Experimental Determination and Correlation of Artemisinin’s Solubility in Supercritical Carbon Dioxide

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The measurement and correlation of the experimental solubility of the antimalarial artemisinin (Artemisia annua L.) in supercritical carbon dioxide is reported. Results were obtained using a static analytical method at 308.2, 318.2, and 328.2 K, and in a pressure range from 10.0 up to 25.0 MPa. Solubility experimental data were correlated with three density-based models (Chrastil, Bartle, and Méndez-Santiago—Teja models) and with two cubic equation of state (EOS) models, namely, the Peng—Robinson EOS and the Soave—Redlich—Kwong EOS, together with the conventional van der Waals mixing and combining rules. Good correlation results were obtained between the calculated and the experimental solubility to all fitted models. Results clearly show the feasibility of processing this antimalarial drug using supercritical fluid technologies and processes.

Introduction

Solvents and processes in solution play a central role in the majority of chemical and pharmaceutical industrial processes. The pharmaceutical industry is one of the major industries worldwide and wherein, for comprehensible reasons, safety and ecological considerations on the use of volatile organic solvents (VOCs) and other harmful solvents must be seriously taken into account. The actual severe regulations on the use of these solvents and on their residual level in the final products are a major limitation to most of the traditional pharmaceutical processes. Likewise, both the generation of polluted aqueous waste streams and the energy used to remove water (or other solvents) from final or intermediate products (i.e., drying steps) make important contributions to global pollution. As such, it seems obvious that there are economical, safety, and ecological reasons and a real need to consider, innovate, and optimize either organic solvent-free pharmaceutical processes or the use of “green and environmental friendly” solvents. Supercritical fluids (SCFs) have already proved to be an excellent alternative to replace VOCs, harmful solvents, and other additives in many types of chemical and pharmaceutical process operations. Furthermore, SCFs also present unique properties that may improve these processes as well as offer new and innovative possibilities for the development of new products, with better chemical, physical, morphological, and mechanical properties and, consequently, leading to novel and improved final pharmaceutical applications and products. In recent years, several reviews of pharmaceutical processing (studied systems and applied techniques) using SCFs have been published, demonstrating the existing opportunities offered by these processes and technologies.1–5

Carbon dioxide is the most used SCF due essentially to its relatively low critical temperature and critical pressure \( (T_c = 304.3 \text{ K}, \quad P_c = 73.7 \text{ bar}) \), nontoxicity, noninflammability, and low cost. Because of these favorable properties combined with other typical properties of SCFs like their low viscosities, high diffusivities, and liquid-like densities, supercritical carbon dioxide (scCO\(_2\)) has found many uses in the nutraceutical and pharmaceutical fields, where its nontoxic nature displays a great advantage. Moreover, its low critical temperature permits supercritical processing at mild temperature conditions, avoiding the possible degradation of thermally labile substances (like most pharmaceuticals and nutraceuticals). Another important advantage is that the elimination of residual solvent is complete, and the recovery of final products is easier and cheaper when compared with many traditional processes. Extraction and separation of natural products,6–8 recrystallization and drug particle formation,9–12 preparation of sustained drug delivery systems,13–15 and as a solvent for pharmaceutical synthesis and enzymatic catalysis16–18 are some examples of scCO\(_2\) potential applications in the pharmaceutical, cosmetics, and nutraceutical industries.

Artemisinin (Figure 1), also known by the Chinese name Quinghaosu, is an endoperoxide sesquiterpene lactone produced by the aerial parts of Artemisia annua L. (Asteraceae, formerly Compositae), which has been used as a potential and effective antimalarial agent to vitiate the impact of multidrug resistant strains of the malarial parasites, Plasmodium falciparum and Plasmodium vivax, including the human cerebral malaria.19–23 In addition, ethanolic extracts of A. annua L. also proved to be antifungal and antitumoral, and its essential oils can be used as repellents, bactericides, and antioxidants.5 Recently, artemisinin and some of its derivatives also showed a strong antifungal activity against the opportunistic pathogen Cryptococcus neoformans.24

Although the chemical synthesis of this drug and of its derivatives (dihydroartemisinin, arteether, artether, artesunic acid, and artelinic acid) is already possible, the synthetic products are not yet as competitive in price as the natural ones, obtained by extraction and isolation from A. annua L.25–27 On the other hand, apparently the pharmaceutical industry is not interested in investing and producing antimalarial drugs because...
most of the infected people live in nondeveloped and developing countries, where the pharmaceutical market is not attractive enough, and there is insufficient patent protection. Therefore, the most used method to obtain artemisinin is by liquid organic solvent extraction from *A. annua* L. dried aerial parts (leaves, stems, buds, and flowers). Typical employed solvents are toluene, *n*-hexane, cyclohexane, ethanol, chloroform, and petroleum ether. Microwave-assisted liquid solvent extraction was also employed in order to increase liquid extraction rates. However, and in general, the extracts obtained by liquid solvent extraction contain large amounts of undesired compounds such as chlorophyll and other organic molecules. This will decrease the extraction selectivity and will introduce difficulties in the drug purification process, leading to low extraction yields.

Most authors decide to use several empirical correlations such as density-based correlations or the Ziger–Eckert semiempirical correlation. These models are based on simple error minimization using least-squares methods, and for the majority of them, there is no need to estimate and use critical and thermophysical properties of the involved solids.

Despite the above referred disadvantages and difficulties associated to these correlation models, they are widely employed and normally used to fit and correlate solubility experimental data for a given envisaged practical purpose. Thus, they are very helpful for the development of supercritical applications and processes that require the accurate knowledge of solid solubility in SCFs. However, and like most correlation models, even for other applications, they should be preferably employed just in the experimental data range (i.e., for interpolation of results). Using these models to extrapolate to outside the experimental data range should be performed very carefully (it can be done, but for regions very near to the limits of the experimental data range). Extrapolation for other regions, far from this range, can originate unreliable results.

Only recently the solubility of artemisinin in scCO₂ was measured, at four isotherms, correlated and reported, using a flow-type apparatus equipped with a high-pressure UV detector. Correlation on the experimental data was done using a density- and temperature-based equation. In the present work, the equilibrium solubility of artemisinin in scCO₂ was measured, from 10.0 up to 25.0 MPa, and at 308.2, 318.2, and 328.2 K, using a static analytical method. Results were compared to the ones obtained by Ren and co-workers. Experimental data were correlated using three different density-based correlations (Charristil, Bartle, and Méndez-Santiago–Teja models) and by the PR and SRK EOSs, together with the conventional van der Waals mixing and combined rules.

Experimental Section

Materials. Carbon dioxide (CAS 124-38-9) (purity > 99.998 %) was purchased from Praxair, dichloromethane (CAS 75-09-2) (purity > 99.9 %) was obtained from Fluka. Artemisinin...
Operational temperature and pressure were attained, the solid was prepared standard samples, with concentrations between 0.5 and 3 mg/mL. To ensure that all solute was recovered, a cleaning solvent (dichloromethane) was injected through the sample loop and the expansion lines and recollected in the glass trap. Lines were also cleaned with fresh CO2, smoothly pressurized. The gas in the sample was expanded into a large precalibrated and the precipitated solid was collected in a small glass trap. The amount of solubilized solid drug was calculated based on the resulting sub-atmospheric pressure increase, which was measured with a high precision low-pressure transducer (Setra, model 204, 0.0–0.175 ± 1.9 × 10⁻⁴ MPa). To ensure that all solute was recovered, a cleaning solvent (dichloromethane) was injected through the sample loop and the expansion lines and recollected in the glass trap. Lines were also cleaned with fresh CO2, smoothly pressurized.

Analytical Method. The amount of solubilized solid drug was determined by spectrophotometric UV analysis. The collected samples, containing the solid drug, were diluted in dichloromethane to a convenient volume, and the absorbances of the resulting sample solutions were measured, at fixed wavelength (229 nm), by a UV/VIS spectrophotometer (JASCO V-530). Calibration curve was obtained by UV analysis of previously prepared standard samples, with concentrations between 0.5 and 3 mg/mL.

For each sample, the amount of CO2 was calculated using the Virial EOS (applied to pure CO2), the values of the precalibrated expansion volumes, the resulting sub-atmospheric pressure increase due to expansions, the temperature of the water bath (± 0.01 K), and the temperature of the glass trap (which was considered to be 273.15 K).

Correlation of Experimental Solubility Data

Density-Based Models. The Chrastil model^4^ relates the solubility of a solid solute in a SCF as a function of the density of the pure SCF and of the absolute temperature. It is based on the supposition that one molecule of solute, A, associates with k molecules of solvent, B, to form a solvate complex, ABk, in equilibrium with the system. Taking into consideration several thermodynamic considerations, it is easy to obtain the following expression for the solid solubility in a SCF:

\[
\ln S = k \ln \rho + \alpha T + \beta \tag{1}
\]

In this expression, S (kg·m⁻³) is the solubility of the solid in the supercritical fluid; ρ (kg·m⁻³) is the density of the pure supercritical fluid; k is the association number; α is a constant, defined as ΔH/R (where ΔH is the sum of the enthalpies of vaporization and solvation of the solute and R the gas constant); and β is another constant related to the molecular weight of the solute and solvent. The parameters k, α, and β are obtained performing a multiple linear regression on the obtained experimental solubility data.

Bartle et al.\(^4^4\) proposed another simple density-based semiempirical model to correlate the solubility of solids in SCFs:

\[
\ln \left(\frac{\gamma_{p}}{\rho_{ref}}\right) = A + C(\rho - \rho_{ref}) \tag{2}
\]

\[
A = a_1 + a_2\frac{1}{T} \tag{3}
\]

\[
\ln \left(\frac{\gamma_{p}}{\rho_{ref}}\right) = a_1 + a_2\frac{1}{T} + C(\rho - \rho_{ref}) \tag{4}
\]

In these expressions, ρref is assumed as a standard pressure of 0.1 MPa (1.0 bar); ρref is a reference density, assumed as 700 kg·m⁻³; and a1, a2, A, and C are empirical constants, determined in the following way: from the experimental solubility data, each isotherm is fitted using eq 2, to obtain the values of A and C. In this model, the parameter a2 is related to the enthalpy of sublimation of the solid solute, ΔHsub, by the expression ΔHsub = -RT (R is the gas constant).

Finally, and based on the theory of dilute solutions, Méndez-Santiago and Teja\(^4^5\) proposed a simple linear expression to correlate the solubility of solids in SCFs:

\[
T \ln(\gamma_p) = A' + B'ρ + C'T \tag{5}
\]

where A', B', and C' are constants, considered as temperature independent, and obtained by a multiple linear regression of solubility experimental data.

EOS-Based Models. The solubility of a solid solute (2) at equilibrium with a fluid at high pressures (1) can be calculated using the following well-known expression:

\[
\gamma_2 = \frac{\rho_{sub}^2}{p} \frac{1}{\varphi_{2}^{SCF}} \exp \left( \frac{v_2(p - \rho_{sub}^2)}{RT} \right) \tag{6}
\]

In this expression, \(\rho_{sub}^2\) is the sublimation pressure of the pure solid at temperature \(T\), \(v_2\) is the molar volume of the solid, and \(\varphi_{2}^{SCF}\) is the fugacity coefficient of the solid in the fluid phase, which expresses the nonideality of the fluid phase. This fugacity coefficient is usually evaluated using an EOS. In this work, the Peng–Robinson\(^33\) EOS (eq 7) and the Soave–Redlich–Kwong\(^35\) EOS (eq 8) were used:

\[
p = \frac{RT}{v - b} - \frac{a}{v(v + b) + b(v - b)} \tag{7}
\]

\[
p = \frac{RT}{v - b} - \frac{a}{v(v + b)} \tag{8}
\]

To use the above EOSs, for a binary solid + SCF mixture, we employed the classical van der Waals (vdW) mixing and
The binary interaction parameters, $k_{ij}$

Results and Discussion

Table 1. Experimental Solubility ($\gamma$) of Artemisinin in Supercritical Carbon Dioxide

<table>
<thead>
<tr>
<th>$p$/MPa</th>
<th>$\rho$/kg·m$^{-3}$</th>
<th>$\gamma$</th>
<th>$T$ = 308.2 K</th>
<th>$T$ = 318.2 K</th>
<th>$T$ = 328.2 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.4</td>
<td>720.7</td>
<td>0.701</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.2</td>
<td>786.5</td>
<td>0.925</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.3</td>
<td>828.5</td>
<td>1.134</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.6</td>
<td>851.0</td>
<td>1.521</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.6</td>
<td>876.3</td>
<td>1.716</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.2</td>
<td>900.4</td>
<td>1.788</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At the studied conditions, the solubility of artemisinin in scCO$_2$, in terms of mole fraction, ranges from $10^{-4}$ to $10^{-3}$, which is higher than the typical solubilities of many drugs and molecules of biological and pharmaceutical interest. Generally, these compounds have a relatively low solubility, usually around or inferior to $10^{-4}$, in terms of mole fraction, at the same investigated pressure range and temperatures.

It is well-known that the solubility of a solid in a SCF depends essentially on the specific interactions between the solid solute and the SCF as well as on the molecular weight of the solid (and on pressure and temperature). If the SCF is a small nonpolar molecule (like CO$_2$), one should anticipate that strong polar high molecular weight substances (like most drugs) are hard to dissolve (or even insoluble) in scCO$_2$. From Figure 1, we can see that artemisinin is a large molecule ($M_w = 282.33$ g·mol$^{-1}$) and from its structure, we may expect that it is a strong polar molecule. Polarity can be discussed in terms of the dipole moments of substances. Even when using molecular simulation programs to estimate these values, it is a very difficult task because most drugs possess stereoisomers and each stereoisomer can present several conformers, having different dipole moments.

Artemisinin’s dipole moment was found to be around 6.14 D, calculated by a molecular mechanics (MM2) force field model and by a semiempirical molecular orbital model (MOPAC). Therefore, we should expect a low solubility in scCO$_2$ and not a relatively high solubility like the one experimentally observed. Thus, these high solubility values may be due to some specific interactions that may occur between artemisinin and scCO$_2$ like, for example, specific interactions that may take place between its carbonyl group and scCO$_2$. It is known that CO$_2$ has a large quadrupole moment as a result of its highly electronegative oxygen atoms, and it is credible that it may lead to a favorable quadrupole–dipole interaction between CO$_2$ and artemisinin.

In Figure 2, we compare our experimental data, at 318.2 K and 328.2 K, with the experimental solubility data previously reported by Ren and co-workers at 318.1 K and 328.1 K, measured with a flow-type apparatus, equipped with a high-pressure UV detector. As can be seen, and despite the different employed experimental methods, our results are in quite good agreement with theirs.
They obtained the following fitted parameters (for AARD experimental solubility data (for four isotherms (310.1 K, 318.1 K, 308.2 K, 328.2 K), where the discrepancy is generally higher).

In the above cited work, Ren and co-workers fitted their experimental solubility data (for four isotherms (310.1 K, 318.1 K, 308.2 K, 328.2 K), where the correlation parameters were determined. The three density-based (Chrastil, Bartle, and Méndez-Santiago–Teja models) correlation results are presented in Table 2.

Table 2. Comparison between the Solubility Data

<table>
<thead>
<tr>
<th>Temperature</th>
<th>$\ln(y) = a \ln(pT) + b \ln$</th>
<th>$cT + d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>308.2 K</td>
<td>$\gamma \times 10^{10}$</td>
<td>$\gamma \times 10^{10}$</td>
</tr>
<tr>
<td>318.2 K</td>
<td>$\gamma \times 10^{10}$</td>
<td>$\gamma \times 10^{10}$</td>
</tr>
<tr>
<td>328.2 K</td>
<td>$\gamma \times 10^{10}$</td>
<td>$\gamma \times 10^{10}$</td>
</tr>
</tbody>
</table>

They obtained the following fitted parameters (for AARD referred as 4.24 %): $a = 2.162; b = 0.002238; c = -2795.485$; and $d = -26.311$. In Table 2, we present the calculated artemisinin’s solubility using Ren’s correlation and fitted parameters (for each temperature and pressure data point), and we compared these results with our experimental values. As referred at the graphical analysis (Figure 2), results are, in general, in good agreement except for lower values of pressure. These differences may be due to the diverse employed experimental methods. A possible cause to these different values may be due the different fluid phase saturation periods used at each method. Ren’s method, at lower pressures, just allowed an initial total saturation period of less than 20 min and then pressure was increased in sequential steps, while we used around 80 min of saturation time for every point. Therefore, at 318.2 K and 328.2 K and because of lower fluid phase densities, incomplete saturation can be achieved at these lower pressures, originating lower solubility values than the ones obtained in our work. At 308.2 K, Ren and co-workers did not report the experimental solubility results, but we also determined these values using their correlation. For this isotherm, Ren’s correlation originated higher solubility values than the ones obtained in our work (for lower pressures). However, we cannot be sure if their correlation can be confidently used outside the experimental temperature range for which the correlation parameters were determined.

The three density-based (Chrastil, Bartle, and Méndez-Santiago–Teja models) correlation results are presented in Table 3.

Table 3. Correlated Parameters and Correspondent AARD Values, Obtained from Experimental Data Correlation Using Chrastil, Bartle, and Méndez-Santiago–Teja Models

<table>
<thead>
<tr>
<th>Chrastil Model, eq 1</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha/K$</td>
<td>-3846.1</td>
</tr>
<tr>
<td>$\beta$</td>
<td>-13.35</td>
</tr>
<tr>
<td>$\Delta H/(kJ/mol^{-1})$</td>
<td>-32.0</td>
</tr>
<tr>
<td>AARD%</td>
<td>8.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bartle Model, eq 4</th>
<th>$\alpha_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_i/K$</td>
<td>-6720.6</td>
</tr>
<tr>
<td>$C/(m^3/kg^{-1})$</td>
<td>0.008</td>
</tr>
<tr>
<td>$\Delta H_{sub}/(kJ/mol^{-1})$</td>
<td>55.9</td>
</tr>
<tr>
<td>AARD%</td>
<td>11.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Méndez-Santiago–Teja Model, eq 5</th>
<th>$A/K$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B'(K^-m^3/kg^{-1})$</td>
<td>2.4</td>
</tr>
<tr>
<td>$C'$</td>
<td>26.1</td>
</tr>
<tr>
<td>AARD%</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Figure 3. Logarithmic relationship between the solubility of artemisinin in scCO2 and the density of pure CO2. Experimental: ▲ 308.2 K; ○ 318.2 K; ■ 328.2 K; —, calculated by eq 1, Chrastil’s model.

Figure 4. Solubility of artemisinin in scCO2 as a function of the density of pure CO2. Experimental: ▲ 308.2 K; ○ 318.2 K; ■ 328.2 K; —, calculated by eq 4, Bartle’s model.

Figure 5. Relationship between the solubility of artemisinin and the density of pure CO2. Experimental: ▲ 308.2 K; ○ 318.2 K; ■ 328.2 K; —, calculated by eq 5, Méndez-Santiago–Teja’s model.
sometimes are not very trustworthy. Consequently, this may introduce additional errors on the EOS correlation results or may originate very unlike adjusted parameters results, depending on the applied methods. Therefore, some prudence should be taken when selecting and applying these estimation methods. In some previous work, we already discussed the influence of these group-contribution methods on the estimation of these required properties and their consequences on the final EOS correlation results. Accordingly, for artemisinin, these properties were estimated using the group-contribution methods indicated in Table 4.\(^{51,61,62}\)

In Table 5, we present the optimal fitted binary parameters and the respective AARD values, obtained by experimental data correlation using the PR-EOS and the SRK-EOS, combined with the van der Waals mixing and combining rules, with one adjustable parameter (vdW1) and with two adjustable parameters (vdW2).

Correlation results obtained with the PR-EOS and SRK-EOS, in respect to AARD values, are very similar, both for vdW1 and vdW2 mixing and combining rules. As expected, the best correlations, for both EOSs, were obtained for the vdW2 mixing and combining rule, with two adjustable parameters. Of course, this can be explained by the fact that a model with two adjustable parameters has more “flexibility” to fit the experimental data than a model with only one adjustable parameter, such as vdW1. Figure 6 shows the correlation of experimental solubility data obtained with the PR-EOS, using vdW2 mixing and combining rule. Correlated curves evidence the retrograde solubility behavior characteristic of most of the solid/SCF systems, which is caused by the opposite effect of temperature on the density of the supercritical fluid and on the sublimation pressure of the solid solute. For this system, this so-called “crossover region”, where one can observe the intersection of the solubility isotherms, is located between 13.0 MPa and 17.0 MPa.

One of our objectives in determining the experimental solubility of artemisinin in scCO\(_2\) is to make use of the obtained data (experimental and correlated) for the design and development of supercritical processes based on this drug (like particle formation and supercritical solvent impregnation techniques). And, for these purposes, the accurate knowledge of drug solubility and the quality and confidence of the applied correlations is indispensable (for interpolations inside the experimental ranges investigated). To improve the confi-

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Table 4. Estimated Critical and Other Required Thermophysical Properties of Artemisinin

<table>
<thead>
<tr>
<th>(T_c)</th>
<th>(T_e)</th>
<th>(p_c)</th>
<th>(10^6 \times \omega)</th>
<th>(p_y^{ab} \times 10^5/\text{MPa})</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>K</td>
<td>MPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>308.2 K</td>
<td>318.2 K</td>
<td>328.2 K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>560.1 (^a)</td>
<td>767.7 (^a)</td>
<td>2.445 (^b)</td>
<td>0.603 (^b)</td>
<td>211.5 (^b)</td>
</tr>
</tbody>
</table>

\(^a\) Estimated by Constantinou–Gani (first-order) method. \(^b\) Estimated by the Ambrose–Walton corresponding states method.\(^{51,61}\) \(^c\) Estimated by Fedors’ method.\(^{62}\)

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Table 5. Correlation Results for the Solubility of Artemisinin in scCO\(_2\), Obtained with the Peng–Robinson and the Soave–Redlich–Kwong Equations of State

<table>
<thead>
<tr>
<th>(T/K)</th>
<th>Mixing rule</th>
<th>PR-EOS</th>
<th>SRK-EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_{12})</td>
<td>(l_{12})</td>
<td>AARD%</td>
<td>(k_{12})</td>
</tr>
<tr>
<td>308.2</td>
<td>vdW1</td>
<td>0.188</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>vdW2</td>
<td>0.250</td>
<td>0.144</td>
</tr>
<tr>
<td>318.2</td>
<td>vdW1</td>
<td>0.184</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>vdW2</td>
<td>0.219</td>
<td>0.075</td>
</tr>
<tr>
<td>328.2</td>
<td>vdW1</td>
<td>0.186</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>vdW2</td>
<td>0.233</td>
<td>0.100</td>
</tr>
</tbody>
</table>

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Figure 6. Solubility of artemisinin in scCO\(_2\): Experimental: \(\Delta\), 308.2 K; \(\bigodot\), 318.2 K; \(\blacksquare\), 328.2 K; \(\sim\), calculated with the PR-EOS and vdW2 mixing and combining rule (two adjustable parameters).

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Table 6. Correlation Results for the Solubility of Artemisinin in scCO\(_2\), Obtained with the PR-EOS, and the vdW2 Mixing and Combining Rule

<table>
<thead>
<tr>
<th>(y) (-\text{OU})</th>
<th>(y) (+\text{OU})</th>
<th>PR-EOS–vdW2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_{12})</td>
<td>(l_{12})</td>
<td>AARD%</td>
</tr>
<tr>
<td>308.2</td>
<td>0.276</td>
<td>0.189</td>
</tr>
<tr>
<td>(y) (+\text{OU})</td>
<td>0.250</td>
<td>0.144</td>
</tr>
<tr>
<td>(y) (-\text{OU})</td>
<td>0.233</td>
<td>0.115</td>
</tr>
</tbody>
</table>

\(^a\) Applied to the average experimental solubility \((y)\). \(^b\) Applies to the average experimental solubility, added by the overall uncertainty \((y + \text{OU})\).

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dence on our correlated results, we must also try to perceive the effect of the overall uncertainty of the experimental data on the correlation results. A feasible way to do this is to consider the obtained overall uncertainty associated with all experimental data points and then, “create” two new sets of “experimental” data points: one consisting of their average experimental value added by the overall uncertainty and the other consisting of their average values subtracted by the same overall uncertainty. Subsequently, we must correlate the models, using these two new “experimental” sets of data points. Applying this procedure, we will obtain an “area” in which drug solubility, with some degree of confidence, should be comprised.

As an illustrative example of this procedure, we applied the PR-EOS, together with the vdW2 mixing and combining rule (vdW2, with two adjustable parameters), for the experimental results obtained at 308.2 K. Results are summarized in Table 6 and presented in Figure 7.

As can be seen, we will get an area of “probable” drug solubility, as a function of pressure, for each isotherm, which is located between the curves obtained for the correlation of \((y + \text{OU})\) and \((y - \text{OU})\) data. Interaction parameters showed a relative error (to the experimental average solubility correlated parameters) of 6.8 to 10.4 % (for \(k_{12}\)) and 25.2 to 31.3 % (for \(l_{12}\)). AARD values are similar for the three performed correlations.

Therefore, this procedure may provide more confidence for the selection of the operational \((p, T)\) conditions to apply in the development of any supercritical process that requires the solubility data of this drug in scCO\(_2\). However, as as already referred, this should be employed just in the experimental data range (i.e., for interpolation of results). Similar procedures can be done for other EOS models as well as for the presented density-based models (Chrustil, Bartle, and Méndez-Santiago–Teja models).
Conclusions

The solubility of artemisinin in scCO₂ was measured and correlated at various pressures and temperatures (at 308.2 K, 318.2 K, and 328.2 K, in the pressure range from 10.0 MPa up to 25.0 MPa). Experimental results were compared with those in the existing literature, and good agreement was found despite different experimental methods are different. Results clearly show the feasibility of processing this antimalarial drug using supercritical fluid technologies and processes. Furthermore, these results may be an indication that, possibly, other artemisinin’s derivatives will be also soluble in scCO₂.

The obtained high solubility values were discussed in terms of possible and potential specific interactions that may occur between artemisinin and scCO₂ like, for example, those that may take place between its carbonyl group and scCO₂ as well as other interactions which may occur between the lone pairs of electrons at oxygen atoms of artemisinin (peroxide, ether, and lactone groups) and scCO₂ (quadrupole–dipole interaction between CO₂ and artemisinin).

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Figure 7. Correlation of artemisinin’s solubility in scCO₂, at 308.2 K, and using the PR-EOS-vdW2 model. ▲, experimental average solubility; —, calculated for the average experimental solubility (y + OU); - - -, calculated for the average experimental solubility, subtracted by the overall uncertainty (y − OU).

Conclusions

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Results were correlated with several models found in the literature: three density-based models (Chrstil, Bartle, and Méndez-Santiago–Teja models), and with two cubic EOS models, namely, the PR-EOS and the SRK-EOS, together with the conventional van der Waals mixing and combining rules. All fitted models were shown to be able to successfully correlate experimental solubility data.

The correlation models used in this work proved to be very helpful for the development of supercritical applications and processes that require the precise knowledge of artemisinin’s solubility in scCO₂. A simple procedure, introducing the effect of the experimental overall uncertainty, was suggested in order to provide more assurance for the selection of the operational (p, T) conditions to apply in the development of these supercritical processes. However and like most correlation models, they should be employed just in the experimental data range (i.e., for interpolation of results). Extrapolation for other regions, far from this range, can originate unreliable results.

Literature Cited
