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EXPERIMENTAL SOLUBILITY MEASUREMENT OF CEPHALEXIN IN SUPERCRITICAL CARBON DIOXIDE

Article Highlights
\begin{itemize}
  \item Solubility of cephalexin in supercritical carbon dioxide was measured in wide range of temperature and pressure
  \item Solubility of cephalexin was in range of $1.13 \times 10^{-5}$ to $4.89 \times 10^{-3}$ based on mole fraction
  \item Obtained solubilities were correlated using four different semi-empirical correlations
\end{itemize}

Abstract
In recent years, the use of supercritical carbon dioxide for different chemical processes, in particular particle micronization, has surprisingly increased. Knowing the substance solubility in supercritical solvent is a critical parameter during the particle size reduction processes. In this direction, solubility of cephalexin was measured in the supercritical carbon dioxide by changing the temperature and pressure between 308.15 and 338.15 K and from 16 to 40 MPa, respectively. The measured solubility of cephalexin in supercritical carbon dioxide was in the range of $1.13 \times 10^{-5}$ to $4.89 \times 10^{-3}$ based on the mole fraction at the different operational condition. Besides the experimentally measurement of cephalexin solubility, modeling of the results using four commonly used correlations, namely Mendez-Santiago and Teja (MST), Bartle, Kumar and Johnston and Chrastil models were utilized. The results revealed that the Chrastil model was the most accurate used semi-empirical correlation in the present study with the lowest average absolute relative deviation percent of (AARD) of 9.43%.

Keywords: solubility, cephalexin, supercritical carbon dioxide, semi-empirical correlation.

Using conventional pharmaceutical techniques such as emulsification and solvent evaporation introduces several disadvantages; in particular, the remaining residual organic solvent in the product reduces the final product quality [1]. The increasing health concerns about the presence of solvents such as methylene chloride in the products motivate the investigators and scientists to direct their research to finding replacements that are "environmentally benign" for the conventional solvents. In other words, the researchers around the world are trying to find a new kind of solvent which are green and highly efficient [2].

So, over the last thirty years, research has focused on supercritical carbon fluids (SCFs), especially carbon dioxide, as a replacement for the conventional solvents. The mild critical conditions of temperature and pressure of carbon dioxide ($\text{CO}_2$) compared with several other possible solvents makes it a good candidate for the supercritical based-technologies [3-6]. Generally, supercritical carbon dioxide ($\text{SC-CO}_2$)-based technologies seem efficient for the drug processing considering the aforementioned disadvantages of traditional pharmaceutical industries accompanied with the advantages of the SC-$\text{CO}_2$.

Among the different applications of the SC-$\text{CO}_2$, the precipitation of drug particles using supercritical and near SC-$\text{CO}_2$ both as a solvent and anti-solvent has been increasingly investigated, since it can be industrialized [7-12]. Common SC-$\text{CO}_2$ based-technologies for particle engineering are rapid expansion of supercritical fluid solutions (RESS), gas antisolvent...
(GAS), precipitation by compressed anti-solvent (PCA), etc. [13,14].

It should be highlighted that the crucial parameter that must be known during the equipment sizing is the solubility (one of the most important phase behavior parameters) of a compound in the SC-CO$_2$, to enable the designer to select the best pharmaceutical processing method and operational conditions. Often, the solubility of substances is a limiting factor during the particle size engineering processes [15]. In this regard, many research groups around the world have measured and reported solubility of different substances in SC-CO$_2$ at different temperatures and pressures and at the presence and absence of co-solvents [16-24].

However, experimental measurement is not always a feasible tool, i.e., due to a wide range of operational conditions including pressure and temperature and many possible substances, it is expensive and in some cases impossible to experimentally measure the equilibrium solubility of substances in the SCF. Thus, apart from the measurements of the solubility of substances, researchers have been focused on proposing accurate and simple correlations and models to correlate/estimate the solubilities of solids such as the pharmaceutical compounds in CO$_2$ [25-37].

The two most widely used methods for correlating the solubilities of solid substances in SC-CO$_2$ are equations of state (EoSs) and semi-empirical correlations. In some cases, using EoSs is not recommended since these methods needs several properties such as critical pressure and temperature, acentric factor, etc., that cannot be easily measured experimentally. Therefore, it would be necessary to use the predicted/estimated parameters, introducing errors into the obtained predicted solubilities.

Based on these facts, cephalexin solubility in SC-CO$_2$ was measured using a simple gravimetric method coupled with static method. To the best of our knowledge, no reported experimental data on the cephalexin solubility is reported. Since there are limited reports on the solubility on the active pharmaceutical ingredients (APIs) in the SCF [14], it seems applicable to measure the cephalexin solubility in the SC-CO$_2$ in a different temperatures and pressures.

Cephalexin (also called Cefalexin), an active pharmaceutical ingredient drug (API drug), is a semi-synthetic cephalosporin antibiotic intended for oral administration with the molecular formula of $\text{C}_{16}\text{H}_{17}\text{N}_{3}\text{O}_{4}\text{S}$ and molecular weight of 347.41 g/mol. Cephalexin, which is commonly found in monohydrate form, introduces a low water solubility of about 1 or 2 mg/mL. Cephalexin is commonly prescribed to cure different disease and disorders such as urinary tract infections, respiratory tract infections, and skin and soft tissue infections. Generally, due to a vast range of application, cephalexin is one of the most prescribed antibiotics around the world.

**EXPERIMENTAL**

**Material**

Cephalexin supplied by Alma Concept Company (France) was used as a model drug without any further purification as received. Before the main experiments, cephalexin was exposed to SC-CO$_2$ under the pressure and temperature of 40 Mpa and 308.15 K, respectively, for 3 h. Also, carbon dioxide (99.8% purity) was kindly supplied by Abughadareh Industrial Gas Company (Iran) was used as a solvent for all the measurements. Before and after each experiment, the cephalexin powder was heated up to 318.15 K in an oven (Behdad, Iran) overnight to ensure no presence of carbon dioxide in the sample.

**Laboratory apparatus**

In this investigation, a home-made apparatus rated for pressures of 60 MPa at 673 K equipped with a sapphire window was used to measure the solubility of model drug using a static method coupled with a gravimetric method [23,24,33-36]. The used apparatus in this study was the modified form of its last version used in the previous works [33]. The volume of the modified equilibrium cell was increased so that it can handle a larger amount of carbon dioxide. As a result, the capability of supercritical carbon dioxide to dissolve the model drug was increased, which led to reduction of the error of weighing the sample.

In other words, a higher volume of supercritical carbon dioxide at the desired pressure and temperature means a higher amount of solubilized solid, which enhances the accuracy of weighing the sample. In this regard, the volume of the equilibrium cell was enhanced to 50 cm$^3$. The used procedure of the measurements in this study was as follows: CO$_2$ was filled into the upper section of a displacer. The lower section of the displacer was filled by fresh water pressurized via a reciprocating manual pump (Haskel Pump, Burbank, USA). The pressure of displacer was indicated by a pressure gauge ranged up to 45 MPa in increments of 0.1 MPa (DEWIT).

After pressurizing to the desired value, CO$_2$ was allowed to flow into the homemade variable volume cell. The pressure of the equilibrium cell was monitored using WIKA type pressure indicator in the range...
of 0-40 MPa with precision of 0.01 MPa. A PT-100 resistance thermometer with precision of 1 K was used to control the temperature of the system at desire value using a PID controlling method. Also, the system pressure was maintained constant within ±0.5% of the desired value throughout the experiment. For each experiment, 1 g of pure model drug powder was compacted (with no additives) in a compactor instrument (Compactor, T555228, Mellat Mashin Sazi Company, Iran) under a pressure of 2 MPa, to change the powder into a 5 mm diameter tablet. After charging the sample into the equilibrium cell, the piston inside the cell was moved forward in order to reduce the available volume as much as possible. After that, the carbon dioxide was allowed to pass through the equilibrium cell while the outlet valve was open. After a few seconds, the outlet valve was closed, and the piston inside the equilibrium cell was moved backward to increase the volume to its maximum value of 50 cm³. Then, the system was pressurized to the desired value. This step was done to discharge the air from the equilibrium cell, which might affect the composition of supercritical carbon dioxide. During the experiments, compacted drug powder was held at constant desired pressure and temperature in contact with SC-CO₂ for about 2.5-3 h and the equilibrium cell was shaken in order to ensure the attainment of equilibrium. Finally, the equilibrium cell was suddenly depressurized to the ambient conditions and the remaining drug was weighed to 0.1 mg using a Sartorius BA110S Basic series balance. The potential error due to weighing was 2 wt.% since the typical mass of solute for each experiment was greater than 5 mg. Now by dividing the difference between the initial and final weight of solute the mole value of solubilized drug calculated. Then, the weight of used carbon dioxide in each experiment was obtained by using the density of carbon dioxide at the specific temperature and pressure reported by Yamini et al. [18], while the used volume of carbon dioxide for all the experiments was 50 cm³.

Similar to the previous stage, by dividing the weight of carbon dioxide to its molar mass, the used mole of carbon dioxide for each experiment calculated. Finally, the solubility of cephalexin calculated as:

\[ y = \frac{\text{moles of cephalexin}}{\text{moles of cephalexin} + \text{moles of carbon dioxide}} \]  

RESULTS AND DISCUSSION

The cephalexin solubility was measured at seven pressure values (16, 20, 24, 28, 32, 36 and 40 MPa) and four temperatures (308.15, 318.15, 328.15 and 338.15 K). For each data point, at least three independent measurements were performed and then the average of those measurements was reported as the solubility of that point. In addition, the statistical and error analysis revealed that measurements introduce a maximum percent relative standard deviation of ±7.5% during the solubility measurements.

In statistics, the value of the coefficient of the variation is generally called the relative standard deviation. The relative standard deviation has its own importance in the field of science and plays a vital role in the calculation and measurement process. In general, standard deviation is a measure of how precise the average is, that is, how well the individual numbers agree with each other. In total, lower relative standard deviation means higher repeatability capability of the measurements. Relative standard deviation is calculated by dividing the standard deviation of values by the average of the values (Eq. (2)):

\[ \text{Relative standard deviation (RSD)} = \frac{100 \times \text{Standard deviation}}{\text{Average of solubility at each point}} \]  

It must be noted that the accuracy of the used method (along to the application of pellet instead of drug powder) was previously examined by measuring the solubility of piroxicam (Table 1) [33]. Although the measured solubilities revealed a systematic lower measured solubility of piroxicam, the general average absolute relative deviation of 6.28% showed a rather good accuracy of the used method. So, it seems that although there is no direct mixing in the equilibrium cell, shaking of the system can compensate to some extent the shortage of direct mixing. In other words, due to no direct mixing of equilibrium cell content, it is possible to measure lower solubility than its real

<table>
<thead>
<tr>
<th>Pressure /MPa</th>
<th>Literature</th>
<th>This work</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.30</td>
<td>1.21</td>
</tr>
<tr>
<td>13</td>
<td>2.08</td>
<td>1.92</td>
</tr>
<tr>
<td>16</td>
<td>3.12</td>
<td>2.92</td>
</tr>
<tr>
<td>19</td>
<td>4.41</td>
<td>4.23</td>
</tr>
</tbody>
</table>
value. However, the prior examinations revealed that this method and settling time can lead to rather accurate measurements of the solubility.

In more details, the used procedure was validated in the previous work with a typical AARD error lower than 7% [33]. Also, using this established, validated and published method solubility of other pharmaceuticals including ceterizine [24], diclofenac acid [33], phenylephrine hydrochloride [36], sulindac [35], fluoxetine hydrochloride [34], mefenamic acid [23] were successfully measured.

The measured solubility data points of cephalixin have been reported in Table 2. Considering the solubility trend variation, one can find that cephalixin solubility shows a direct relation to pressure while a slightly more complex effect was obtained for temperature.

The obtained pressure pattern can be contributed to the phenomenon that the carbon dioxide pressure increases when the pressure enhances. Besides, the pressure enhancement decreases the mean distance between the CO₂ and solute molecules increases the specific interaction between the model drug and supercritical fluid molecules [38]. However, temperature introduces different effects, including variation of solute vapor pressure, density of SC-CO₂ and the interaction between the molecules in the fluid phase.

The obtained results revealed that when the pressures are below the crossover pressure (for the cephalixin 16–18 MPa), solvent densities significantly reduce as the temperature increases. However, above the crossover pressure, the solvent density is more independent of temperature, in which the solubility increases under the effect of higher solid vapor

### Table 2. The solubility of the cephalixin (mol solute/10⁵ mol CO₂) at different pressures and temperatures based on the mole fraction; Overall relative standard deviation: 7.5%

<table>
<thead>
<tr>
<th>Pressure, MPa</th>
<th>Solubility</th>
<th>Standard deviation</th>
<th>Relative standard deviation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T = 308.15 K</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.68</td>
<td>0.126</td>
<td>7.5</td>
</tr>
<tr>
<td>20</td>
<td>2.21</td>
<td>0.135</td>
<td>6.1</td>
</tr>
<tr>
<td>24</td>
<td>3.98</td>
<td>0.221</td>
<td>5.6</td>
</tr>
<tr>
<td>28</td>
<td>6.89</td>
<td>0.345</td>
<td>5.0</td>
</tr>
<tr>
<td>32</td>
<td>11.3</td>
<td>0.520</td>
<td>4.6</td>
</tr>
<tr>
<td>36</td>
<td>15.4</td>
<td>0.698</td>
<td>4.5</td>
</tr>
<tr>
<td>40</td>
<td>20.8</td>
<td>0.984</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>T = 318.15 K</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.42</td>
<td>0.108</td>
<td>7.5</td>
</tr>
<tr>
<td>20</td>
<td>3.87</td>
<td>0.169</td>
<td>4.4</td>
</tr>
<tr>
<td>24</td>
<td>9.31</td>
<td>0.365</td>
<td>3.9</td>
</tr>
<tr>
<td>28</td>
<td>18.7</td>
<td>0.875</td>
<td>4.7</td>
</tr>
<tr>
<td>32</td>
<td>36.5</td>
<td>0.112</td>
<td>3.1</td>
</tr>
<tr>
<td>36</td>
<td>52.3</td>
<td>0.387</td>
<td>7.4</td>
</tr>
<tr>
<td>40</td>
<td>73.2</td>
<td>0.552</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>T = 328.15 K</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.13</td>
<td>0.0850</td>
<td>7.5</td>
</tr>
<tr>
<td>20</td>
<td>5.21</td>
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<td>24</td>
<td>1.76</td>
<td>0.124</td>
<td>7.0</td>
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<td>28</td>
<td>41.1</td>
<td>2.89</td>
<td>7.0</td>
</tr>
<tr>
<td>32</td>
<td>74.5</td>
<td>4.58</td>
<td>6.1</td>
</tr>
<tr>
<td>36</td>
<td>131</td>
<td>9.89</td>
<td>7.5</td>
</tr>
<tr>
<td>40</td>
<td>179</td>
<td>11.9</td>
<td>6.6</td>
</tr>
<tr>
<td><strong>T = 338.15 K</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>5.54</td>
<td>0.235</td>
<td>4.2</td>
</tr>
<tr>
<td>24</td>
<td>25.4</td>
<td>0.987</td>
<td>3.9</td>
</tr>
<tr>
<td>28</td>
<td>72.1</td>
<td>4.25</td>
<td>5.9</td>
</tr>
<tr>
<td>32</td>
<td>154</td>
<td>8.88</td>
<td>5.8</td>
</tr>
<tr>
<td>36</td>
<td>301</td>
<td>10.3</td>
<td>3.4</td>
</tr>
<tr>
<td>40</td>
<td>489</td>
<td>22.2</td>
<td>4.5</td>
</tr>
</tbody>
</table>
pressure [38]. But, plotting the measured solubility data as a function of density, it is completely obvious that the crossover effect that has been observed in Figure 1 (solubility vs. pressure plot) is a density effect. In other words, if pressure replaced by density (see Figure 2), the solubility isotherms no longer cross each other. So, it can be concluded that within the pressure region investigated, there is still a monotonous increase of solubility. In addition, Foster et al. [39] reported that the reliability and consistency of experimental solubility data can be examined by the existence of a crossover pressure in solid-SCF systems.

In the second stage of this investigation, four different correlations were applied to model the obtained solubility data measured experimentally in this study (Table 3).

Table 3. The obtained fitting constants for four density based correlations

<table>
<thead>
<tr>
<th>Model</th>
<th>Constants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
</tr>
<tr>
<td>Bartle [28]</td>
<td>52.710</td>
</tr>
<tr>
<td>Mendez-Santiago-Teja [27]</td>
<td>27123</td>
</tr>
<tr>
<td>Kumar and Johnston [30]</td>
<td>26.35</td>
</tr>
<tr>
<td>Chrastil [29]</td>
<td>-17362</td>
</tr>
</tbody>
</table>

For the first stage of the modeling, the solubility of cephalexin was correlated using MST model as the functions of temperature, pressure and density of supercritical fluid. The general form of the MST model (Eq. 3) comprises of three adjustable parameters, which were calculated using a simple linear regression:

\[ T \ln \left( \frac{y \rho}{\rho_T} \right) = a + b(K^{-1})T(K) + c(K^{-1} m^3) \rho (kg m^{-3}) \]  

The regression results revealed a high capability of the MST model to accurately model the cephalexin solubility with an AARD of 11.5%. In addition, the extrapolative capability of the MST model was examined by a self-consistency test. The result of this test (Figure 3) not only shows a linear behavior of cephalexin solubility illustrated consistent measured solid solubility data at all experimental conditions, but also can be used to extrapolate the solubility of cephalexin.
In the second stage, the measured cephalexin solubility was correlated by the Bartle et al. model [28]:

$$\ln \left( \frac{y_p}{\rho_{ref}} \right) = a + \frac{b(K)}{T(K)} + c(kg^{-1} m^3)(\rho - \rho_{ref})$$  \hspace{1cm} (4)

where $a$, $b$ and $c$ are fitting parameters, $y$ is the solute solubility and $\rho$ is the density of carbon dioxide at a specific pressure and temperature modified by subtracting 700 kg m$^{-3}$ considering as the reference density, $\rho_{ref}$.

In this regard, using the least-squares regression method and plotting $\ln(y_p/\rho_{ref})$ against density, leads to a straight line which parameter of $c$ can be easily obtained from it. Theoretically in this stage, according to the Bartle et al. model one expects to observe straight lines with similar slopes through the plots. But, the scattering nature of the experimental measurements leads to different slopes makes to use average of these slope values for the rest of modeling procedure. Then, by using the average value of $c$ and solubility data values of $a$ and $b$ for the Bartle et al. model can be obtained by another data regression [28]. The obtained results graphically demonstrated in Figure 4 revealed that using the Bartle et al. model leads to an AARD of 10.7%.

It should be mentioned is that the fitting parameter of $b$ in the Bartle et al. model is a parameter that one can roughly obtain heat of sublimation using the following equation [40]:

$$\Delta H_{sub} = -Rb$$  \hspace{1cm} (5)

where $R$ is the gas universal constant. Finally, the measured solubility of cephalexin was correlated with the aid of two other semi-empirical correlations of Chrastil [29] and KJ [30].

The Chrastil correlation was based on this assumption that the solute molecules surrounded by $c$ molecules of a solvent form a solute-solvent complex. In other words, in the Chrastil model (Eq. (6)), the fitting parameter $c$ indicates the number of solvent molecules surrounding the solute molecule:
\[ \ln S = a + b(K) / T(K) + c \ln \rho \]  

where \( a, b \) and \( c \) are the fitting parameters and \( S \) is the solute solubility in kg m\(^{-3}\). The \( b \) parameter can be utilized to estimate the solute heat of sublimation \( (\Delta H_{\text{sub}} = -Rb) \).

Also, the K-J model proposed in 1988 (see Eq. (7)) is:

\[ \ln y = a + b(K) / T(K) + c(m^3 \text{ kmol}^{-1})\rho(m^3 \text{ kmol}) \]  

The fitting parameters of this correlation can be easily obtained by a simple data regression. In details, in the first step, the logarithm of the solute solubility data was plotted versus density of carbon dioxide in for all isotherms. Then, the slopes of the curves were calculated by passing a linear curve. The average of each slope was used for the rest of calculations. In other words, by plotting \( \ln y - \text{average} \rho \) against \( T^{-1} \), \( a \) and \( b \) can be obtained and now it is possible to correlate the solubility of cephalexin (Table 3).

In total, similar to the previous sections, using a simple curve fitting leads to find the fitting parameters of these two correlations reported in the Table 3. In addition, for better representation, the obtained results for the K-J model shown in Figure 5 revealed a rather good agreement between the experimental and correlated solubilities. The obtained results revealed that the Chrastil and K-J models lead to AARD of 9.43 and 10.8%, respectively which Chrastil model leads to the lowest AARD among the examined correlation in this study.

We finally note that although a rather good correlation capability of used semi-empirical models are observed, the self-consistency test results (Figure 4) revealed a deviation from the linear behavior of these correlations. This observed deviation can possibly relate to the fact that at the higher pressures which the density of the of compressed carbon dioxide amounts to a value of 972.3 kg m\(^{-3}\), which is not so far away from water at ambient conditions, can lead to a phenomenon called “squeezing out”. In other words, at higher pressure and liquid-like densities, the effect of “squeezing out”, that is a retrograde solubility, can often be observed leads to this fact that the density-based models do no longer work willingly in that regions. This phenomenon was reported by Kurnik and Reid [41] while further similar behavior was observed by Kraska et al. [42] for \( \beta \)-carotene solubility. They have described this observed trend based on this fact that the deviation of the experimental data at pressures above 125 MPa can be due to a special isomerization occurred by an enrichment of cis-isomers in the solution while the all-trans \( \beta \)-carotene is squeezed out of the solution and crystallizes.

CONCLUSIONS

Solubility of cephalexin in supercritical carbon dioxide at different temperatures and pressures was measured experimentally using a static method coupled with gravimetric method. The measurements were applied in the temperature and pressure range...
of 308.15 to 338.15 K and 16 to 40 MPa, respectively. The solubility measurements revealed that the solubility of the cephalexin ranged between $1.13 \times 10^{-5}$ to $4.89 \times 10^{-3}$ (based on the mole fraction) at the different operational conditions. The obtained results that an increase in pressure increases the solubility. However, a complex behavior of temperature effect on the solubility was observed. In other words, the obtained results revealed that the cephalexin-SC-CO$_2$ system shows a crossover pressure of about 16 to 18 MPa. In addition, the possible mechanisms were discussed in details. Finally, the measured solubility data were correlated using four semi-empirical density based correlations, namely Mendez-Santiago and Teja (MST), Bartle, Kumar and Johnston, and Chrastil models with AARD of 11.5, 10.7, 10.8 and 9.43%, respectively. Finally, it was found that at higher temperatures, more deviation was observed in the solubility data correlation, which was related to the phenomenon of “squeezing out”.

REFERENCES

Prethodnih godina naglo je poraslo interesovanje za upotrebu superkritičnog ugljen dioksida u raznim hemijskim procesima koji se koriste za mikronizaciju čestica. Poznanje rastvorljivosti odgovarajuće supstance u superkritičnom rastvaraču je vrlo važno za procese usitnjavanja čestica. Zbog toga je ispitana rastvorljivost cefaleksina u superkritičnom ugljen-dioksidu pri promeni temperature od 308.15 do 338.15 K i pri promeni pritiska od 16 do 40 MPa. Za ove operacione uslove je izmerena rastvorljivost u opsegu od 1,13×10⁻⁵ do 4,89×10⁻³ izražena u molskim frakcijama. Osim eksperimentalnog merenja rastvorljivosti cefaleksina, izvršeno je modelovanje pomoću poznatih korelacija, i to: Mendez-Santjago i Teja (MST), Bartle-Kumar-Džonstona i Črustila. Rezultati pokazuju da je Črustilov model najtačniji semi-empirijski korelacijski model sa najmanjom srednjom apsolutnom relativnom devijacijom od 9,43%.

Ključne reči: rastvorljivost, cefaleksin, superkritičan ugljen-dioksid, semi-empirijska korelacija.