Experimental solubility and thermodynamic modeling of empagliflozin in supercritical carbon dioxide

Gholamhossein Sodeifian1,2,3*, Chandrasekhar Garlapati4, Fariba Razmimanesh1,2,3 & Hassan Nateghi1,2,3

The solubility of empagliflozin in supercritical carbon dioxide was measured at temperatures (308 to 338 K) and pressures (12 to 27 MPa), for the first time. The measured solubility in terms of mole fraction ranged from $5.14 \times 10^{-6}$ to $25.9 \times 10^{-6}$. The cross over region was observed at 16.5 MPa. A new solubility model was derived to correlate the solubility data using solid–liquid equilibrium criteria combined with Wilson activity coefficient model at infinite dilution for the activity coefficient. The proposed model correlated the data with average absolute relative deviation (AARD) and Akaike’s information criterion (AICc), 7.22% and ~637.24, respectively. Further, the measured data was also correlated with 11 existing (three, five and six parameters empirical and semi-empirical) models and also with Redlich-Kwong equation of state (RKEoS) along with Kwak-Mansoori mixing rules (KMmr) model. Among density-based models, Bian et al., model was the best and corresponding AARD% was calculated 5.1. The RKEoS + KMmr was observed to correlate the data with 8.07% (corresponding AICc is ~635.79). Finally, total, sublimation and solvation enthalpies of empagliflozin were calculated.

List of symbols

| Symbol | Description |
|--------|-------------|
| A–D    | New model constants |
| $A_1$  | Alwi–Garlapati model constants |
| $A_2$  | Bartle model constants |
| $A_3$  | Bian model constants |
| $A_4$  | Chrastil model constants |
| $A_5$  | Garlapati–Madras model constants |
| $A_6$  | Kumar–Johnstone model constants |
| $A_7$  | Mahesh–Garlapati model constants |
| $A_8$  | Mendez–Teja model constants |
| $A_9$  | Sodeifian model constants |
| $A_{10}$ | Reformulated Chrastil model constants |
| $A_{11}$ | Tippana–Garlapati model constants |
| AARD   | Absolute average relative deviation |
| Adj.R² | Adjusted $R^2$ |
| AIC    | Akaike’s information criterion |
| $a_{ij}$ | EoS energy parameter |
| $b_{ij}$ | EoS volume correction |
| $C$    | Solubility in Chrastil model |
| $C_p$  | Heat capacity |
| EoS    | Equation of state |
| $H_{sol}$ | Solvation enthalpy |

1Department of Chemical Engineering, Faculty of Engineering, University of Kashan, Kashan 87317-53153, Iran. 2Laboratory of Supercritical Fluids and Nanotechnology, University of Kashan, Kashan 87317-53153, Iran. 3Modeling and Simulation Centre, Faculty of Engineering, University of Kashan, Kashan 87317-53153, Iran. 4Department of Chemical Engineering, Puducherry Technological University, Puducherry 605014, India. *email: sodeifian@kashanu.ac.ir


\[
\begin{align*}
H_{\text{sub}} & \quad \text{Sublimation enthalpy} \\
H_{\text{Total}} & \quad \text{Total enthalpy} \\
H^m & \quad \text{Melting enthalpy of the solute} \\
M_{\text{mcf}} & \quad \text{Molecular weight of supercritical fluid} \\
N & \quad \text{Number of data points} \\
P & \quad \text{Total pressure} \\
P_{\text{sub}} & \quad \text{Sublimation pressure} \\
R & \quad \text{Redlich–Kwong} \\
P_r & \quad \text{Critical pressure} \\
Q & \quad \text{Number of parameters of a model} \\
R & \quad \text{Universal gas constant} \\
R^2 & \quad \text{Square of correlation coefficient} \\
\text{RMSE} & \quad \text{Root mean square deviation} \\
\text{SSE} & \quad \text{Error sum of squares} \\
T & \quad \text{Temperature} \\
T_c & \quad \text{Critical temperature} \\
T_m & \quad \text{Melting temperature} \\
T_r & \quad \text{Reduced temperature} \\
y_2 & \quad \text{Solubility in molefraction} \\
\Delta & \quad \text{Difference} \\
\hat{\phi}^S_i & \quad \text{Fugacity coefficient of the pure substance at saturation} \\
\hat{\phi}^{\text{ScCO}_2}_i & \quad \text{Solute fugacity in supercritical carbon dioxide (ScCO}_2) \\
\alpha & \quad \text{Acentric factor} \\
\rho & \quad \text{Density} \\
\rho_r & \quad \text{Reduced density} \\
\kappa_{ij} & \quad \text{EoS mixing rule parameter} \\
l_{ij} & \quad \text{EoS mixing rule parameter} \\
\lambda_{12}, \lambda_{21} & \quad \text{Wilson model parameters} \\
\gamma_2^\infty & \quad \text{Infinite dilution activity coefficient} \\
\end{align*}
\]

**Greek symbols**

**Sub and superscripts**

exp \quad \text{Experimental} \\
cal \quad \text{Calculated} \\
1 \quad \text{Solvent (CO}_2) \\
2 \quad \text{Solute (drug)} \\
c \quad \text{Critical} \\
m \quad \text{Melting} \\
r \quad \text{Reduced}

Supercritical carbon dioxide (ScCO}_2) is a fluid above its critical point. It has physical properties (density, diffusivity, viscosity and surface tension) intermediate to that of gas and liquid\textsuperscript{1,2}. ScCO}_2 has been used as a solvent in various process applications, because it has gas like diffusivity and liquid like density with low viscosity and surface tension\textsuperscript{1,3–5}. The major applications are in drug particle micronization, food processing, textile dyeing, ceramic coating, extraction and many more\textsuperscript{4,6–12}. Although, several supercritical fluids are utilized as solvent in process industry, ScCO}_2 is the most desirable solvent\textsuperscript{8,13–17}. In general, phase equilibrium information is necessary to implement supercritical fluid technology (SFT)\textsuperscript{6,7,9}. The solubility is the basic information for the design and development of SFT. In literature, solubility of many drug solids in ScCO}_2 is readily available\textsuperscript{18–30}; however, the solubility of empagliflozin has not been reported, therefore in this work for the first time, its solubility in ScCO}_2 has been measured. This data may be used in the particle micronization process using ScCO}_2. The molecular formula of empagliflozin is C\textsubscript{23}H\textsubscript{27}ClO\textsubscript{7} and its molecular weight is 450.91. The chemical structure is shown in Fig. 1. 

**Empagliflozin** is an inhibitor of sodium-glucose co-transporter-2 (SGLT2), the transporters primarily responsible for the re-absorption of glucose in the kidney. Further, it is useful in reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease\textsuperscript{31}. Sufficient drug dosage is very essential for those treatments and this is achieved through a proper particle size. Therefore, the present study is quite useful in particle micronization using ScCO}_2. Solubility measurement at each desired condition is very cumbersome and hence, there is a great need to develop a model that correlates/predicts the solubility\textsuperscript{32}. Recent developments such as machine learning methods may be considered with the improvement of artificial intelligence prediction methods for the data correlation\textsuperscript{33–35}. However, in general, the solubility models are classified into five types; however, only three are user friendly, and they are equation of state, density-based and mathematical models\textsuperscript{36}. Directly or indirectly all of them are derived based on thermodynamic frame work. The derived models make use of the basic concepts related to phase equilibrium criteria (solid–gas or solid–liquid), solvent–solute association theory, dilute solution theory, solution theory and Wilson model or any other model\textsuperscript{37}. In fact, most of the literature models correlate the solubility of the solid solutes in ScCO}_2 quite well. A solid–gas equilibrium models need the
critical properties and vapour pressure of the solute, while these properties are rarely available in literature, due to this, the group contribution methods are commonly used. On the other hand, the solid–liquid equilibrium (SLE) criterion requires an appropriate model for activity coefficient calculation. A recent study reveals that SLE model in combination with Van Laar activity coefficient model can be a simple approach in model development, but this method resulted in an implicit expression in terms of mole fraction. Therefore, there is a need to develop an explicit solubility model and hence, this task is taken up in this work.

The main motives of this study were in two levels. In the first level, empagliflozin solubility in ScCO₂ was determined and in the second level, a new explicit solubility model was developed based on solid–liquid equilibrium criterion in combination with Wilson activity coefficient model for the activity coefficient calculation.

**Experimental Materials.** Gaseous CO₂ (purity > 99.9%) was obtained from Fadak company, Kashan (Iran), empagliflozin (CAS Number: 864070-44-0, purity > 99%) was purchased from Amin Pharma company, and dimethyl sulfoxide (DMSO, CAS No. 67-68-5, purity > 99%) was provided from Sigma Aldrich company. Table 1 indicates all the information about the chemicals utilized in this work.

**Experiment details.** The detailed discussion of the solubility apparatus and equilibrium cell has been presented in our earlier studies (Fig. 2). However, a brief description about the apparatus is presented in this section. This method may be classified as an isobaric-isothermal method. Each measurement was carried out with high precision and temperatures and pressures were controlled within ±0.1 K and ±0.1 MPa, respectively. For all measurement, 1 g of empagliflozin drug was used. As mentioned in our previous works, the equilibrium was observed within 60 min. After equilibrium, 600 µL saturated ScCO₂ sample was collected via 2-status 6-way port valve in a DMSO preloaded vial. After discharging 600 µL saturated ScCO₂, the port valve was washed with 1 ml DMSO. Thus, the total saturation solution was 5 ml. Each measurement was repeated thrice and their average values were reported. Mole fraction is obtained as follows:

\[ y_2 = \frac{n_{\text{drug}}}{n_{\text{drug}} + n_{\text{CO}_2}} \]  

where \( n_{\text{solute}} \) is the moles number of the drug, and \( n_{\text{CO}_2} \) is the moles number of \( \text{CO}_2 \) in the sampling loop.

Further, the above quantities are given as:

\[ n_{\text{solute}} = \frac{C_s \cdot V_s}{M_s} \]  
\[ n_{\text{CO}_2} = \frac{V_1 \cdot \rho}{M_{\text{CO}_2}} \]

where \( C_s \) is the drug concentration in saturated sample vial in g/L. The volume of the sampling loop and vial collection are \( V_s(L) = 600 \times 10^{-6} \text{ m}^3 \) and \( V_v(L) = 5 \times 10^{-3} \text{ m}^3 \), respectively. The \( M_s \) and \( M_{\text{CO}_2} \) are the molecular weight of drug and \( \text{CO}_2 \), respectively. Solubility is also described as

\[ S = \frac{C_s V_s}{V_1} \]

The relation between \( S \) and \( y_2 \) is

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| Compound        | Formula     | \( M_s \) (g/mol) | \( T_m \) (K) | \( \lambda_{\max} \) (nm) | CAS number   | Minimum purity by supplier |
|-----------------|-------------|-------------------|---------------|-------------------------|--------------|---------------------------|
| Empagliflozin   | C₂₃H₂₇ClO₇ | 450.9             | 426.1         | 276                     | 864070-44-0 | 99%                       |
| Carbon dioxide  | CO₂        | 44.01             |               |                         |              |                           |
| DMSO            | C₅H₇OS     | 78.13             |               |                         |              | 99%                       |

**Table 1.** Some physicochemical properties of the used materials.

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**Figure 1.** Empagliflozin chemical structure.
A UV–Visible spectrophotometer (Model UNICO-4802) and DMSO solvent were used for the measurement of empagliflozin solubility. The samples were analyzed at 276 nm.

**Existing and new models and their correlations**

In this section, the details of various solubility models are presented along with a new explicit solubility model.

**Existing models.**  

- **Alwi–Garlapati model (three parameters model)**[^43]: It is one of the latest models for the solubility correlation. It is mathematically explained as

  \[ S = \frac{\rho M_s y_2}{M_{CO_2} (1 - y_2)} \]  

  (5)

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- **Bartle et al., model (three parameters model)**[^44]: It is an empirical model and mathematically stated as:

  \[ \ln \left( \frac{y_2 P}{P_{ref}} \right) = A_2 + \frac{B_2}{T} + C_2 (\rho - \rho_{ref}) \]  

  (7)

  where \( A_2 - C_2 \) are model constants. From parameter \( B_2 \), one can estimate sublimation enthalpy using the relation, \( \Delta_{sub}H = -B_2 R \), in which \( R \) is universal gas constant.

- **Bian et al., model (five parameters model)**[^45]: It is an empirical model and mathematically formulated as:

  \[ y_2 = \rho_1^{(A_3 + B_3 \rho_1)} \exp \left( C_3 / T + D_3 \rho_1 / T + E_3 \right) \]  

  (8)

  where \( A_3 - E_3 \) are model constants.

- **Chrastil model (three parameters model)**[^46]: It is a semi-empirical model and mathematically stated as:

  \[ c_2 = \rho_1^\kappa \exp \left( A_4 + \frac{B_4}{T} \right) \]  

  (9)

  where \( \kappa, A_4 \) and \( B_4 \) are model constants.

  In terms of mole fraction, it is written as[^47]:

Figure 2. Experimental setup for solubility measurement, E1—CO2 cylinder; E-2—Filter; E-3—Refrigerator unit; E-4—Air compressor; E-5—High pressure pump; E-6—Equilibrium cell; E-7—Magnetic stirrer; E-8—Needle valve; E-9—Back-pressure valve; E-10—Six-port, two position valve; E-11—Oven; E-12—Syringe; E13—Collection vial; E-14—Control panel.
Garlapati–Madras model (five parameters model)\(^48\). It is a mathematical model and mathematically formulated as

\[
\ln \left( y_2 \right) = A_5 + (B_5 + C_5 \rho_1) \ln \left( \frac{D_5}{T} \right) + E_5 \ln \left( \rho_1 T \right)
\]

where \(A_5 - E_5\) are model constants.

Kumar–Johnstone model (three parameters model)\(^49\). It is a semi empirical model and mathematically described as:

\[
\ln \left( y_2 \right) = A_6 + B_6 \rho + C_6 / T
\]

where \(A_6 - C_6\) are model constants.

Mahesh–Garlapati model (three parameters model)\(^50\). It is one of the latest models. It is based on degree of freedom and mathematically stated as:

\[
\ln \left( y_2 \right) = A_7 + B_7 \rho_T + C_7 \rho_T T^2
\]

where \(A_7 - C_7\) are model constants.

Mendez–Teja model (three parameters model)\(^50\). It is a semi-empirical model and mathematically explained as:

\[
T \ln \left( y_2 P \right) = A_8 + B_8 \rho + C_8 T
\]

where \(A_8 - C_8\) are model constants.

Sodefian et al., model (six parameters model)\(^40\). It is a mathematical model and stated as:

\[
\ln \left( y_2 \right) = A_9 + B_9 P^2 + C_9 \ln \left( \rho_1 T \right) + E_9 \ln \left( \rho_1 T \right) + F_9 \ln \left( \rho_1 \right)
\]

where \(A_9 - F_9\) are model constants.

Reformulated Chrastil model (three parameters model)\(^47,51\). It is a semi-empirical model and mathematically explained as:

\[
y_2 = \left( \frac{RT \rho_1}{M_{CEF}} \right)^{\kappa'} \exp \left( \frac{A_{11} B_{11}}{T} \right)
\]

where \(\kappa', A_{10}\) and \(B_{10}\) are model constants.

Tippana–Garlapati model (six parameters model)\(^52\). It is a degree of freedom model and mathematically stated as:

\[
y_2 = \left( A_{12} + B_{11} P_T + C_{11} P_T^2 \right) T^2_T + \left( D_{11} + E_{11} P_T + F_{11} P_T^2 \right)
\]

where \(A_{11} - F_{11}\) are model constants.

New model. According to solid–liquid phase equilibrium criteria, the fugacity of the solute in the solid phase and liquid phase is equal at equilibrium. The liquid phase is considered as an expanded liquid phase of ScCO\(_2\). At equilibrium, the solubility may be expressed as\(^53–57\)

\[
y_2 = \frac{1}{\gamma_2^\infty} \frac{f_S^\infty}{f_L^\infty}
\]

where \(\gamma_2^\infty\) is drug activity coefficient at infinitesimal dilution in ScCO\(_2\) and \(f_S^\infty\) and \(f_L^\infty\) are fugacities of drug in the solid and ScCO\(_2\) phases, respectively. The \(f_S^\infty/f_L^\infty\) ratio may be expressed as follows:

\[
\ln \left( \frac{f_S^\infty}{f_L^\infty} \right) = \frac{\Delta H_m^m}{RT} \left( \frac{T}{T_m} - 1 \right) - \int_{T_m}^{T} \frac{1}{RT^2} \int_{T}^{T_m} \left[ \Delta C_p \right] dT \ dT
\]
\[
\ln \left( \frac{f_i^S}{f_i^L} \right) = \frac{\Delta H_m^{m^S}}{RT} \left( \frac{T}{T_m} - 1 \right)
\]

(19)

Combining Eq. (19) with Eq. (17) give the expression for the solubility model (Eq. (20)).

\[
y_2 = \frac{1}{y_2} \exp \left[ \frac{\Delta H_m^m}{RT} \left( \frac{T}{T_m} - 1 \right) \right]
\]

(20)

In order to use Eq. (20), the appropriate model for \( y_2^\infty \) is essential.

In this work, the required activity coefficient is obtained from Wilson activity coefficient model\(^{56} \) at infinite dilution and it is given by the Eq. (21).

\[
y_2^\infty = \exp \left[ -\ln (\lambda_{21}) + 1 - \lambda_{12} \right]
\]

(21)

where \( \lambda_{12} = \left( \frac{V_2}{V_1} \right) \exp (-a_{12}/RT) \) and \( \lambda_{21} = \left( \frac{V_1}{V_2} \right) \exp (-a_{21}/RT) \), \( V_1 \) and \( V_2 \) are molar volumes of solvent and solute, respectively.

When \( \rho_1 = 1/V_1 \), the final expression for the infinite dilution activity coefficient is obtained as:

\[
y_2^\infty = \exp \left[ 1 + \ln (\rho_1 V_2) + \frac{a_{21}}{RT} - \rho_1 V_2 \exp \left( \frac{-a_{12}}{RT} \right) \right]
\]

(22)

The quantities \( a_{12} \) and \( a_{21} \) are assumed to be functions of reduced solvent density\(^{57} \), and molar volume of the solute is assumed as a constant value. In this work, \( a_{12} \) and \( a_{21} \) are assumed to have the following form:

\[
a_{12} = A(\rho_r)^B
\]

(23)

\[
a_{21} = C(\rho_r)^D
\]

(24)

Combining Eqs. (22), (23) and (24) with Eq. (20), give the following new explicit solubility model:

\[
y_2 = \exp \left[ \frac{\Delta H_m^m}{RT} \left( \frac{T}{T_m} - 1 \right) \right] / \exp \left[ 1 + \ln (\rho_1 V_2) + \frac{A(\rho_r)^B}{RT} - \rho_1 V_2 \exp \left( \frac{-C(\rho_r)^D}{RT} \right) \right]
\]

(25)

Equation (25) has four temperature independent adjustable variables namely \( A,B,C \) and \( D \).

**Equation of state (EoS) model.** The solubility of drug \( i \) (solute) in ScCO\(_2\) (solvent) is expressed as\(^{59-61} \):

\[
y_i = \frac{P_i^S}{P_i^{ScCO_2}} \exp \left[ \left( \frac{P}{P_i^S} \right) V_i \right] \exp \left[ \left( \frac{P}{P_i^S} \right) V_i \right]
\]

(26)

where \( P_i^S \) is the sublimation pressure of the pure solid at system temperature \( T \), \( P \) is the system pressure, \( V_i \) is the molar volume of the pure solid, \( R \) is the universal gas constant. The fugacity coefficient of the pure solute at saturation (\( \phi_i^S \)) is usually taken to be unity. In this work, the fugacity coefficient of the solute in the supercritical phase \( \phi_i^{ScCO_2} \) is calculated using EoS along with KMM\(^{35} \). The expression used for calculation of \( \phi_i^{ScCO_2} \) is obtained from the following basic thermodynamic relation\(^{60} \):

\[
\ln \left( \phi_i^{ScCO_2} \right) = \frac{1}{RT} \int_v^\infty \left[ \left( \frac{\partial P}{\partial N_i} \right)_{T,V,N_j} \right] dv - \ln Z
\]

(27)

The expression for \( \phi_i^{ScCO_2} \) is:

\[
\ln \left( \phi_i^{ScCO_2} \right) = \ln \left( \frac{v}{v-b} \right) + \frac{2 \sum x_i b_{ij} - b}{v-b} - \ln (Z) + \left( a \frac{\sum x_i b_{ij} - b}{b^2 RT^{3/2}} \right) \ln \left( \frac{v+b}{v} \right) - \frac{b}{v+b} + \left( 3 \alpha^{1/2} \sum x_i a_{ij}^{2/3} b_{ij}^{1/3} \right) / b^{1/2} - \alpha^{2/3} \left( \sum x_i b_{ij} / b^{3/2} \right) / b^{1/2}
\]

(28)

where \( \alpha = \sum_i \sum_j x_i a_{ij}^{2/3} b_{ij}^{1/3} \)

and the associated mixing rules are:
The main reason for considering RKEoS is that it has only two adjustable constants $k_{ij}$ and $l_{ij}$. All the models (density-based, new and RKEoS models) are correlated with the following objective function\(^{58}\):

$$\text{OF} = \sum_{i=1}^{N} \left( \frac{y_{2i}^{\text{exp}} - y_{2i}^{\text{calc}}}{y_{2i}^{\text{exp}}} \right)^2$$  \hspace{1cm} (33)

The regression ability of a model is indicated in terms of an average absolute relative deviation percentage (AARD %).

$$\text{AARD} (\%) = \frac{100}{N} \sum_{i=1}^{N} \left| \frac{y_{2i}^{\text{exp}} - y_{2i}^{\text{calc}}}{y_{2i}^{\text{exp}}} \right|$$  \hspace{1cm} (34)

For the regression, fminsearch (MATLAB 2019a) algorithm has been used.  

**Results and discussion**

Table 1 shows some physicochemical properties of the used materials. Empagliflozin solubility in ScCO$_2$ is reported at various temperatures (T = 308 to 338 K) and pressures (P = 12 to 27 MPa). Table 2 indicates the solubility data and ScCO$_2$ density. The reported ScCO$_2$ density is obtained from the NIST data base. Figure 3 shows the effect of pressure on various isotherms. The cross over region is observed at 16.5 MPa. From Fig. 3, below the cross over region, solubility decreases with increase in temperature, and on the other hand, above the cross over region, the solubility increases with increase in temperature. The EoS model requires critical properties which are computed with standard group contribution methods based on the chemical structure\(^{62-65}\). The summary of the critical properties computed are shown in Table 3. Figure 4 presents the self-consistency of the measured data with MT model.  

The density-based models considered in this work have different number of adjustable parameters. These parameters range from three to six numbers. The regression results of all the models are indicated in Tables 4 and 5. The correlating ability of the models is depicted in Figs. 5, 6, 7, 8, 9, 10, 11. From the results, it is clear that all the models are able to correlate the data reasonably well and maximum AARD% is observed to be 10.4%. It is believed that, more parameter models are able to correlate the data more accurately. Sodefan et al., model is able to correlate the data with AARD = 5.84% and Akaike’s information criterion (AIC = 637.59) (more relevant information is presented in the following section). Among density models, Bian et al., model (five parameters model) is able to correlate the data well and corresponding AARD% is 5.1%. Interestingly, Chrastil (three parameters model) and Reformulated Chrastil models (three parameters model) are also able to correlate the data quite well. Further, Chrastil and Reformulated Chrastil models are able to provide the total enthalpy. Whereas, Bartle et al., model parameters are able to provide sublimation enthalpy of the emoglfloxin drug. From the magnitude difference between the total and sublimation enthalpies, a solvation enthalpy is calculated. Where, Bartle et al., model parameters are able to sublimation enthalpy of the emoglfloxin drug. From the magnitude difference between the total and sublimation enthalpies, a solvation enthalpy is calculated. Where, Bartle et al., model parameters are able to provide sublimation enthalpy of the emoglfloxin drug.
Table 2. Solubility of crystalline empagliflozin in ScCO₂ at various temperatures and pressures. The experimental standard deviation was obtained by $S(\bar{y}_k) = \sqrt{\frac{\sum_{j=1}^{N} (y_j - \bar{y})^2}{n-1}}$. Expanded uncertainty ($U$) = $k \cdot u_{\text{combined}}$ and the relative combined standard uncertainty $u_{\text{combined}}/y = \sqrt{\frac{\sum_{i=1}^{N} (P_i u(x_i)/x_i)^2}{N}}$. Standard uncertainty $u$ are $u(T) = \pm 0.1$ K; $u(p) = \pm 0.1$ MPa. The value of the coverage factor $k = 2$ was chosen on the basis of the level of confidence of approximately 95 percent.

| Temperature (K) | Pressure (MPa) | Density of ScCO₂ (kg/m³) | $y_j \times 10^4$ (mole fraction) | Experimental standard deviation, $S(\bar{y}_k) \times (10^4)$ | $S$ (equilibrium solubility) (g/L) | Expanded uncertainty of mole fraction ($10^4 U$) |
|----------------|----------------|---------------------------|----------------------------------|-------------------------------------------------|----------------------------------|--------------------------|
| 308            | 12             | 769                       | 0.0814                           | 0.0021                                          | 0.0643                           | 0.0055                   |
|                | 15             | 817                       | 0.1266                           | 0.0042                                          | 0.1060                           | 0.0098                   |
|                | 18             | 849                       | 0.1327                           | 0.0010                                          | 0.1156                           | 0.0062                   |
|                | 21             | 875                       | 0.1411                           | 0.0051                                          | 0.1265                           | 0.0118                   |
|                | 24             | 896                       | 0.1501                           | 0.0063                                          | 0.1378                           | 0.0137                   |
|                | 27             | 914                       | 0.1806                           | 0.0071                                          | 0.1692                           | 0.0161                   |
| 318            | 12             | 661                       | 0.0706                           | 0.0023                                          | 0.0479                           | 0.0052                   |
|                | 15             | 744                       | 0.1182                           | 0.0031                                          | 0.0901                           | 0.0081                   |
|                | 18             | 791                       | 0.1515                           | 0.0032                                          | 0.1228                           | 0.0091                   |
|                | 21             | 824                       | 0.1601                           | 0.0041                                          | 0.1353                           | 0.0107                   |
|                | 24             | 851                       | 0.2040                           | 0.0064                                          | 0.1812                           | 0.0151                   |
|                | 27             | 872                       | 0.2079                           | 0.0093                                          | 0.1858                           | 0.0202                   |
| 328            | 12             | 509                       | 0.0611                           | 0.0031                                          | 0.0319                           | 0.0066                   |
|                | 15             | 656                       | 0.1044                           | 0.0023                                          | 0.0702                           | 0.0062                   |
|                | 18             | 725                       | 0.1620                           | 0.0032                                          | 0.1203                           | 0.0094                   |
|                | 21             | 769                       | 0.1860                           | 0.0042                                          | 0.1467                           | 0.0115                   |
|                | 24             | 802                       | 0.2248                           | 0.0091                                          | 0.1849                           | 0.0206                   |
|                | 27             | 829                       | 0.2260                           | 0.0021                                          | 0.1920                           | 0.0107                   |
| 338            | 12             | 388                       | 0.0514                           | 0.0023                                          | 0.0204                           | 0.0047                   |
|                | 15             | 557                       | 0.0928                           | 0.0011                                          | 0.0530                           | 0.0047                   |
|                | 18             | 652                       | 0.2002                           | 0.0101                                          | 0.1338                           | 0.0219                   |
|                | 21             | 710                       | 0.2266                           | 0.0112                                          | 0.1650                           | 0.0242                   |
|                | 24             | 751                       | 0.2637                           | 0.0103                                          | 0.2030                           | 0.0231                   |
|                | 27             | 783                       | 0.2590                           | 0.0091                                          | 0.2079                           | 0.0213                   |

Figure 3. Empagliflozin solubility in ScCO₂ vs. pressure.
Table 3. Critical and physical properties of emagliflozin and CO₂. Tc: critical temperature; Pc: critical pressure; ω: acentric factor; Vs: solid molar volume; T: temperature. a Estimated by Fedors method. b Estimated by Joback and Reed method. c Estimated by Lee-Kesler vapour pressure relations (the required normal boiling temperature (at 1.0 atm), T₀ is estimated with Klincewicz relation, Tc = 50.2−0.16 M + 1.41 T₀, where M is molecular weight). d Estimated by Immirzi, A., Perini, B method. e Estimated by Lee-Kesler vapour method.

| Substance | Tc (K) | Pc (Pa) | ω | Vs × 10⁻⁶ (m³/mol) | T(K) | Psub (Pa) |
|-----------|--------|---------|---|-------------------|------|-----------|
| Empagliflozin | 870.367a | 18.7565b | 0.479c | 184.397d | 0.0034 | 0.0089 0.022 0.0508 |
| CO₂ | 304.18 | 73.8 | 0.225 |

Figure 4. Self-consistency plot based on MT model.

Table 4. Correlation constants for the exiting empirical models.

| Name of the empirical model | Correlation parameters | AARD% | R² | R² adj |
|----------------------------|------------------------|-------|----|--------|
| Alwi–Garlapati model | A₁ = 1.8293; B₁ = − 14.218; C₁ = 2.8519 | 6.58 | 0.941 | 0.932 |
| Bartle et al., model | A₁ = 12.195; B₁ = − 5972.3; C₁ = 7.7336 × 10⁻⁴ | 10.4 | 0.922 | 0.910 |
| Bian et al., model | A₁ = − 0.062205; B₁ = − 5.7629 × 10⁻⁴; C₁ = − 0.62308; D₁ = 2.9473; E₁ = 4.5582 | 5.1 | 0.951 | 0.938 |
| Chrastil model | κ = 3.9083; A₄ = − 18.97; B₄ = − 3674.3 | 9.21 | 0.943 | 0.934 |
| Garlapati–Madras model | A₃ = − 750.2; B₃ = 852.82; C₃ = 1.0855; D₃ = − 7397.7; E₃ = − 11.163 | 7.09 | 0.946 | 0.930 |
| Kumar–Jonstone model | A₄ = − 14.274; B₄ = − 0.53652; C₄ = 2.1216 | 27.3 | 0.902 | 0.892 |
| Mahesh_Garlapati model | A₄ = − 14.266; B₄ = − 0.52714; C₄ = 2.0972 | 8.14 | 0.931 | 0.921 |
| Mendez–Teja model | A₅ = − 7775.4; B₅ = 2.3557; C₅ = 12.694 | 9.95 | 0.924 | 0.912 |
| Sodefan et al., model | A₅ = − 23.94; B₅ = 1.6043 × 10⁻²; C₅ = 2.4939; D₅ = 2.6639 × 10⁻²; E₅ = − 9.5238 × 10⁻³; F₅ = − 1.037 × 10⁻³ | 5.84 | 0.956 | 0.940 |
| Reformulated Chrastil model | κ′ = 3.8748; A₁₀ = − 33.58; B₁₀ = − 2705.8 | 9.14 | 0.943 | 0.935 |
| Tippana–Garlapati model | A₁₁ = − 6.4027 × 10⁻⁵; B₁₁ = − 1.1813 × 10⁻⁵; C₁₁ = 2.0367 × 10⁻⁵; D₁₁ = 4.4544 × 10⁻⁷; E₁₁ = 3.5989 × 10⁻⁷; F₁₁ = − 2.4670 × 10⁻³ | 6.63 | 0.927 | 0.924 |

Table 5. Calculated result for the new model and RKEoS + Kwak-Mansoori mixing rule model.
where \( AIC, N, Q \) and \( SSE \) are \( N \ln \left( \frac{SSE}{N} \right) + 2Q \), the number of observations, the number of adjustable parameters of the model and the error sum of squares, respectively. According to \( AIC_c \) criterion, the best model has the least \( AIC_c \) value. Table 7 shows \( AIC_c \) values for various models considered in this study. In terms of \( AIC_c \), all the models are able to correlate the data closely. However, Reformulated Chrastil model has \( AIC_c \) value \(-637.02\), hence it is treated as the best model and at the same time, Tippana–Garlapati model has the highest \( AIC_c \) value \(-621.69\), therefore, it is considered as a poorly correlating model. Three parameters models namely Chrastil, Alwi–Garlapati and Mendez–Teja models have \( AIC_c \) values \(-636.95\), \(-635.3\) and \(-635.4\), respectively. The new model which has four parameters, indicating comparable performance with the best model (\( AIC_c \) value of \(-637.24\)).

**Conclusion**

Solubilities of empagliflozin in \( \text{ScCO}_2 \) at temperatures \((T = 308–338 \text{ K})\) and pressures \((P = 12–27 \text{ MPa})\) were reported for the first time. The measured solubility in terms of mole faction ranged from \(5.14 \times 10^{-6}\) to \(25.9 \times 10^{-6}\). The data was successfully correlated with several models, Bian et al., model (AARD = 5.1\%) was observed to be the best model in correlating the solubility data. All the models are able correlate the data reasonable. However,
the correlating ability in ascending order of various models in terms of the lowest AICc values is as follows: Bian et al., Reformulated Chrastil, Chrastil, new solid–liquid equilibrium, Mendez–Teja, RKEoS + KMmr, Alwi–Garlapati, Sodefian et al., Mahesh–Garlapati, Bartle et al., Tippana–Garlapati models. The new model proposed in this work may be useful for correlating solids solubility in any SCF.
Empagliflozin solubility vs. ScCO\textsubscript{2} density. Solid lines and broken lines are calculated solubilities with Tippana–Garlapati and Sodeifian et al., models, respectively.

Figure 9.

Empagliflozin solubility vs. ScCO\textsubscript{2} density. Solid lines are calculated solubilities with new model.

Figure 10.
Data availability
The datasets generated and/or analysed during the current study are not publicly available due to confidential cases are available from the corresponding author on reasonable request.

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Author contributions
G.S. conceptualization, methodology, validation, investigation, supervision, project administration, writing—review and editing; C.G. methodology, investigation, software, writing—original draft; F.R. investigation, validation, resources; H.N. measurement.

Competing interests
The authors declare no competing interests.
Additional information

Correspondence and requests for materials should be addressed to G.S.

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