Solubility of the Ketoconazole (an Antifungal Drug) in Supercritical Carbon Dioxide and Menthol as a Cosolvent (Ternary System): Experimental Data and Empirical correlations

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Abstract
One of the main steps in choosing the drug nanoparticle production processes by supercritical carbon dioxide (SC-CO$_2$) is determining the solubility of the solid solute. For this purpose, the solubility of Ketoconazole (KTZ) in the SC-CO$_2$, binary system, as well as in the SC-CO$_2$-menthol (cosolvent), ternary system, was measured at 308–338 K and 12-30 MPa using the static analysis method. The KTZ solubility in the SC-CO$_2$ ranged between 1.70×10$^{-6}$ and 8.02×10$^{-4}$, while drug solubility in the SC-CO$_2$ with cosolvent varied from 2.7×10$^{-5}$ to 1.96×10$^{-4}$. This difference indicated the significant effect of menthol cosolvent on KTZ solubility in the SC-CO$_2$. Moreover, KTZ solubilities in the two systems were correlated by several empirical and semiempirical models. Among them, Sodeifian et al., Bian et al., MST, and Bartle et al. models can more accurately correlate experimental data for the binary system than other used models. Also, the Sodeifian and Sajadian model well fitted the solubility data of the ternary system with AARD, % = 6.45, $R_{adj}$ = 0.995.

Keywords: Ketoconazole, Menthol, Solubility, Ternary system, Modeling

1. Introduction
Serious fungal infections can increase due to the development of the human immunodeficiency virus (HIV), anti-cancer chemotherapy, and/or the greater utilization of the immuno-suppressive treatments in transplanting the organs. Ketoconazole (KTZ) is mainly applied as a synthetic imidazole antifungal drug to treat fungal infections in different forms (oral tablets, topical creams, and gels). It has been applied in immunocompromised patients and advanced prostatic carcinoma. KTZ has very low solubility (17 µg/ml) in the water and higher penetrability; therefore, it has been considered as a class II drug in the biopharmaceutics classification system (BCS). Improving the solubility of pharmaceutical compounds is a challenging subject as it can significantly reduce the oral bioavailability and, thus, the therapeutic efficacy of drugs.

Reducing particles' size and hence increasing the available surface area can enhance the solubility and bioavailability of pharmaceutical compounds with lower water solubility. Therefore, researchers have applied different processes (such as high-pressure homogenization, evaporation, milling, and sublimation) to reduce particle size in the pharmaceutical industry. Meanwhile, supercritical fluid (SCF) technology has received much attention in medicine to decrease the size of the particles, hence, increasing their dissolution rate and bioactivity. According to studies conducted in this field, the application of supercritical solution methods in particle formation has rapidly expanded. The solubility of drugs in SCFs should be experimentally measured for designing pharmaceutical processes.

Numerous investigators have demonstrated that solute solubility in the SCFs can be substantially improved with the addition of cosolvents (polar or non-polar). measured the solubility of o- and m-hydroxy-benzoic acid in acetone-SC-CO2 and methanol-SC-CO2 binary mixtures at the temperature range of 318-328 K and the pressure range of 90-200 bar using a continual flow apparatus. Their results indicated that the addition of little amounts of the cosolvents to SC-CO2 largely enhanced o- and m-hydroxy-benzoic acid
solubility. Huang et al.\textsuperscript{11} evaluated the equilibrium mole fraction of aspirin in SC-CO\textsubscript{2} with and without acetone cosolvent. Their results showed that acetone cosolvent could cause a 5-fold increase in aspirin solubility. Also, Koga et al.\textsuperscript{9} investigated influences of cosolvents (octane & ethanol) on the solubility of fatty acids, stearic acid, and stearyl alcohol in SC-CO\textsubscript{2} using a flow-type apparatus and showed the higher effectiveness of ethanol on the solubilities of fatty acids than octane. Hosseini et al.\textsuperscript{12} determined the solubility of clozapine and lamotrigine in SC-CO\textsubscript{2} with menthol cosolvent at the temperature range of 313-323 K and the pressure range of 123-337 bar. The applied cosolvent enhanced the solubility of both solutes in SC-CO\textsubscript{2}. Consequently, the solubility of numerous compounds has been experimentally determined in the SCFs\textsuperscript{13-20}. However, the measurement of the solubility of drugs in the SCFs under diverse pressure and temperature conditions is costly and laborious. In this regard, thermodynamic models have been developed to decrease the number of required experimental measurements. Compared to the other SCFs, SC-CO\textsubscript{2} has been widely employed in SCF processes due to its special thermodynamic and heat transfer properties. Additionally, CO\textsubscript{2} is non-toxic, non-flammable, cost-effective, abundant at high levels of purity, and environmentally-friendly with comparatively lower critical pressures and temperatures (7.38 MPa & 304.1 K)\textsuperscript{22-27}. Several models have been applied to correlate and predict solids solubility at supercritical conditions, among which empirical and semiempirical methods\textsuperscript{28-34}, equations of state (EoS) (including cubic and non-cubic models)\textsuperscript{35-43}, intelligent computational techniques (e.g. artificial neural networks (ANN) and least square support vector machine (LS-SVM) networks), and combination of grey wolf optimizer and support vector machines (GWO-SVM) networks\textsuperscript{27,44} can be mentioned. Some characteristics such as acentric factor, and molar volume, as well as the solid vapor pressures, are essential for the calculations of EoS based models. These parameters are, however, unavailable and thus must be estimated by the group contribution techniques leading to attenuated accuracy. To overcome this drawback, several
researchers have developed different empirical and semiempirical models to correlate the solubility data\textsuperscript{45-52}.  
In this study, a static analysis procedure was employed to determine the solubility of KTZ in SC-CO$_2$ at different temperature and pressure conditions with and without cosolvent. The solubility of KTZ in the SC-CO$_2$ with cosolvent has not been experimentally measured so far. Moreover, drug solubility in the SC-CO$_2$ (i.e., the binary system) was correlated by ten semi-empirical models, including Chrastil\textsuperscript{28}, Sparks \textit{et al}.\textsuperscript{34}, Bian \textit{et al}.\textsuperscript{41}, Bartle \textit{et al}.\textsuperscript{50}, MST\textsuperscript{32}, Kumar-Johnston\textsuperscript{29}, Jouyban \textit{et al}.\textsuperscript{33}, as well as Sodeifian \textit{et al}.\textsuperscript{14}, models. Consequently, MST\textsuperscript{32}, González \textit{et al}.\textsuperscript{51}, Soltani-Mazloumi\textsuperscript{48}, and Sodeifian-Sajadian\textsuperscript{53} models were applied to fit the solubility data of KTZ in the ternary system. Finally, the ability of different models was investigated in terms of three statistical measures: $AARD$, $\%$, and $R_{adj}$.  

\textbf{Experimental  

2.1. Materials  

In this work, Fadak Company (Kashan: Iran) provided carbon dioxide (CAS Number 124-38-9) with the purity of 99.99\%. KTZ with the purity of 99\% (CAS Number 65277-42-1) was provided by Arasto Pharmaceutical Company (Tehran, Iran). The above materials were applied with no additional treatment. Consequently, menthol with the purity (Ph Eur) of 99.0\% (CAS Number 2216-51-5) and methanol (GC) at the purity level of 99\% (CAS Number 67-56-1) were purchased from Merck (German). Tables 1 presents the structures and physicochemical features of KTZ.
Table 1.
The utilized solute structure and the respective physico-chemical features (M<sub>w</sub>: Molecular weight, T<sub>m</sub>: melting point, λ<sub>max</sub>: λ with maximum absorbance).

| Compound         | Formula       | Structure          | M<sub>w</sub> (g/mol) | CAS Number | T<sub>m</sub> (K) | λ<sub>max</sub> (nm) |
|------------------|---------------|--------------------|------------------------|------------|-----------------|---------------------|
| Ketoconazole     | C<sub>26</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub> | ![Structure](image) | 531                    | 65277-42-1 | 423 ± 2         | 243                 |
| L-Menthol        | C<sub>10</sub>H<sub>20</sub>O           |                    | 156.26                 | 2216-51-5  | 314-317         |                     |
| Carbon dioxide   | CO<sub>2</sub> |                    | 44.01                  | 124-38-9   |                 |                     |

2.2. Experimental apparatus

Figure 1 shows the laboratory setup used for determining solubility data of KTZ in SC-CO<sub>2</sub> with/without cosolvent (static method). The experimental setup was completely explained in our previous paper<sup>53</sup>. It includes a carbon dioxide tank, filter, refrigerator unit, reciprocating pump equipped with air compressor for supplying driving force, solubility cells, pressure gauge, digital pressure transmitter, digital thermometer, oven, microliter valve, sample collector, flow meter, 1/8" piping, and connections. Pressure quantities were recorded at the accuracy of ± 0.1 MPa using both the pressure gauge (WIKA, Germany, Code EN 837-1) and pressure transmitter. To maintain the experimental temperature, the equilibrium cell was located in a precise oven (Froilabo Model, AE-60, France), which could retain the temperature within ± 0.1 K.
The amount of menthol and drug in saturator cell 1 (S1) and saturator cell 2 (S2) were 5 and 2 g, respectively. A magnetic stirrer (100 rpm) was applied to accelerate the equilibration and improve saturation of the particles in cells. The sintered filter was put on the top of the column to prevent the escape of menthol particles (as either powder or liquid droplets). In this research, the equilibrium time was considered 60 min (as determined by preliminary experiments). At the end of static time, 600 ± 0.6 μL of the saturated SC-CO₂ was depressurized into the collection vial containing 5 ml methanol. Eventually, the loop was washed with the solvent collected in the collection vial, and the final volume of the solution was adjusted to 5 mL ± 0.6%. It should be noted that the experiments were carried out in triplicates. Consequently, the solubility of KTZ was determined by measuring the absorbance at λₘₐₓ (220 nm) on the UNICO-4802 UV-Vis spectro-photometer with 1-cm pass length quartz cells. Finally, the calibration curve (with regression coefficient 0.996) was applied to obtain the medicine concentrations in the collection vial.

As presented in Tables 2 and 3, solubilities of KTZ (in the equilibrium mole fraction of the solute (y) and the grams of solute (S) per liter of SC-CO₂ with/without cosolvent) were evaluated at the pressure range of 12-30 MPa and temperature range of 308-338 K. Finally, Span–Wagner equation was used to obtain the CO₂ density.

3. Result and discussion

3.1. Binary system

In our previous study, the reliability of the solubility setup was evaluated by determining the solubility of naphthalene and alpha-tocopherol in SC-CO₂ at different pressures and temperatures and comparing them with the corresponding data in the literature. In general, the authors systematically check and calibrate the device before testing naphthalene and alpha-tocopherol solubilities in SC-CO₂.
It should be mentioned that the mole fraction and solubility ($S(g/L)$) of KTZ in SC-CO$_2$ were measured at different temperature and pressure conditions (Table 2). Each experimental data was measured in triplicate to enhance the data reliability. The relative standard uncertainty of the solubility data was below 0.05. The relative standard uncertainty ($U_s$) can be calculated by the following equation:

$$U_s = \frac{S(y_k)}{\bar{y}}$$  \hspace{1cm} (1)

$$S(y) = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \bar{y})^2}{n-1}}$$  \hspace{1cm} (2)
Table 2. The experimental data of KTZ solubility in SC-CO\textsubscript{2} based on distinct conditions (The experimental standard deviation and the experimental standard deviation of the mean (SD) were obtained by $S(y_j) = \sqrt{\frac{\sum (y_j - \bar{y})^2}{n-1}}$ and $SD(\bar{y}) = \frac{S(y_j)}{\sqrt{n}}$ respectively. $n$ is the number of times each experimental data was measured ($n$=3, in this work). Expanded uncertainty is $U = k \times u_{combined}$ and the relative combined standard uncertainty is defined as $u_{combined}/\bar{y} = \frac{\sum P_i u(x_i) / x_i}{\sum P_i}$ in which $u(x_i)/x_i$ is the relative standard uncertainty of each input estimate ($x_i$) and $P_i$ is known positive or negative number having negligible uncertainties. $y_2$ and $S$ are mole fraction of solute in binary system and solubility of solute in SC-CO\textsubscript{2}, respectively.

| Temperature * (K) | Pressure * (MPa) | Density * (kg/m$^3$) | $y_2 \times 10^5$ (Mole Fraction) | Standard deviation of the mean, SD($\bar{y}$) × 10$^5$ | Expanded uncertainty of mole fraction (10$^2$ U) | $S$ (Solubility (g/l)) |
|-------------------|------------------|----------------------|----------------------------------|-----------------------------------------------|---------------------------------------------|---------------------|
| 308               | 12               | 768.42               | 0.17                             | 0.001                                         | 0.008                                       | 0.016               |
|                   | 15               | 816.06               | 0.34                             | 0.003                                         | 0.016                                       | 0.034               |
|                   | 18               | 848.87               | 0.44                             | 0.017                                         | 0.039                                       | 0.045               |
|                   | 21               | 874.4                | 0.62                             | 0.017                                         | 0.044                                       | 0.066               |
|                   | 24               | 895.54               | 0.80                             | 0.034                                         | 0.077                                       | 0.087               |
|                   | 27               | 913.69               | 0.94                             | 0.017                                         | 0.054                                       | 0.104               |
|                   | 30               | 929.68               | 1.09                             | 0.051                                         | 0.114                                       | 0.122               |
| 318               | 12               | 659.73               | 0.07                             | 0.003                                         | 0.007                                       | 0.006               |
|                   | 15               | 743.17               | 0.32                             | 0.010                                         | 0.027                                       | 0.036               |
|                   | 18               | 790.18               | 0.85                             | 0.034                                         | 0.079                                       | 0.081               |
|                   | 21               | 823.7                | 1.31                             | 0.035                                         | 0.090                                       | 0.130               |
|                   | 24               | 850.1                | 1.68                             | 0.069                                         | 0.157                                       | 0.173               |
|                   | 27               | 872.04               | 2.11                             | 0.035                                         | 0.113                                       | 0.222               |
|                   | 30               | 890.92               | 2.59                             | 0.086                                         | 0.207                                       | 0.279               |
| 328               | 12               | 506.85               | 0.04                             | 0.001                                         | 0.003                                       | 0.003               |
|                   | 15               | 654.94               | 0.30                             | 0.002                                         | 0.015                                       | 0.026               |
|                   | 18               | 724.13               | 0.98                             | 0.035                                         | 0.082                                       | 0.086               |
|                   | 21               | 768.74               | 1.82                             | 0.052                                         | 0.131                                       | 0.169               |
|                   | 24               | 801.92               | 2.76                             | 0.050                                         | 0.160                                       | 0.267               |
|                   | 27               | 828.51               | 4.02                             | 0.087                                         | 0.247                                       | 0.402               |
|                   | 30               | 850.83               | 4.81                             | 0.068                                         | 0.252                                       | 0.494               |
| 338               | 12               | 384.17               | 0.02                             | 0.0006                                        | 0.001                                       | 0.001               |
|                   | 15               | 555.23               | 0.22                             | 0.010                                         | 0.023                                       | 0.015               |
|                   | 18               | 651.18               | 0.90                             | 0.017                                         | 0.056                                       | 0.077               |
Standard uncertainty $u$ are $u(T) = 0.1$ K; $u(p) = 1$ bar. Also, the relative standard uncertainties are obtained below 0.05 for mole fractions and solubilities. The value of the coverage factor $k=2$ was chosen on the basis of the level of confidence of approximately 95 percent.

Data from the Span–Wagner equation of state [62].

Table 3. The experimental data of KTZ solubility in SC-CO$_2$ – menthol based on distinct conditions.

$y_3$, $y_2$ and $e$ are mole fraction of menthol, mole fraction of solute in ternary system and cosolvent effect, respectively. The experimental standard deviation of the mean (SD) were obtained by $SD(\bar{y}) = \frac{\sum y_i}{\sqrt{n}}$. $n$ is the number of times each experimental data was measured ($n=3$, in this work). Expanded uncertainty is $U = k \times u_{\text{combined}}$ and the relative combined standard uncertainty is defined as $u_{\text{combined}} / y = \sqrt{\sum_{i=1}^{n} P_i u(x_i) / x_i y}$ in which $u(x_i)$/$x_i$ is the relative standard uncertainty of each input estimate ($x_i$) and $P_i$ is known positive or negative number having negligible uncertainties.

| Temperature * (K) | Pressure * (MPa) | Menthol | Ternary | $y_3 \times 10^4$ (Mole Fraction) | $y_2 \times 10^4$ (Mole Fraction) | Standard deviation of the mean, SD ($\bar{y} \times 10^4$) | Expanded uncertainty of mole fraction ($10^4 U$) | $e$ (cosolvent effect) |
|-------------------|------------------|---------|---------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|----------------|
| 308               | 12               | 16.40   | 0.27    | 0.03                          | 0.014                         | 16.1                          | 9.7                           |
| 15                | 17.32            | 0.38    | 0.001   | 0.017                         | 9.4                           |
| 18                | 18.69            | 0.43    | 0.003   | 0.020                         | 9.4                           |
| 21                | 19.43            | 0.46    | 0.005   | 0.022                         | 9.7                           |
| 24                | 20.43            | 0.54    | 0.003   | 0.024                         | 6.8                           |
| 27                | 22.17            | 0.59    | 0.002   | 0.026                         | 5.3                           |
| 30                | 23.63            | 0.62    | 0.008   | 0.032                         | 4.9                           |
| 318               | 12               | 14.70   | 0.21    | 0.001                         | 0.010                         | 30.6                          | 12.3                          |
| 15                | 16.32            | 0.39    | 0.003   | 0.019                         | 11.1                          |
| 18                | 17.34            | 0.53    | 0.008   | 0.029                         | 7.7                           |
| 21                | 19.42            | 0.69    | 0.003   | 0.031                         | 5.2                           |
| 24                | 21.09            | 0.87    | 0.003   | 0.039                         | 4.0                           |
| 27                | 24.34            | 1.02    | 0.007   | 0.047                         | 3.3                           |
| 30                | 26.36            | 1.11    | 0.009   | 0.051                         | 3.3                           |
| 328               | 12               | 12.36   | 0.18    | 0.005                         | 0.013                         | 45.9                          | 16.6                          |
| 15                | 15.84            | 0.41    | 0.006   | 0.023                         | 11.5                          |
| 18                | 18.45            | 0.63    | 0.005   | 0.030                         | 11.5                          |
Standard uncertainty $u$ are $u(T) = 0.1$ K; $u(\rho) = 1$ bar. Also, the relative standard uncertainties are obtained below 0.05 for mole fractions and solubilities. The value of the coverage factor $k=2$ was chosen on the basis of the level of confidence of approximately 95 percent. 

\[b\]

Data from the Span–Wagner equation of state.$^{62}$

Where $S(y_k)$ and $n$ are the experimental standard deviation and the number of measurements of each experimental data ($n=3$, in this work), respectively.

| Temperature | $y_k$ | $S$ (g/ L) | $n$ | $y_k$ | $S$ (g/ L) |
|-------------|-------|------------|-----|-------|------------|
| 21          | 19.94 | 0.90       | 0.008 | 0.043 | 5.9        |
| 24          | 22.34 | 1.12       | 0.004 | 0.050 | 3.9        |
| 27          | 26.34 | 1.31       | 0.009 | 0.060 | 3.5        |
| 30          | 29.70 | 1.65       | 0.017 | 0.080 | 2.9        |
| 338         | 12    | 12.09      | 0.12  | 0.003 | 0.008      | 61.2      |
| 15          | 16.12 | 0.45       | 0.001 | 0.020 | 34.4       |
| 18          | 19.18 | 0.76       | 0.003 | 0.034 | 11.6       |
| 21          | 25.33 | 1.01       | 0.015 | 0.054 | 5.5        |
| 24          | 24.59 | 1.34       | 0.020 | 0.072 | 3.7        |
| 27          | 30.82 | 1.70       | 0.017 | 0.082 | 2.8        |
| 30          | 32.87 | 1.96       | 0.025 | 0.100 | 2.4        |

$^a$ Data from the Span–Wagner equation of state.$^{62}$

Where $S(y_k)$ and $n$ are the experimental standard deviation and the number of measurements of each experimental data ($n=3$, in this work), respectively.

$y$ and $S$ (g/ L) values respectively ranged between $1.70 \times 10^{-6}$ and $8.02 \times 10^{-4}$, and 0.016 and 0.784. Finally, the greatest and least values of KTZ solubility were observed at (338 K, 30 MPa) and (338 K, 12 MPa), respectively.

Figure 2a shows an increase in the solubility of KTZ with pressure increment at each isotherm. An enhancement in the density also increased the solubility at the elevated pressures. Generally, SC-$\text{CO}_2$ density and solute vapor pressure are the two key factors contributing to the solubility of the solute in SC-$\text{CO}_2$. The solubility showed an ascending trend with increasing density and solute vapor pressure. At pressures below the crossover region, where the influence of increased solvent density on the solute solubility dominates over decreased solute vapor pressure, the solid solute exhibited higher solubility at lower temperatures rather than higher ones. At the top of the crossover region, when temperature increased, the solubility incremented more rapidly with pressure enhancement, which might be due to the competing effects of the reduction of SC-$\text{CO}_2$ density and the increase of solute vapor pressure.
Figure 2a presents a pressure range of 19-20 MPa that was considered as the crossover pressure area for KTZ in the binary system. In general, several studies demonstrated that the solute vapor pressure and SC-CO\textsubscript{2} density are the major parameters below and top of the crossover area\textsuperscript{26,55-58}. Yamini and Moradi\textsuperscript{1} measured KTZ solubility in SC-CO\textsubscript{2} at 12.2–35.5 MPa and 308–348 K considering the absorbance at \(\lambda_{\text{max}}\) (220 nm). In the present work, the mole fraction of KTZ dissolved in SC-CO\textsubscript{2} (in pressure and temperature spans of 12-30 MPa and 308–338 K) was 1.70×10\textsuperscript{-5} and 8.02×10\textsuperscript{-4}. Their solubility data at this condition ranged from 1.6×10\textsuperscript{-5} to
8.16×10⁻⁴. The mean standard deviation between their experimental data and the present work was 2%. The effects of temperature and pressure on the solubility were the same for both works.

### 3.2. Ternary systems

Figure 2b and Table 3 report KTZ solubility in SC-CO₂ with cosolvent (menthol) under different pressures and temperatures. Accordingly, solubility based on the solute mole fraction (y) ranged from 2.7×10⁻⁵ to 1.96×10⁻⁴. Each experimental data was measured three times to enhance the reliability of the solubility data. Figure 2b presents an increase in KTZ solubility with the pressure increment at all isotherms. The increase of density with rising the pressure led to the more powerful solvation ability of SC-CO₂ and thus enhanced the solid solubility. The largest increment in solubility with rising pressure was observed at the highest temperature, which can be assigned to the impacts of the temperatures and pressures on the solvent density and pressure of the solute vapor. As stated previously, temperature influences the solvating power by two challenging factors: the solvent density and pressure of the solute vapor. Therefore, an increment in temperature will decrease the solubility below the crossover pressure area and also increased the solubility above the crossover pressure area. Finally, the crossover point in the ternary system was between 13 and 15 MPa.

In the ternary system (solute-SC-CO₂-cosolvent), the enhancement factor has been considered to study the cosolvent effect. This factor is the ratio of the obtained solubility of solute within the ternary system to that of the binary system. By investigating the presented results in Table 3, it can be found out that the solubility was increased by adding menthol to SC-CO₂. The cosolvent effect “e” was applied to better evaluate the solubility enhancement:

\[
e = \frac{y'_2(P, T, y_3)}{y_2(P, T)}
\] (3)
Table 3 presents the values of "e" in this study. The highest cosolvent effect was (61.2-fold) is related to the pressure of 12 MPa and a temperature of 338 K. Other researchers also reported the cosolvent effect in their studies. Hosseini et al.\textsuperscript{12}, compared the solubility of clozapine and lamotrigine in SC-CO\textsubscript{2} (with solid cosolvent (menthol)) with the cosolvent-free condition. The solubility of clozapine showed an approximate 56-fold enhancement while that of lamotrigine was increased almost 8 times. Sabet \textit{et al.} \textsuperscript{60} measured acetaminophen solubility in SC-CO\textsubscript{2} with and without menthol solid cosolvent under different temperatures and pressures. As shown by the results, menthol strongly augmented acetaminophen solubility by (8.27-fold). Gupta and Thakur\textsuperscript{61} investigated the solubility of phenytoin in SC-CO\textsubscript{2}. They concluded that solid solute solubility in SC-CO\textsubscript{2} is only 3 µmol/mol while its solubility increased to 1302 µmol/mol (at 45 °C and at 196 bar) in SC-CO\textsubscript{2} with menthol solid cosolvent. Notably, interactions between menthol and phenytoin resulted in a 400-fold solubility enhancement. Sodeifian and Sajadian\textsuperscript{10} determined the solubility of letrozole under different circumstances in SC-CO\textsubscript{2} with and without menthol. Solid co-solvent could increase letrozole solubility up to 7.1 folds compared to the binary system (without solid cosolvent).

In general, the increase in the solubility of solids in ternary systems (CO\textsubscript{2} +cosolvent) can be attributed to the increase in solvent density, dipole-dipole interactions, and also hydrogen bonding between the solute and the cosolvent\textsuperscript{62}. In this case, upon adding menthol to the cell, the density of the SCF enhanced, leading to an increment in the solubility. The polarity of SC-CO\textsubscript{2} can also be affected by the cosolvent. Menthol enhanced the solubility of KTZ in CO\textsubscript{2} due to the presence of a hydroxyl (polar) group and a hydrocarbon group (nonpolar) in the respective structures. As a result, it can be concluded that stronger attractive polar interaction and hydrogen bonding could lead to greater solubility. Also, by comparing values of $e$ in Table 3, it can be inferred that cosolvent effects decreased with the increment of the pressure, which is compatible with the published studies\textsuperscript{4-6,11}.
3.3. Correlation of the binary system

The present study considered ten semiempirical equations for correlating KTZ solubility in SC-CO₂, as listed in Table 4. Figure 3 depicts the outputs of the correlation at different temperatures. Then, statistical criteria were employed to investigate the abilities of semiempirical models. As a general rule, the more adjustable parameters lead to more accurate correlations. To provide a reliable accuracy criterion to compare the models with different numbers of adjustable parameters, AARD and $R_{adj}$ with the following equations were used:

$$\text{AARD} = \frac{1}{N} \sum_{i=1}^{N} \left| \frac{y_i - \hat{y}_i}{y_i} \right|$$

$$R_{adj}^2 = 1 - \frac{(1 - R^2)(N-1)}{N-p-1}$$
AARD, % = \frac{100}{N - Z} \sum_{i=1}^{N} \left[ \frac{y_{2,\text{calc}} - y_{2,\text{exp}}}{y_{2,\text{exp}}} \right],
(4)

So that \( Z \) represents the number of the adjustable variables for each model.

\[ R_{adj} = \sqrt{R^2 - (Q(1-R^2)/(N-Q-1))} \]
(5)

where \( N \) refers to the numbers of data points in each set. Moreover, \( Q \) stands for the numbers of the independent variables in each equation. \( R_{adj} \) can be used to compare models with different numbers of independent variables and \( R^2 \) represents the correlation coefficient.

\[ R^2 = 1 - \frac{SS_E}{SS_T} \]
(6)

\[ SS_T = \sum (y_{exp})^2 - \frac{(\sum y_{exp})^2}{N} \]
(7)

\[ SS_E = \sum (y_{exp} - y_{model})^2 \]
(8)

Where \( SS_E \) is the error of the sum of squares and \( SS_T \) is the total sum of squares.

Correlation outputs and optimal values of the parameters are presented in Table 5. The mean-values of AARD% for Chrastil, Sparks \textit{et al.}, K-J, Bian \textit{et al.}, Bartle \textit{et al.}, MST, Jouyban \textit{et al.}, and Sodeifian \textit{et al.}, models were 10.01, 11.52, 09.93, 09.22, 07.55, 09.61, 15.11 and 06.94%, respectively. According to the ANOVA results, it can be concluded that Bian \textit{et al.}, \((R_{adj} = 0.991)\), MST \((R_{adj} = 0.996)\), and Sodeifian \textit{et al.}, \((R_{adj} = 0.999)\) models could more accurately correlate KTZ solubility (Figure 3).

The energy term; that is, the temperature term coefficient in Chrastil, Sparks \textit{et al.}, and Bartle \textit{et al.}, models were considered to determine the heat of solvation (\( \Delta H_{sol} \)), the vaporization heat of the solute (\( \Delta H_{vap} \)), and total heat (\( \Delta H_{t} \)). The second tunable variables of Chrastil, Sparks \textit{et al.}, and Bartle \textit{et al.}, models were used to calculate \( \Delta H_{t} \) and \( \Delta H_{vap} \), respectively. Also, \( \Delta H_{sol} \) was calculated based on the difference between \( \Delta H_{vap} \) and \( \Delta H_{total} \). Based on Table 6, the enthalpy of KTZ dissolution in SC-CO\(_2\) and \( \Delta H_{total} \) were 99.32 and 101.70 kJ.mol\(^{-1}\), respectively. Also, \( \Delta H_{vap} \) was calculated by Bartle \textit{et al.}, as 121.80 kJ.mol\(^{-1}\). According to our
data, solvation and vaporization processes are endothermic and exothermic, respectively. The value of $\Delta H_{\text{vap}}$ was bigger than $\Delta H_{\text{total}}$. Due to differences between $\Delta H_{\text{total}}$ and $\Delta H_{\text{vap}}$ values, $\Delta H_{\text{sol}}$ values from different models were calculated -22.48 and -20.10 kJ.mol$^{-1}$.

Table 4.
A brief statement of the density-based models utilized in the present research ($c, \rho, T, P, P_{\text{ref}}, \rho_{\text{ref}}, y_2$ and $a_0-a_5$ are solubility of solute, density of SC-CO$_2$, temperature, pressure, reference pressure, reference density, mole fraction in binary system and adjustable parameters, respectively.

| Model          | Formula                                                                 |
|----------------|--------------------------------------------------------------------------|
| Chrastil [36]  | $c = \rho^a \exp\left(\frac{a_1}{T} + a_2\right)$                      |
| K-J[37]        | $\ln(y_2) = a_0 + a_1 \rho + \frac{a_2}{T}$                           |
| Bartle et al.[58], | $\ln\left(\frac{y_2 P}{P_{\text{ref}}}\right) = a_0 + a_1 + a_2(\rho - \rho_{\text{ref}})$ |
| MST[60]        | $T \ln(y_2 P) = a_0 + a_1 \rho + a_2 T$                                |
| Sparks et al.,[42] | $c^*_2 = \rho^{a_0} \rho^{a_1} \exp \left(\frac{a_2}{T} \right)$ |
| Bian et al.,[49] | $y_2 = \rho^{(a_0 + a_1 \rho)} \exp \left(\frac{a_2}{T} + \frac{a_3 \rho}{T} + a_4\right)$ |
| Jouyban et al.,[72] | $\ln y_2 = a_0 + a_1 \rho + a_2 \rho^2 + a_3 \rho T + \frac{a_4 T}{P} + a_5 \ln(\rho)$ |
| Sodeifian et al.,[20] | $\ln y_2 = a_0 + a_1 \frac{\rho^2}{T} + a_2 \ln(\rho T) + a_3 (\rho \ln \rho) + a_4 \rho \ln T + a_5 \frac{\ln \rho}{T}$ |

3.4. Correlation of the ternary system

The present research assessed the correlation of KTZ solubilities in SC-CO$_2$ with menthol by five semiempirical models (Table 7). Menthol solubility in SC-CO$_2$ was reported in previous works $^{53}$. The statistical criteria ($i.e., R_{\text{adj}}$ and AARD$\%$) were applied to examine the capability of the presented models. A genetic algorithm was also used to obtain adjustable parameters. Figure 4 and Table 8 present the compatibility of KTZ solubility data with the semiempirical results. The highest accuracy was offered by the Sodeifian and Sajadian model.
(AARD, % = 06.45, $R_{adj} = 0.995$), followed by those of González et al. (AARD, % = 07.51, $R_{adj} = 0.991$), MST (AARD, % = 08.97, $R_{adj} = 0.986$) and Soltani and Mazloumi (AARD, % = 07.09, $R_{adj} = 0.992$), respectively.

**Table 5.**
The correlation results of the KTZ – CO$_2$ system provided by semi-empirical models (AARD, $R_{adj}$ and $a_0$-$a_5$ are average absolute relative deviation, adjusted correlation coefficient and adjustable parameters, respectively).

| Model         | $a_0$   | $a_1$    | $a_2$    | $a_3$    | $a_4$ | $a_5$ | AARD% | $R_{adj}$ |
|---------------|--------|---------|---------|---------|------|------|-------|----------|
| Chrastil      | 11.107 | -11945.812 | -39.215 | -       | -    | -    | 10.01 | 0.990    |
| Sparks et al.,| 5.9141 | 2.3629  | 25.666  | -41.5872| -    | -    | 11.52 | 0.989    |
| K-J           | 16.75  | 0.0144  | -1273.9 | -       | -    | -    | 09.93 | 0.985    |
| Bian et al.,  | -4.0301| 0.0020  | -10553.8 | -2.2336 | -10.6230 | - | 09.22 | 0.991    |
| Bartle et al.,| 37.82  | -14650.1| 0.0175  | -       | -    | -    | 07.55 | 0.989    |
| MST           | -18858.47 | 245948.22 | 38.761 | -       | -    | -    | 09.61 | 0.996    |
| Jouyban et al.,| -56.512| -53.3345 | -0.0002 | 0.00007 | -1.5936 | 37.1537 | 15.11 | 0.989    |
| Sodeifian et al.,| -25.7435| -0.503 | 3.2028  | 0.0027  | 0.003600 | -1910.229 | 06.94 | 0.999    |

**Table 6.**
The vaporization ($\Delta H_{vap}$), approximated total ($\Delta H_{total}$), and solvation ($\Delta H_{solv}$) enthalpy for KTZ.

| Compound              | $\Delta H_{total}$ (kJ mol$^{-1}$) | $\Delta H_{vap}$ (kJ mol$^{-1}$)$^a$ | $\Delta H_{solv}$ (kJ mol$^{-1}$)$^d$ |
|-----------------------|----------------------------------|------------------------------------|-------------------------------------|
| Ketoconazole          | 99.32$^a$                        | 121.80                             | -22.48                              |
|                       | 105.09$^b$                       | 121.80                             | -16.71                              |

$^a$ Obtained from the Chrastil’s model.
$^b$ Obtained from the Bartle et al., model.
$^c$ Obtained from the Sparks et al., model.
$^d$ Obtained from the difference between the $\Delta H_{vap}$ and $\Delta H_{total}$.

**Table 7.**
A brief statement of the density-based models utilized in the present research ($\rho_1$, $T$, $P$, $P_{ref}$, $y'_2$, $y_3$ and $a_0$-$a_6$ are density of SC-CO$_2$, temperature, pressure, reference pressure, mole fraction in ternary system, mole fraction of cosolvent and adjustable parameters, respectively).

| Model                  | Formula                                                                 |
|------------------------|------------------------------------------------------------------------|
| MST [60]               | $T \ln \left( \frac{y'_2 P}{P_{ref}} \right) = a_0 + a_1 \rho_1 + a_2 T + a_3 y_3$ |
| Sodeifian-Sajadian [62] | $\ln(y'_2) = (a_0 + \frac{a_1 \rho_1}{T}) \ln(\rho_1) + a_2 \rho_1 + a_3 \ln(y_3 P)$ |
| González et al. [59]   | $\ln(y'_2) = a_0 \ln(\rho_2) + a_1 \ln(y_3) + \frac{a_2}{T} + a_3$ |
| Soltani-Mazloumi [56]  | $\ln(y'_2) = a_0 + \frac{a_1}{T} + \frac{a_2}{T} \rho_1 - a_3 \ln(P) + a_4 \ln(y_3 \rho_1 T)$ |
Table 8.
The correlation results of the KTZ–Menthol-CO$_2$ system provided by the semi empirical models (AARD, $R_{adj}$ and $a_0$-$a_6$ are average absolute relative deviation, adjusted correlation coefficient and adjustable parameters, respectively).

| Model                  | $a_0$      | $a_1$     | $a_2$     | $a_3$     | $a_4$ | AARD % | $R_{adj}$ |
|------------------------|------------|-----------|-----------|-----------|-------|--------|-----------|
| MST                    | -10884.4360 | 3.1002 | 21.7610 | 28.803 | -     | 8.97   | 0.986     |
| González et al.        | 2.902      | -0.657   | -4544.27 | -12.26  | -     | 7.51   | 0.991     |
| Sodeifian - Sajadian   | -2.852     | -1.0502  | 0.0339   | 0.153   | -     | 6.45   | 0.995     |
| Soltani-Mazloumi       | 10.489     | -8213.5  | 2.155    | 0.4203  | 0.2776 | 7.09   | 0.992     |

Conclusions

In this research, the KTZ solubility in SC-CO$_2$ (with and without menthol) was experimentally measured at the temperature range of 308-338 K and the pressure range of 12-30 MPa using spectrophotometric analysis. The tests were carried out in triplicates to enhance the reliability of the solubility data. Moreover, the mole fractions ($y$) and KTZ solubility ($S$ (g/L)) in SC-CO$_2$ (binary system) ranged between 0.016 and 0.784 and 1.70×10^{-6} and 8.02×10^{-4}, while the mole fractions of the drug in the SC-CO$_2$ with cosolvent (i.e., the ternary system) ranged in 2.7×10^{-5}-1.96×10^{-4}. Therefore, it can be concluded that the solubility increased in the presence of menthol. Several semi-empirical and empirical models were utilized for correlating experimental results of binary and ternary systems. Among them, Sodeifian et al. model managed to correlate the experimental data for the mentioned binary system at higher accuracy. In the case of the ternary system, the highest accuracy was provided by the Sodeifian and Sajadian model.

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Fig. 4. The experimental (points) and calculated (line) of KTZ solubility (ternary system) a. Sodeifian and Sajadian, b. Soltani-Mazloumi, c. González et al., and d. MST models.
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