting related to surgery or caused by stomach flu. It is also used to study the mechanism of photocatalytic decomposition of aqueous solutions of acetic acid, acetamide and acetonitrile in the presence of semiconductors. Cetirizine is an antihistamine used to relieve allergy symptoms, i.e., allergic rhinitis, hay fever, and urticaria, such as watery eyes, runny nose, itching eyes/nose, sneezing, and itching. It has also been shown to inhibit eosinophil chemotaxis and LTB4 release. Metaxalone is a muscle relaxant used to relax muscles and relieve pain caused by strains, sprains, and other musculoskeletal conditions. It is considered a moderately strong muscle relaxant, with a relatively low incidence of side effects. Niflumic acid is a drug used for joint and muscular pain. In addition to anti-inflammatory actions, they have analgesic, antipyretic, and platelet-inhibitory actions.

In previous studies, different modelings were performed for solubility correlation of quercetin, mefenamic acid, sulindac, spironolactone, epicatechin, carvedilol and other solid compounds in supercritical CO2 using different equations of state. As there are various thermodynamic models and equations of state for the estimation of solid solubility in supercritical fluids, it is important to present an approach with fewer adjustable parameters.

In the present work, a thermodynamic approach based on the PR and SRK equations of state coupled with vdW1 (van der Waals with only one binary interaction parameter) and vdW2 (van der Waals with two binary interaction parameter) mixing rules is proposed for the determination of the solubility of some pharmaceutical solids, such as benzamide, cetirizine, metaxalone and niflumic...
acid, in supercritical CO₂. In addition to the determination of the solubility, the impact of inclusion of interaction parameters was also investigated. Thus, the solubility of these common drug compounds in supercritical CO₂ could be correlated at other temperatures and pressures using the proposed approach without the need for additional experiments. The ranges of pressure and temperature for experimental data applied for the present modeling for benzamide were 110–210 bar and 308–328 K based on experimental data in the literature.¹⁷ These ranges for cetirizine and metaxalone were 160–400 bar and 308.15–338.15 K, and 119––240 bar and 308.2–328.2 K, respectively.¹⁸,¹⁹ Finally, for niflumic acid the ranges were in 190–310 bar and 313.2–353.2 K.²⁰

MODEL DEVELOPMENT

Using phase equilibrium relations for a mixture of solid and SCF, the solid solubility in SCF could be computed. In this study, the PR and SRK equations of state along with vdW1 and vdW2 mixing rules were used and a comparison was made with experimental data for four typical solid pharmaceutical compounds.

Using phase equilibrium relations for a mixture of solid and supercritical fluid, one has:

\[ f_2^s = f_2^{scf} \]  

(1)

Subscript 2 represents the heavy component. \( f^s \) and \( f^{scf} \) are fugacities of solid compound and supercritical fluid, respectively. The solid phase is pure and supercritical fluid exhibits non-ideal behavior. As a result, the fugacity of the pure solid component at a specific pressure and temperature is calculated as follows:

\[ f_2^{sat} = P_2^{sat} \phi_2^{sat,s} \exp \left( \frac{v_2^{sat} (P - P_2^{sat})}{RT} \right) \]  

(2)

\( P_2^{sat} \) is the vapor pressure of heavy component. \( \phi_2^{sat,s} \) and \( v_2^{sat} \) are saturation fugacity coefficient, and molar volume of the solid solute. Due to the low vapor pressure of a solid compound, \( \phi_2^{sat,s} \) is assumed to equal 1. On the other hand, the fugacity of solid compound in SCF is obtained as:

\[ f_2^{ref} = y_2 \phi_2^{ref} P \]  

(3)

where, \( \phi_2^{ref} \) is the fugacity coefficient of the solid compound in SCF. Now, with the assumption of equilibrium between the two phases and equating Eqs. (2) and (3), the solubility of solid compound in the SCF, \( y_2 \), is calculated by:

\[ y_2 = \left( \frac{P_2^{sat}}{P} \right) \left( \frac{1}{\phi_2^{ref}} \right) \exp \left[ \frac{v_2^{sat} (P - P_2^{sat})}{RT} \right] \]  

(4)

Prediction of \( \phi_2^{ref} \) has a significant effect on the accuracy of the solubility estimation, which depends on the proper selection of the equation of state and mixing rule.

The two parameters PR and SRK equations of state can be written as below:²¹,²²

\[ P = \frac{RT}{v-b} \left( \frac{a}{(v+c_1 b)(v+c_2 b)} \right) \]  

(5)
where $P$, $T$ and $v$ are pressure, temperature and molar volume, respectively. The constants of Eq. (5) for PR and SRK equations of state and vdW1 and vdW2 mixing rules are given in the Supplementary material to this paper.

The optimum binary parameters, $k_{ij}$ and $l_{ij}$ in vdW1 and vdW2 mixing rules (see Supplementary material) were found by fitting the experimental data for each set of EOS and mixing rule couples based on the solubility data for four drug compounds at different temperatures and pressures mentioned in Figs. 1–4. $\phi^i$ in Eq. (6) is identical to $\phi^{2scf}$ in Eq. (3) and therefore this equation was used for the calculation of $\phi^{2scf}$ using PR and SRK equations of state:

$$\ln \phi^i = -\ln(Z - B) + \frac{b^i}{b}(Z - 1) + \frac{a}{bRT(c_1 - c_2)} \left[ \frac{b^i}{a} + \frac{b^i}{b} \right] \ln \frac{Z + c_1B}{Z + c_2B}$$  \hspace{1cm} (6)

where $\phi^i$ and $Z$ are the fugacity coefficient and compressibility factor, respectively. $a^i$ and $b^i$ are derivatives related to the attractive and repulsive parameters of the EOS, which are calculated from equations in the Supplementary material.

The compressibility factor, $Z$, for each of the EOSs was obtained from Eqs. (7) and (8):

**PR EOS:**

$$Z^3 - (1 - B)Z^2 + (A - 3B^2 - 2B)Z - (AB - B^2 - B^3) = 0$$  \hspace{1cm} (7)

**SRK EOS:**

$$Z^3 - Z^2 + (A - B - B^2)Z - AB = 0$$  \hspace{1cm} (8)

Parameters $A$ and $B$ are defined as follows:

$$A = \frac{aP}{R^2T^2}$$  \hspace{1cm} (9)

$$B = \frac{bP}{RT}$$  \hspace{1cm} (10)

The adjustable parameters in the mixing rules ($k_{ij}$ and $l_{ij}$) were fitted to the experimental data by the following objective function (OF):

$$OF = \sum_{i=1}^{N} \left( \frac{y_{i}^{exp} - y_{i}^{calc}}{y_{i}^{exp}} \right)^2$$  \hspace{1cm} (11)

The accuracy of the calculations of solubility data was evaluated by the absolute average relative deviations (AARD), defined as:

$$AARD, \% = 100 \sum_{i=1}^{N} \left( \frac{|y_{i}^{exp} - y_{i}^{calc}|}{y_{i}^{exp}} \right) \frac{1}{n}$$  \hspace{1cm} (12)

where $y_{i}^{exp}$ and $y_{i}^{calc}$ are the experimental and calculated amounts of solubilities, respectively.

**RESULTS AND DISCUSSION**

The specifications and physical properties of the investigated compounds are given in Tables I and II. Since some of the proposed methods for the prediction of physical properties were not accurate and the drug compounds used in this study have not previously been investigated by other researchers, great effort was directed on the prediction of different properties. The critical temperature and pressure were estimated using the Joback group contribution methods.23 Other
properties such as molecular weight, density at 20 °C and atmospheric pressure and molar volume of the solid compounds were obtained from the Molbase Chemical E-commerce Platform site based on their CAS numbers. The acentric factor and vapor pressure values were estimated using the Ambrose–Walton corresponding-state method.23

TABLE I. Specifications of four solid drug compounds

<table>
<thead>
<tr>
<th>Component</th>
<th>Chemical formula</th>
<th>CAS number</th>
<th>Molecular weight, g mol⁻¹</th>
<th>Density, g cm⁻³ (20 °C)</th>
<th>Molecular structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzamide</td>
<td>C₇H₇NO</td>
<td>55-21-0</td>
<td>121.140</td>
<td>1.340</td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>C₂₁H₂₅ClN₂O₃</td>
<td>83881-51-0</td>
<td>388.888</td>
<td>1.237</td>
<td></td>
</tr>
<tr>
<td>Metaxalone</td>
<td>C₁₂H₁₅NO₃</td>
<td>1665-48-1</td>
<td>221.252</td>
<td>1.138</td>
<td></td>
</tr>
<tr>
<td>Niflumic acid</td>
<td>C₁₃H₉F₃N₂O₂</td>
<td>4394-00-7</td>
<td>282.218</td>
<td>1.4490</td>
<td></td>
</tr>
</tbody>
</table>

TABLE II. Physical properties of solid compounds

<table>
<thead>
<tr>
<th>Component</th>
<th>Tc / K</th>
<th>Pc / MPa</th>
<th>v_b² / m³ kmol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon dioxide (solvent)</td>
<td>304.200</td>
<td>7.3700</td>
<td>–</td>
</tr>
<tr>
<td>Benzamide</td>
<td>749.853</td>
<td>4.8292</td>
<td>0.11225</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>1068.795</td>
<td>1.8016</td>
<td>0.32407</td>
</tr>
<tr>
<td>Metaxalone</td>
<td>935.015</td>
<td>2.9061</td>
<td>0.19442</td>
</tr>
<tr>
<td>Niflumic acid</td>
<td>846.700</td>
<td>2.3000</td>
<td>0.19477</td>
</tr>
</tbody>
</table>

Regarding the solution model presented in the previous section, the optimized values of parameter k_ij for vdW1 and k_ij and l_ij for vdW2 mixing rules along with the corresponding AARD for solubility of benzamide, cetirizine, metaxalone and niflumic acid at various pressures (11–40 MPa) and temperatures (308–353.2 K) are given in Table III. The optimized values of binary interaction parameters were evaluated using the DE (differential evolution) optimization strategy. This strategy has several advantages over other conventional optimization methods, including its simplicity.24 The values of k_ij and l_ij for vdW1 and vdW2 mixing rules show inconsistency with temperature variations.

The results obtained for the drug compounds with two (AARD of 8.3 %) and one-parameter (AARD of 9.4 %) solution models are demonstrated in Figs. 1–4. Since the model results for these typical solid components are quite similar to the experimental data, the experimental and calculated solubilities of these com-
pounds at different temperatures and pressures are presented in Figs. 1–4 to show the trends in the variations of the solubilities.

TABLE III. Optimized values of the binary interaction parameters for the solubility of solid drug compounds in supercritical CO2

| Parameter | Mixing rule | | | | |
|-----------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| T / K     | Pressure range, MPa | No. of points | Ref. | EOS | kij | AARD / % | kij | l ij | AARD / % |
| Component: benzamide | | | | | | | | | | | | | |
| 308       | 11.0–21.0   | 5   | 17  | PR  | 0.1292 | 6.6004 | 0.1291 | 0.1498 | 6.5835 |
|           |             |     |     | SRK | 0.1479 | 6.7920 | 0.1477 | 0.1579 | 6.7393 |
| 318       | 11.0–21.0   | 5   | 17  | PR  | 0.1092 | 15.5403 | 0.1091 | 0.1094 | 14.5036 |
|           |             |     |     | SRK | 0.1269 | 17.5754 | 0.1266 | 0.1425 | 17.4640 |
| 328       | 11.0–21.0   | 5   | 17  | PR  | 0.2437 | 12.3953 | 0.0886 | 0.0987 | 11.5095 |
|           |             |     |     | SRK | 0.1054 | 31.1019 | 0.1049 | 0.1128 | 30.9280 |
| Component: cetirizine | | | | | | | | | | | | | |
| 308.15    | 16.0–40.0   | 7   | 18  | PR  | –0.0268 | 18.7893 | –0.0344 | –0.0562 | 16.3517 |
|           |             |     |     | SRK | –0.0040 | 19.6857 | –0.0242 | –0.0428 | 18.9297 |
| 318.15    | 16.0–40.0   | 7   | 18  | PR  | –0.0161 | 10.6637 | –0.0145 | –0.0282 | 9.3685 |
|           |             |     |     | SRK | –0.0106 | 19.6928 | –0.0111 | –0.0452 | 18.0998 |
| 328.15    | 16.0–40.0   | 7   | 18  | PR  | –0.0309 | 6.4405 | –0.0300 | –0.0703 | 6.2208 |
|           |             |     |     | SRK | –0.0046 | 10.4695 | –0.0032 | –0.0971 | 7.9097 |
| Component: metamalone | | | | | | | | | | | | | |
| 308.2     | 11.9–24.0   | 7   | 19  | PR  | 0.0079  | 5.2235 | 0.0078  | –0.0199 | 5.1620 |
|           |             |     |     | SRK | 0.0337 | 6.9798 | 0.0339 | –0.0105 | 6.9180 |
| 318.2     | 11.9–24.0   | 7   | 19  | PR  | 0.2421 | 7.6411 | 0.2276 | –0.0300 | 6.9022 |
|           |             |     |     | SRK | 0.2375 | 8.3680 | 0.2375 | –0.0183 | 8.3612 |
| 328.2     | 11.9–24.0   | 7   | 19  | PR  | 0.0086 | 5.8585 | 0.0084 | –0.0282 | 5.8167 |
|           |             |     |     | SRK | 0.0324 | 5.6826 | 0.0320 | –0.0348 | 5.6229 |
| Component: niflumic acid | | | | | | | | | | | | | |
| 313.2     | 19.0–31.0   | 7   | 20  | PR  | 0.1381 | 1.6791 | 0.1381 | –1.4988 | 1.6041 |
|           |             |     |     | SRK | 0.1542 | 4.4223 | 0.1542 | –1.0874 | 4.4091 |
| 333.2     | 19.0–31.0   | 7   | 20  | PR  | 0.1501 | 4.6266 | 0.1501 | –0.9738 | 4.6263 |
|           |             |     |     | SRK | 0.1639 | 2.6127 | 0.1639 | –1.2113 | 2.6123 |
| 353.2     | 19.0–31.0   | 7   | 20  | PR  | 0.1713 | 2.8805 | 0.1712 | –0.9809 | 2.8135 |
|           |             |     |     | SRK | 0.1823 | 3.4120 | 0.1824 | –0.8274 | 2.4121 |

The average values of AARD are 7.51 and 5.31 % for PR/vdW1 and PR/vdW2 combinations, respectively. In the case of SRK/vdW1 and SRK/vdW2 combinations, the average errors take the values of 11.05 and 10.24 %, respectively. These ranges of errors are satisfactory for different applications. The small differences between the modeling results and experimental data are due to the application of cubic equations of state in supercritical fluid regions. These results confirm that the given solution model yielded satisfactory accuracy for solubility

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correlation of solid drugs. Among these compounds, benzamide and cetirizine had AARD larger than 10.0 % at some desired conditions of temperature and pressure.

Fig. 1. Experimental and correlated solubility data of Benzamide in supercritical CO2.

Fig. 2. Experimental and correlated solubility data for Cetirizine in supercritical CO2.
Fig. 3. Experimental\textsuperscript{19} and correlated solubility data of Metaxalone in supercritical CO\textsubscript{2}.

Fig. 4. Experimental\textsuperscript{20} and correlated solubility data for niflumic acid in supercritical CO\textsubscript{2}.

In the case of benzamide, the content of \textit{AARD} is higher at 328 K than at other temperatures. This is because more important factors, such as the molecular structure and molecular interaction of the compounds, affect the non-ideality of the system. Real systems are made up of atoms and molecules that actually
occupy some finite volume, and interact with each other through intermolecular forces. The effect of intermolecular forces is much more prominent at high pressures and/or low temperatures because the molecules have less kinetic energy to overcome the intermolecular attractions. At low temperatures, intermolecular forces become significant and molecules can be captured by one another due to their attractive forces more easily than at high temperatures. The closer it gets to the temperature at which the gas would turn into a liquid, the more non-ideal becomes the gas.

All the parameters in the compressibility factor expression (Eqs. (7) and (8)) are either known or can be accurately measured. However, this is not the case for pressure and volume. The actual volume occupied by the molecules cannot be measured. Hence, the amount of volume put into the compressibility factor equation is too high. As a result, for real gases, the value of the compressibility factor is too high at high pressures. As a gas is more compressed, the error would further increase. On the other hand, as the pressure increases, the molecules are forced closer together, and intermolecular forces will become more important. First, the value of the compressibility factor decreases, but soon it begins rising again because at this point, the effect of the size of the molecules starts to become more important. This effect becomes dominant at higher pressures.

Sparks et al.\textsuperscript{25} and Bitencourt et al.\textsuperscript{26} reported that the type of the solid compound, the density of CO\textsubscript{2}, temperature and pressure are the important factors that affect the solubility of a solid compound in supercritical CO\textsubscript{2}. Since the base of the present approach is theoretical and factors such as physical and thermodynamic properties of solid compounds would affect the calculation results, the accuracy is lower at some desired conditions.

The experimental and calculated solubilities of benzamide in supercritical CO\textsubscript{2}, determined using the one-parameter and two-parameter solution approaches are compared in Fig. 1. By adding the second adjustable parameter, the correlated results were improved a little. Therefore, by inclusion of one adjustable parameter in the solution approach, the solid solubility is acceptably correlated. This shows that in some complicated circumstances, the second parameter can be neglected and the vdw1 mixing rule employed with the introduction of a small difference in the AARD.

The results of thermodynamic modeling using the different EOS and mixing rules are in good agreement with experimental data for the investigated conditions of the components. The solubility data for all compounds showed an increase with increasing pressure at constant temperature. With increasing pressure, the intermolecular distance reduces, and hence the density of supercritical CO\textsubscript{2} increases. This leads to enhancement of the solvating strength of the solvent and increases the solubility of the solid compound in SCF. In addition, the solubility increases with temperature at constant pressure. Increasing the temperature has
two inverse effects. First, it increases the density and hence, decreases the solvating strength. However, the solid vapor pressure increases with temperature and enhances the solubility of the solid in SCF. Generally, the net effect of these two factors shows that the temperature increase enhances the solubility values. In most of the figures, the differences between the experimental data and the four various correlated results are less at lower pressures and become greater at higher pressures. This is due to the weakness of cubic equations of state for calculation of solid solubilities in SCF at high pressures. Moreover, as the scale of the vertical axis in the different Figures changes, the difference between the experimental data and the correlated results shows fluctuations for various temperatures and drug compounds.

The PR results match better than the SRK EOS with the experimental solubility data. This shows that for the systems of a solid and SCF, the PR EOS can calculate the solubility data more accurately than the SRK EOS. Of the two mixing rules, vDW2 is a bit better than vDW1, as was expected. The obtained results showed that the PR equation of state is more accurate than SRK and vDW2 predicts better than the vDW1 mixing rule.

Besides, a correlation is given by fitting the experimental data for the four solid compounds investigated in this study at various temperatures and pressures:

\[
y = A + \frac{B}{T} + C \ln P + \frac{D}{T^2} + \frac{E(\ln P)^2}{T} + \frac{F \ln P}{T} + \frac{G}{T^3} + \frac{H(\ln P)^3}{T} + \frac{I (\ln P)^2}{T} + J \ln P \frac{P}{T^2} \tag{13}
\]

where \( A, B, C, D, E, F, G, H, I \) and \( J \) are the constants of the equation, \( T \) is in K and pressure is in bar. This equation was generated by fitting the experimental data for each compound into a series of different equations and introducing the \( R \)-squared value (\( r^2 \)) for each equation that are given in Table IV. This semi-empirical equation is useful for the correlation of the solubility of these four solid compounds in supercritical \( \text{CO}_2 \) at the desired temperatures and pressures without the need for performing additional experiments.

In order to include all compounds investigated in this study and to encompass all combinations of the two independent parameters of pressure and temperature, the number of constants was selected as the minimum error of fitting the experimental data was achieved among different kinds of equations. The constants of the proposed equation for each component are given in Table IV along with \( AARD \) obtained from comparing experimental data and the results of Eq. (13) for several sets of data. \( AARD \) for benzamide, cetirizine, metaxalone and niflumic acid are 2.71, 18.56, 18.09 and 6.52 %, respectively.
SOLUBILITY OF DRUG COMPOUNDS

TABLE IV. Constants of Eq. (13) correlated from solubility data of different solid components in supercritical CO2

<table>
<thead>
<tr>
<th>Component</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzamide</td>
<td>-0.0220226</td>
<td>10.1723552</td>
<td>0.0048686</td>
<td>2960.990985</td>
<td>0.0015857</td>
<td>-7.3370542</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>-0.2659835</td>
<td>636.8106819</td>
<td>-0.2194841</td>
<td>-237593.8893</td>
<td>0.0286668</td>
<td>39.6922595</td>
</tr>
<tr>
<td>Metaxalone</td>
<td>-0.2771330</td>
<td>62.1461206</td>
<td>0.1272951</td>
<td>37785.49049</td>
<td>-0.0024090</td>
<td>-72.8750127</td>
</tr>
<tr>
<td>Niflumic acid</td>
<td>0.0078133</td>
<td>0.7834608</td>
<td>-0.0048909</td>
<td>-53.1111807</td>
<td>0.0009381</td>
<td>-0.1393787</td>
</tr>
</tbody>
</table>

Here, a single semi-empirical equation was used to show the minimum AARD for all four solid compounds of this study. However, due to the different properties of the drug compounds, two of them showed higher errors than the others. If for each compound a separate equation is proposed, a lower AARD is certainly obtained.

As can be seen, the results of the semi-empirical equation are in good agreement with the experimental data. However, for benzamide, the semi-empirical equation yields smaller average deviations than the present solution approach. In the case of niflumic acid, the amounts of errors for the semi-empirical equation and the solution approach are similar to each other. For the other two solid compounds, namely cetirizine and metaxalone, the deviations for the solution approach are lower than those for the proposed equation. Although a semi-empirical equation is a less theoretical consideration and has a lack of generalization and limited application, in the absence of experimental data at different temperatures and pressures, and due to the high expense and time-consumption of experiments, the proposed equation can be used to correlate the solubility of solid compound in supercritical CO2 with acceptable accuracy. On the other hand, the solution approach has the advantages of more simplification, generalization and feasibility than the semi-empirical equations. Furthermore, the solution approach could be modified into a predictive approach. Cubic equations of state, such as the PR and SRK equations of state, are more applicable because of their simplicity.

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CONCLUSIONS

In the present study, a thermodynamic approach was applied for the calculation of the solubility of typical solid compounds with pharmaceutical applications, namely, benzamide, cetirizine, metaxalone and niflumic acid in supercritical CO₂. To achieve this purpose, two equations of state, PR and SRK, and two mixing rules, vdW1 and vdW2, were used. The results for these components at different temperatures and pressure ranges in which experimental data were reported are in good agreement with the experimental data. In comparison between the different equation of states and mixing rules, the PR results are more precise than the SRK ones and the vdW2 mixing rule is better than the vdW1 mixing rule. The results in some cases are not very different from each other. The solubility data increases with increasing temperature and pressure. The \textit{AARD} values reported are acceptable and hence, it can concluded that the applied thermodynamic approach for these solids can be trusted and used for the calculation of the solubility of solids, especially drug compounds, in supercritical CO₂. Based on the proposed semi-empirical equation in this study, the solubility of these four solid compounds in supercritical CO₂ can be obtained at different further temperatures and pressures. A separate equation can be obtained for other drug compounds in a similar way to the present method to predict their solubility in supercritical CO₂ without performing expensive and time-consuming experiments.

NOMENCLATURE

\begin{tabular}{ll}
\textit{AARD} & Absolute average relative deviations \\
\textit{OF} & Objective function \\
\textit{P}_c & Critical pressure \\
\textit{p}^{sat} & Saturation vapor pressure \\
PR & Peng–Robinson \\
SCFs & Supercritical fluids \\
SRK & Soave–Redlich–Kwong \\
\textit{T}_c & Critical temperature \\
\textit{T}_r & Reduced temperature \\
\textit{Z} & Compressibility factor \\
a & Indicative of intermolecular attractive energy \\
b & Indicative of size of the molecule \\
f^s & Fugacity of solid \\
f^{scf} & Fugacity of supercritical fluid \\
k_{ij} & Binary interaction parameter \\
l_{ij} & Binary interaction parameter \\
n & Number of points \\
v_{dW1} & One-parameter van der Waals \\
v_{dW2} & Two-parameter van der Waals \\
y & Solubility of solid solute \\
y_{calc} & Calculated mole fraction of component \textit{i} \\
\end{tabular}
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_i^{\text{exp}}$</td>
<td>Experimental mole fraction of component $i$</td>
</tr>
<tr>
<td>$\phi_{\text{sat}}$</td>
<td>Saturation fugacity coefficient</td>
</tr>
<tr>
<td>$v$</td>
<td>Molar volume</td>
</tr>
<tr>
<td>$v^s$</td>
<td>Molar volume of the solid solute</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Acentric factor</td>
</tr>
<tr>
<td>$\phi_i^*$</td>
<td>Fugacity coefficient</td>
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</tbody>
</table>

**SUPPLEMENTARY MATERIAL**

Additional data are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

**ИЗВОД**

ТЕРМОДИНАМИЧКИ ПРИСТУП КОРЕЛИСАЊУ РАСТВОРЉИВОСТИ ЛЕКОВА У СУПЕРКРИТИЧНОМ $\text{CO}_2$ КОРИШЋЕЊЕМ PENG–ROBINSON и SOAVE–REDLICH––KWONG ЈЕДНАЧИНА СА van der WAALS ПРАВИЛАМА МЕШАЊА

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У овом раду испитван је утицај примене једначине стања и правила мешања на корелисање растворљивости четири фармацевутске компоненте у чврстом стању, бензамид, цетризина, метахалона и нифлуминске кисeline у суперкритичном $\text{CO}_2$ на различитим температурама и притисцима. Примењен се две јединичне стања, Peng–Robinson (PR) и Soave–Redlich–Kwong (SRK) у којима су као правила мешања коришћена једнопaramетарско van der Waals (vdW1) и двопaramетарско (vdW2) правило мешања, за које су одређени бинарни интеракциони параметри. Тачност примењеног приступа и нумеричке методе потврђене су уз помоћ раније објављених експерименталних података на различитим температурама и притисцима. Израчунате средње апсолутне релативне девијације (AARD) су 7,51 и 5,31 % за PR/vdW1 и PR/vdW2, редом, односно 11,05 и 10,24 % за SRK/vdW1 и SRK/vdW2, редом. Такође је утврђено да је PR једначина стања била успешнија у моделишућу од SRK једначине, док је vdw2 правило мешања било успешније од vdw1 правила мешања. Ови резултати јасно показују да је коришћени комбиновани приступ примењив за корелисање растворљивости појединих чврстих фармацевутских компонената у суперкритичном $\text{CO}_2$. Такође, за прорачун растворљивости фармацевутских компонената у суперкритичном $\text{CO}_2$ предложена је и полу-емпиријска корелација као зависност од притиска и температуре.

(Примљено 5. новембра 2018, ревирирани 27. априла, прихваћено 6. маја 2019)

**REFERENCES**


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