Measurement and modeling of *clemastine fumarate* (antihistamine drug) solubility in supercritical carbon dioxide

Gholamhossein Sodeifian\(^1,2,3\)*, Chandrasekhar Garlapati\(^4\), Fariba Razmimanesh\(^1,2,3\) & Marziehsadat Ghanaat-Ghamsari\(^1,2,3\)

The solubilities of *clemastine fumarate* in supercritical carbon dioxide (ScCO\(_2\)) were measured for the first time at temperature (308 to 338 K) and pressure (12 to 27 MPa). The measured solubilities were reported in terms of mole faction (mol/mol total) and it had a range from \(1.61 \times 10^{-6}\) to \(9.41 \times 10^{-6}\). Various models were used to correlate the data. The efficacy of the models was quantified with corrected Akaike’s information criterion (AIC\(_c\)). A new cluster salvation model was derived to correlate the solubility data. The new model was able to correlate the data and deviation was 10.3% in terms of average absolute relative deviation (AARD). Furthermore, the measured solubilities were also correlated with existing K.-W. Chen et al., model, equation of state model and a few other density models. Among density models, Reddy and Garlapati model was observed to be the best model and corresponding AARD was 7.57% (corresponding AIC\(_c\) was – 678.88). The temperature independent Peng–Robinson equation of state was able to correlate the data and AARD was 8.25% (corresponding AIC\(_c\) was – 674.88). Thermodynamic parameters like heats of reaction, sublimation and solvation of *clemastine fumarate* were calculated and reported.

List of symbols

- \(A_1\)–\(A_3\): Alwi–Garlapati parameters
- \(B_1\)–\(B_3\): Bartel model parameters
- \(D_1\)–\(D_3\): Bian et al., model parameters
- \(E_1\)–\(E_2\): Chrastil model parameters
- \(F_1\)–\(F_2\): Reformulated Chrastil model parameters
- \(G_1\)–\(G_5\): Garlapati–Madras model parameters
- \(H_1\)–\(H_3\): Mendez–Teja model parameters
- \(I_1\)–\(I_6\): Sodefian et al., model parameters
- \(J_1\)–\(J_6\): Tippana–Garlapati model parameters
- \(K_1\)–\(K_3\): Mahesh–Garlapati model parameters
- AARD: Average absolute relative deviation
- AIC: Akaike information criterion
- AIC\(_c\): Corrected Akaike information criterion
- \(a_{ij}\): EoS energy parameter
- \(b_{ij}\): EoS volume correction
- \(C\): Solubility in Chrastil model
- EoS: Equation of State
- \(H_{sal}\): Salvation enthalpy
- \(H_{sub}\): Sublimation enthalpy
- \(H_{Total}\): Total enthalpy

\(1^*\)Department of Chemical Engineering, Faculty of Engineering, University of Kashan, 87317-53153 Kashan, Iran. \(2^*\)Laboratory of Supercritical Fluids and Nanotechnology, University of Kashan, 87317-53153 Kashan, Iran. \(3^*\)Modeling and Simulation Centre, Faculty of Engineering, University of Kashan, 87317-53153 Kashan, Iran. \(4^*\)Department of Chemical Engineering, Puducherry Technological University, Puducherry 605014, India. \(5^*\)email: sodeifian@kashanu.ac.ir
Mscf  Molecular weight of supercritical fluid
N  Number of data points
N_p  Number of parameters of a model
P  Total pressure
P_sub  Sublimation pressure
PR  Peng–Robinson
P_r  Reduced pressure
P_c  Critical pressure
R  Universal gas constant
R^2  Square of correlation coefficient
SSE  Sum of squares error
T  Temperature
T_c  Critical temperature
T_r  Reduced temperature
y_i  Solubility in mole fraction

Greek symbols
Δ  Difference
ϕ^S  Fugacity coefficient of the pure substance at saturation
ϕ_{i,ScCO_2}  Solute fugacity in supercritical carbon dioxide (scCO_2)
σ  Acentric factor
ρ  Density
ρ_r  Reduced density ρ_r
κ_{ji}  Correlation parameter
l_{ji}  Correlation parameter
κ, κ', κ'', κ'''  Association numbers in respective eqs.

Sub and superscripts
exp  Experimental
cal  Calculated
j  Solvent/ScCO_2
i  Solute/drug
c  Critical
r  Reduced

The clemastine fumarate is a special drug and it has specific uses. It is an antihistamine with antimuscarinic and partial sedative properties. One of its forms also acts an antileishmanial drug. It also stimulates a macrophage response to leishmankiainfection. For all the medical studies (for both in vivo and in vitro) a proper dosage is very essential and this may be achieved through proper particle size. The usage of supercritical fluid technology in particle micronisation has gained significant importance in the recent times, wherein, carbon dioxide as a supercritical fluid has been used widely in practice. The application of carbon dioxide as supercritical fluid solvent has several advantages over conventional solvents and it is designated as ScCO_2. It possesses attractive physical properties such as, gas like diffusivity and liquid like density with low viscosity and surface tension. By adjusting pressures and temperatures, one can tune the density of ScCO_2 as desired and it is exploited in various applications. Due to this tunable nature, it has been used as a solvent in various process applications. ScCO_2's major applications include drug particle micronization, extraction, reactions, food processing, textile dyeing, ceramic coating, and many more. To implement SFT, one needs to have exact phase equilibrium information such as saturation solubility. Solubility is one of the basic information that is essential for the design and development of SFT. Drug particle micronization requires precise solubility information and in literature, solubility of many solid drugs in ScCO_2 is readily available, however, the solubility of clemastine fumarate is not reported. Therefore, for the first time, the solubility of clemastine fumarate in ScCO_2 is reported in this work. We believe that this study may be useful in particle micronization using ScCO_2.

The main objectives of the present work are in two stages; in the first stage we determine solubility of clemastine fumarate. Since, measuring experimental solubility data at each pressure and temperature is very difficult, we need a proper model to generate the solubility data. Therefore, in the second stage we have developed a new cluster solubility model. The proposed model is compared with existing cluster solvation model. Furthermore, few density models and equation of state model are evaluated.

**Experimental Materials.** Gaseous CO_2 (purity > 99.9%) was obtained from Fadak company, Kashan (Iran), clemastine fumarate (CAS Number: 14976-57-9, purity > 99%) was obtained from Amin Pharma company. Methanol (CAS No. 67-56-1, purity > 99%) was obtained from Sigma Aldrich company. Table 1 indicates all the information about the chemicals utilized in this work. The molecular formula of clemastine fumarate is C_{21}H_{26}ClNO·C_4H_4O_4 and its molecular weight is 459.97. The chemical structure is shown in Fig. 1.
Experiment details. Figure 2 shows the line diagram of the equipment used in the study. More details about the solubility measuring device have been presented in our earlier studies. However, a brief outline of the same has been presented in this section. This measuring methodology may be classified as an isobaric-isothermal method. Each reading has been reported by controlling temperature and pressure at desired values within ±0.1 K and ±0.1 MPa precision, respectively. For each experiment about 1 g of clemastine fumarate drug has been used in the static cell. The saturation samples have been collected from the static cell after equilibrating for 60 min. Our earlier studies indicated that 60 min is enough for equilibrium. After equilibrium, saturated ScCO₂ samples (600 µL) have been collected via 2-status 6-way port valve in a methanol preloaded vial. Once a sample was collected, the port valve was washed with 1 mL methanol. Thus, the total saturation solution obtained was 5 mL. Each measurement has been repeated thrice and average readings were reported. For calculations, the following formulas have been used.

\[ y^2 = \frac{n_{\text{drug}}}{n_{\text{drug}} + n_{\text{CO}_2}} \]  

Table 1. Basic properties of the used materials.

| Compound                  | Formula            | M₀ (g/mol) | Tm (K)  | λmax (nm) | CAS number | Minimum purity by supplier (%) |
|---------------------------|--------------------|-----------|---------|-----------|------------|--------------------------------|
| Clemastine Fumarate       | C₂₁H₂₆ClNO·C₄H₄O₄ | 459.96    | 451.15  | 270       | 14976-57-9 | 99                             |
| Carbon dioxide            | CO₂                | 44.01     |         |           |            | 99.99                          |
| Methanol                  | CH₃OH              | 32.04     |         |           | 67-56-1    | 99.9                           |

Figure 1. Chemical structure of clemastine fumarate.
where \( n_{\text{drug}} \) denotes the quantity of the drug, and \( n_{\text{CO}_2} \) denotes the quantity of \( \text{CO}_2 \) in the sampling loop.

Further, we quantify moles of drug and moles of \( \text{CO}_2 \) as

\[
\begin{align*}
\text{(2)} & \quad n_{\text{drug}} = \frac{C_s \cdot V_s}{M_s} \\
\text{(3)} & \quad n_{\text{CO}_2} = \frac{V_1 \cdot \rho_1}{M_{\text{CO}_2}}
\end{align*}
\]

where \( C_s \) denotes the drug concentration in saturated sample vial in g/L. The volume of sampling loop, \( V_s = 5 \times 10^{-3} \text{ m}^3 \) and vial collection, \( V_1 = 600 \times 10^{-6} \text{ m}^3 \). The \( M_s \) and \( M_{\text{CO}_2} \) denote the molecular weight of drug and \( \text{CO}_2 \), respectively. Solubility is also described as

\[
\text{(4)} \quad S = \frac{C_s V_s}{V_1}
\]

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

\[
\text{(5)} \quad S = \frac{\rho M_s}{M_{\text{CO}_2}} \frac{y_2}{1 - y_2}
\]

To ensure equilibrium solubility, the experiments were performed with fresh samples at various time intervals. For a specified temperature and pressure in each experiment, the drug sample was contacted with \( \text{ScCO}_2 \) and stirred thoroughly in an equilibrium cell until a specific time (5 min, 10 min, 20 min, 30 min, 40 min, 50 min and 60 min) and the solubility readings were recorded. It was observed that the solubility was independent of time after 30 min. This experimental setup has already been validated in our previous works with alpha-tocopherol and naphthalene\(^1\).

A UV–visible (UNICO-4802) spectrophotometer has been used for the measurements of \( \text{clemastine fumarate} \) solubility. Samples collected for analysis in methanol solvent were analyzed at 270 nm.

**Models**

In this section, a brief note about the existing density models and their mathematical form were presented.

**Existing empirical and semi-empirical models.** *Alwi–Garlapati model\(^2\).* It is a semi-empirical model. It has three parameters. According to this, solubility is represented as a function of reduced temperature and reduced density and it is mathematically stated as

\[
\text{(6)} \quad y_2 = \frac{1}{\rho_1 T_r} \exp \left( A_1 + A_2 \frac{T_r}{T_r} + A_3 \rho_1 T_r \right)
\]

where \( A_1 - A_3 \) are model constants.

*Bartle et al., model\(^3\).* It is based on enhancement factor concept and it has three parameters. According to this, solubility is represented as a function of pressure, temperature and density and it is mathematically stated as

\[
\text{(7)} \quad \ln \left( \frac{y_2 P}{P_{\text{ref}}} \right) = B_1 + B_2 \frac{T}{T_r} + B_3 (\rho_1 - \rho_{\text{ref}})
\]

where \( B_1 - B_3 \) are model constants. From parameter \( B_2 \) one can estimate sublimation enthalpy using the relation, \( \Delta_{\text{sub}} H = -B_2 R \) in which \( R \) is universal gas constant. Reference pressure \( (P_{\text{ref}}) \) and density \( \rho_{\text{ref}} \) are 0.1 MPa and 700 kg/m\(^3\), respectively.

*Bian et al., model\(^4\).* It is a five parameter model. It is an empirical model and it is mathematically stated as

\[
\text{(8)} \quad y_2 = \rho_1^{(D_1 + D_2 \rho_1)} \exp \left( D_3 / T + D_4 \rho_1 / T + D_5 \right)
\]

where \( D_3 - D_5 \) are model constants.

*Chrastil model\(^5\).* It is a three parameter model. It is a semi empirical model and it is mathematically stated as

\[
\text{(9)} \quad c_2 = \rho_1^{E_2} \exp \left( E_1 / T \right)
\]

where \( \kappa, E_1 \) and \( E_2 \) are model constants. In terms of mole fraction it is mathematically stated as

\[
\text{(9a)} \quad y_2 = \frac{(\rho_1)^{\kappa - 1} \exp \left( E_1 + \frac{E_2}{T} \right)}{[1 + (\rho_1)^{\kappa - 1} \exp \left( E_1 + \frac{E_2}{T} \right)]}
\]
Reformulated Chrastil model\textsuperscript{26,27}. It is also a three parameter model. It is a semi-empirical model and it is mathematically stated as

\[
y_2 = \left( \frac{RT_1 \rho_1}{M_{crf}} \right)^{\kappa'} \exp \left( \frac{F_1 + F_2}{T} \right)
\]

where \( \kappa' \), \( F_1 \) and \( F_2 \) are model constants. Reference fugacity \((f^*)\) is 0.1 MPa.

Garlapati–Madras model\textsuperscript{28}. It is a five parameter model. It is a mathematical model and it is mathematically stated as

\[
\ln (y_2) = G_1 + (G_2 + G_3 \rho_1) \ln (\rho_1) + \frac{G_4}{T} + G_5 \ln (\rho_1 T)
\]

where \( G_1 - G_5 \) are model constants.

Mendez–Teja model (MT model)\textsuperscript{29}. It is a semi-empirical model and it has three parameters. It is mathematically stated as

\[
T \ln (y_2 P) = H_1 + H_2 \rho_1 + H_3 T
\]

where \( H_1 - H_3 \) are model constants.

Equation (12) is used in checking self-consistency of the measured solubility data. Accordingly, all the data points lie on a line when they are plotted \( T \ln (y_2 P) - H_3 T \) versus \( \rho_i \).

Sodefian et al., model\textsuperscript{30}. It is a mathematical model and it has six parameters and it is mathematically stated as

\[
\ln (y_2) = I_1 + \frac{J_2 P_2^2}{T} + I_3 \ln (\rho_1 T) + I_4 (\rho_1 \ln (\rho_1)) + I_5 P \ln (T) + I_6 \ln (\rho_1 T)
\]

where \( I_1 - I_6 \) are model constants.

Reddy–Garlapati model\textsuperscript{31}. It is based on degree of freedom. It is a six parameter model. It is an empirical model and it is mathematically stated as

\[
y_2 = (J_1 + J_2 P_r + J_3 P_r^2) T_s^2 + (J_4 + J_5 P_r + J_6 P_r^2)
\]

where \( J_1 - J_6 \) are model constants.

Mahesh–Garlapati model\textsuperscript{11}. It is based on degree of freedom. It is a three parameter model. It is an empirical model and it is mathematically stated as

\[
y_2 = \exp \left( K_1 + K_2 \rho_{1r} T_r + K_3 \rho_{1r} T_s \right)
\]

Equation of state (EoS) model. The solubility of clemastine fumarate drug, \( i \) (solute), in a supercritical carbon dioxide, \( j \) (solvent), is expressed as\textsuperscript{11}

\[
y_i = \frac{P_i^{\kappa_S \phi_{i}^{ScCO_2}}}{P_i^{\kappa_S \phi_{i}^{ScCO_2}}} \exp \left[ \frac{(P - P_i^{\kappa_S \phi_{i}^{ScCO_2}})}{RT} \right]
\]

where \( P_i^{\kappa_S \phi_{i}^{ScCO_2}} \) is solute sublimation pressure; \( V_i \) is solute molar volume; The fugacity coefficient of the pure solute at saturation \( (\phi_{i}^{ScCO_2}) \) is usually taken to be unity. In this work, \( \phi_{i}^{ScCO_2} \) is the fugacity coefficient of the solute in the solvent phase. \( \phi_{i}^{ScCO_2} \) is calculated using Peng–Robinson (PR) EoS along with two parameter van der Waals mixing rule (vdW2)\textsuperscript{32}. The expression used for calculation of \( \phi_{i}^{ScCO_2} \) is obtained from the following basic thermodynamic relation\textsuperscript{32}.

\[
\ln \left( \phi_{i}^{ScCO_2} \right) = \frac{1}{RT} \int_{0}^{\infty} \left[ \left( \frac{\partial P}{\partial N_i} \right)_{T,V,N_j} - \frac{RT}{V} \right] dv \ln Z
\]

The general PREoS form\textsuperscript{32} is

\[
P = \frac{RT}{v - b} - \frac{a(T)}{v(v + b) + b(v - b)}
\]

The pure component parameters \( a \) and \( b \) are

\[
a(T) = 0.45724 \left( \frac{R^2 T_c^2}{P_c} \right) \left[ 1 + \left( 0.37464 + 1.5422w - 0.26992w^2 \left( 1 - \sqrt{\frac{T}{T_c}} \right) \right) \right]
\]
The expression for $\hat{\gamma}_{\text{CO}_2}$ is:
\[
\ln(\hat{\phi}_i) = \frac{\hat{b}}{b} (Z - 1) - \ln \left[ Z \left(1 - \frac{b}{\nu} \right) \right] + \frac{a}{(2\sqrt{2}) bRT} \left( \hat{a} - \frac{\hat{b}}{b} \right) \ln \left( \frac{Z - 0.414b}{Z + 2.414b} \right)
\]
(21)

The expressions for VdW2
\[
a = \sum_i \sum_j x_i x_j a_{ij}
\]
(22)
\[
b = \sum_i \sum_j x_i x_j b_{ij}
\]
(23)
\[
a_{ij} = (1 - k_{ij}) \sqrt{a_{ii} a_{jj}}
\]
(24)
\[
b_{ij} = (1 - l_{ij}) \frac{(b_{ij} + b_{ji})}{2}
\]
(25)

The PR EoS regression may be carried out either temperature independent or temperature dependent. For temperature independent regression suitable sublimation expression is used. The general form$^{34,35}$ used for the regression purpose is
\[
R \ln (p_{\text{sub}}) = \beta + \frac{\gamma}{T} + \Delta_{\text{sub}} \frac{\delta}{T}
\]
(26)

The regression directly results in binary interaction parameters along with sublimation pressure expression coefficients ($\beta/R$, $\gamma/R$ and $\Delta_{\text{sub}}/R$) and from parameters $\gamma$ and $\Delta_{\text{sub}}$ we can estimate sublimation pressure.

The expression for sublimation enthalpy is
\[
\Delta_{\text{sub}} H = -\gamma + \Delta_{\text{sub}} \frac{\delta}{T}
\]
(27)

K.-W. Chen et al., cluster model$^{36}$. According to the model, the formation of solvate complex $AB_k$ is due to the reaction mentioned in Eq. (28), where $A$ is solute and $B$ is supercritical fluid.

\[
A + k'' B \leftrightarrow AB_k
\]
(28)

It is an equilibrium reaction and at equilibrium the following condition is satisfied.
\[
\sum v_i \mathcal{F}_i(T, P, z_i) = 0
\]
(29)

where $\sum$ is summation; $v$ and $\mathcal{F}$ are stoichiometric coefficient and partial molar Gibbs energy, respectively.

In general the partial molar Gibbs energy for species is written as
\[
\mathcal{F}_i(T, P, z_i) = \mathcal{F}_i(T, P^0, z_i^0) + \left( \mathcal{F}_i(T, P, z_i) - \mathcal{F}_i(T, P^0, z_i^0) \right)
\]
(30)

where $P^0$ and $z_i^0$ are reference state pressure and composition of species “i”. The reference pressure is taken as critical pressure of the supercritical fluid and finally the expression for the equilibrium in terms of fugacity coefficients is
\[
\ln \left( \frac{z_{AB_k}}{z_B} \right) = k'' \ln \left( \frac{\phi_B(T, P, z_B) P}{\phi_B(T, P, z_{AB_k}) P_{AB_k}} \right) + \frac{V_r (P - P_{\text{e,scf}})}{RT} \ln \left( \frac{\phi_{AB_k}(T, P, z_{AB_k}) P}{\phi_{AB_k}(T, P, z_{AB_k}) P_{AB_k}} \right) - \frac{\Delta F^{\text{form}}(T, P_{\text{e,scf}})}{RT}
\]
(31)

where $\Delta F^{\text{form}}(T, P_{\text{e,scf}})$ is the change in Gibbs energy as a result of formation of solvate complex.

The model has two parameters $k''$ and $\Delta F^{\text{form}}(T, P_{\text{e,scf}})$. K.-W. Chen et al.$^{36}$, used the following temperature dependent general form$^{38}$ in place of $\Delta F^{\text{form}}(T, P_{\text{e,scf}})$
\[
\Delta F^{\text{form}}(T, P_{\text{e,scf}}) = a' - b'T
\]
(32)

Thus the final model has $k''$, $a'$ and $b'$ (three adjustable parameters).

The Eq. (31) is further simplified with the help of Taylor series on left hand side.
\[
\ln \left( \frac{z_{AB_k}}{1 - \kappa'' z_{AB_k}} \right) = k \ln \left( \frac{\Phi_b(T,P,z_B)P}{\phi_b(T,P,s_{scf})s_{scf}} \right) + \frac{V_i(P-P_{scf})}{RT} - \ln \left( \frac{\Phi_{AB_k}(T,P,z_{AB_k})P}{\phi_{AB_k}(T,P,s_{scf})s_{scf}} \right) - \frac{\Delta F^{ex}(T,P_{scf})}{RT} \tag{33}
\]

The experimental solubility and cluster mole fractions are related as follows
\[
y = z_{AB_k} / (1 + \kappa'' z_{AB_k}) \tag{34}
\]

The fugacity coefficient of the components and mixtures are evaluated with PR EoS. For fugacity coefficient calculations we need mixture properties and they are calculated with the help of solute, solvent and cluster volume and energy parameter. More details about these can be seen elsewhere.

The cluster obeys the following mixing rules for volume and energy parameters
\[
b_{AB_k} = k''b_B + b_A \tag{35}
\]

\[
a_{AB_k} = [k''(a_Bb_B)^{0.5} + (a_Ab_A)^{0.5}] / b_{AB_k} \tag{36}
\]

More details about PR EoS, fugacity coefficient of pure component and mixture can be seen in section "Equation of state (EoS) model" and literature.

The final expression for the solubility is
\[
y = \frac{\exp \left[ \kappa''' \ln \left( \frac{\Phi_b(T,P,z_B)P}{\phi_b(T,P,s_{scf})s_{scf}} \right) + \frac{V_i(P-P_{scf})}{RT} - \ln \left( \frac{\Phi_{AB_k}(T,P,z_{AB_k})P}{\phi_{AB_k}(T,P,s_{scf})s_{scf}} \right) - \frac{(a''-b''+T)}{RT} \right]}{1 + 2\kappa''' \exp \left[ \kappa''' \ln \left( \frac{\Phi_b(T,P,z_B)P}{\phi_b(T,P,s_{scf})s_{scf}} \right) + \frac{V_i(P-P_{scf})}{RT} - \ln \left( \frac{\Phi_{AB_k}(T,P,z_{AB_k})P}{\phi_{AB_k}(T,P,s_{scf})s_{scf}} \right) - \frac{(a''-b''+T)}{RT} \right]} \tag{37}
\]

**New cluster model.** This model is an extension to existing K.-W. Chen et al., model. According to the model the formation of solvate complex \(AB_k\) is according to the reaction mention in Eq. (38), where A is solute and B is supercritical fluid.

\[
A + \kappa'''B \leftrightarrow AB_k \tag{38}
\]

For the solubility model development we have used all arguments similar to that of K.-W. Chen et al., model. The main difference between K.-W. Chen et al. model and the new cluster model lies in selection of temperature dependent general form. The considered temperature dependent general form is

\[
\Delta F^{ex}(T,P_{scf}) = a'' + b''T\ln(T)+c''T \tag{39}
\]

Thus, the final model has four adjustable parameters \(\kappa''', a'', b''\) and \(c''\).

Follow in K.-W. Chen et al., footsteps we get the final expression for the solubility as

\[
y = \frac{\exp \left[ \kappa''' \ln \left( \frac{\Phi_b(T,P,z_B)P}{\phi_b(T,P,s_{scf})s_{scf}} \right) + \frac{V_i(P-P_{scf})}{RT} - \ln \left( \frac{\Phi_{AB_k}(T,P,z_{AB_k})P}{\phi_{AB_k}(T,P,s_{scf})s_{scf}} \right) - \frac{(a''-b''+T)\ln(T)+c''T}{RT} \right]}{1 + 2\kappa''' \exp \left[ \kappa''' \ln \left( \frac{\Phi_b(T,P,z_B)P}{\phi_b(T,P,s_{scf})s_{scf}} \right) + \frac{V_i(P-P_{scf})}{RT} - \ln \left( \frac{\Phi_{AB_k}(T,P,z_{AB_k})P}{\phi_{AB_k}(T,P,s_{scf})s_{scf}} \right) - \frac{(a''-b''+T)\ln(T)+c''T}{RT} \right]} \tag{40}
\]

Hereafter it may be called as cluster model by Sodeifian et al. The major advantage of Eq. (40) over Eq. (37) lies in improved parameterization and efficacy.

For implementing EoS and cluster models we need critical properties and vapour pressures, and they are estimated with the help of group contribution methods. Critical temperature is estimated by Fedors method, critical pressure is estimated by Joback modification of Lydersen's method. Theacentric factor is estimated by Lee–Kesler vapour pressure relations. While calculating vapour pressure, the normal boiling temperature (at 1.0 atm) is required and it is estimated from Klinewicz relation, \(T_b = 50.2 - 0.16 M + 1.41 T_i\) were \(M\) is molecular weight. The required molar volume of drug (solid) is estimated by Immirzi, A. Perini, B method and the vapour pressures are estimated by Lee–Kesler vapour method.

All the models mentioned in sections "Existing empirical and semi-empirical models", "Equation of state (EoS) model", "K.-W. Chen et al., cluster model" and "New cluster model" are evaluated with the following objective function

\[
OF = \sum_{i=1}^{N} \left| \frac{y_i^{exp} - y_i^{cal}}{y_i^{exp}} \right| \tag{41}
\]

Regression results are represented in terms of average absolute relative deviation percentage (AARD %)

\[
\text{AARD} = 100/N \sum_{i=1}^{N} \left| \frac{y_i^{exp} - y_i^{cal}}{y_i^{exp}} \right| \tag{42}
\]
Table 1 indicates some properties of the used materials. Table 2 shows clemastine fumarate solubility in scCO2. The density indicated in Table 2 is obtained from the NIST database. Computed properties of clemastine fumarate are shown in Table 3. Figure 3 indicates the effect of pressure on various isotherms and no crossover region observed, such solubility behavior is observed for some other pharmaceutical compounds in our earlier studies. From Table 3, it is clear that the vapor pressure of clemastine fumarate increases from 0.0114 Pa to 0.1277 Pa, when the temperature is increased from 308 to 338 K, it is a 11.2 fold jump. Due to this, solubility increases from 0.0161 x 10^-4 to 0.0359 x 10^-4 (in mole/mole total) at 12 MPa (it is a 2.23 fold jump) and 0.051 x 10^-4 to 0.0941 x 10^-4 (in mole/mole total) at 27 MPa (it is a 1.845 fold jump). At the same time, densities have changed from 769 kg m^-3 (corresponding to 308 K and 12 MPa) to 338 kg m^-3 (corresponding to 338 K and 12 MPa) and 914 kg m^-3 (corresponding to 308 K and 27 MPa) to 783 kg m^-3 (corresponding to 338 K and 27 MPa), which clearly indicates that density decreases at 12 MPa (i.e., 338/769 = 0.4395) and somewhat increases at 27 MPa (i.e., 783/914 = 0.8567). From preceding arguments we say that the pressure effect is less pronounced with respect to density than the temperature effect. This kind of nonlinearity is well captured with models having more parameters compared to less number of parameter. Therefore, models proposed by Sodeifian et al. (43) are used to assess the correlating efficacy of a model regardless of the number of its parameters.

\[
AIC = N \ln(\text{SSE}/N) + 2N_p
\]

where \(N\) is number of experimental data points; \(N_p\) is model parameters; \(\text{SSE}\) is error sum of squares. When \(N\) is less than 40 corrected AIC is used and it is stated as follows

\[
AIC_c = AIC + 2N_p(N_p + 1)/(N - N_p - 1)
\]

where \(N\) is number of experimental data points; \(N_p\) is model parameters; \(\text{SSE}\) is error sum of squares.

Results and discussion

Table 1 indicates some properties of the used materials. Table 2 shows clemastine fumarate solubility in scCO2. The density indicated in Table 2 is obtained from the NIST database. Computed properties of clemastine fumarate are shown in Table 3. Figure 3 indicates the effect of pressure on various isotherms and no crossover region observed, such solubility behavior is observed for some other pharmaceutical compounds in our earlier studies. From Table 3, it is clear that the vapor pressure of clemastine fumarate increases from 0.0114 Pa to 0.1277 Pa, when the temperature is increased from 308 to 338 K, it is a 11.2 fold jump. Due to this, solubility increases from 0.0161 x 10^-4 to 0.0359 x 10^-4 (in mole/mole total) at 12 MPa (it is a 2.23 fold jump) and 0.051 x 10^-4 to 0.0941 x 10^-4 (in mole/mole total) at 27 MPa (it is a 1.845 fold jump). At the same time, densities have changed from 769 kg m^-3 (corresponding to 308 K and 12 MPa) to 338 kg m^-3 (corresponding to 338 K and 12 MPa) and 914 kg m^-3 (corresponding to 308 K and 27 MPa) to 783 kg m^-3 (corresponding to 338 K and 27 MPa), which clearly indicates that density decreases at 12 MPa (i.e., 338/769 = 0.4395) and somewhat increases at 27 MPa (i.e., 783/914 = 0.8567). From preceding arguments we say that the pressure effect is less pronounced with respect to density than the temperature effect. This kind of nonlinearity is well captured with models having more parameters compared to less number of parameter. Therefore, models proposed by Sodeifian et al.

\[
AIC = N \ln(\text{SSE}/N) + 2N_p
\]
model and Reddy–Garlapati model are able to correlate the solubility in a better manner. Figure 4 indicates the self-consistency of the measured data with MT model. The regression analysis of experimental data is carried out easily with density model, but the regression analysis of EoS model and cluster model requires critical properties of the solute and solvent. The required critical temperature, critical pressure, acentric factor and molar volume of the solute and sublimation pressure of the solute are not readily available; due to this these properties are computed with standard group contribution methods. The empirical and semi empirical models considered in this study have shown different degree of fitting in terms of AARD%. The regression results of various models are indicated in Tables 4, 5 and 6. Among the existing empirical and semi-empirical models, Reddy–Garlapati model is having lower AARD%. Chrastil model parameter \( E_2 \) and Reformulated Chrastil model parameter \( F_2 \) are used in calculating total enthalpy, from Bartel et al., model parameter \( B_2 \) we get sublimation enthalpy of the clemastine fumarate. Heat of solvation is obtained from the magnitude difference between total enthalpy and sublimation enthalpy. The more details about these calculations can be seen in literature. All the computed results are reported in Table 7. EoS model is regressed in two different ways. In the first approach correlation parameter are treated as temperature dependent whereas in second approach the correlation parameters are treated as temperature independent. From regression results (Table 5) temperature independent correlation is better than temperature dependent correlation. EoS model also provide sublimation enthalpy and it is reported in Table 7. From Table 6 it is clear that the cluster model by sodeifian et al., is superior to exiting K.-W. Chen et al., model. The parameters ‘a’ and ‘b’ of cluster model by sodeifian et al., directly results in enthalpy change and entropy change of the cluster formation.

Table 3. Properties of Clemastine fumarate and CO₂.

| Substance    | \( T_c \) (K) | \( P_c \) (MPa) | \( \omega \) | \( V \times 10^{-4} \) (m³/mol) | \( T \) (K) |
|--------------|---------------|-----------------|-------------|-------------------------------|-------------|
| Clemastine Fumarate | 901.25         | 1.409           | 0.337       | 364.764                       | 308         |
| CO₂     | 304.18        | 7.38            | 0.225       | 0.0114                         | 318         |
|             |               |                 |             | 0.02699                        | 328         |
|             |               |                 |             | 0.0603                         | 338         |
|             |               |                 |             | 0.1277                         |             |

Figure 3. Clemastine fumarate solubility in ScCO₂ and effect of pressure on isotherms.
process. The positive sign for entropy change indicates an increase in disorder. The positive change in enthalpy indicates heat absorption from surroundings the by the reaction. The correlating ability of the various models is represented in Figs. 4, 5, 6, 7, 8 and 9.

The models used in correlation exercise, have a varying number of parameters and the best model is obtained with the help of Akaike’s information criterion (AIC) \(^{45–49}\). The data used in this exercise is small (N < 40), hence

**Table 4.** Correlation constants for the exiting empirical models.

| Model                        | Correlation parameters | AARD% | \(R^2\) |
|------------------------------|------------------------|-------|---------|
| Alwi–Garlapati model         | \(A_1 = 1.8759; A_2 = -18.105; A_3 = 2.0667\) | 14.00 | 0.809   |
| Bartel et al., model         | \(B_1 = 14.719; B_2 = -7179.9; B_3 = 6.6739 \times 10^{-3}\) | 20.2  | 0.765   |
| Bian et al., model           | \(D_1 = -4.9614; D_2 = 5.5723 \times 10^{-3}; D_3 = 2030.5; D_4 = -9.9873; D_5 = 9.6915\) | 11.2  | 0.927   |
| Chrastil model               | \(\kappa = 3.0938; E_1 = -11.003; E_2 = 4907.2\) | 16.7  | 0.785   |
| Ref. Chrastil model          | \(\kappa = 3.0813; F_1 = -21.619; F_2 = -4216.6\) | 16.7  | 0.784   |
| Garlapati–Madras model       | \(G_1 = -755.12; G_2 = 859.01; G_3 = 0.9875; G_4 = -8597.4; G_5 = -10.722\) | 14.6  | 0.818   |
| Mendez–Teja model            | \(H_1 = -8479.4; H_2 = 1.9628; H_3 = 14.617\) | 21.69 | 0.706   |
| Sodeifian et al., model      | \(I_1 = -4.2487; I_2 = -6.9315 \times 10^{-3}; I_3 = -4.2127 \times 10^{-3}; I_4 = 1.929 \times 10^{-2}; I_5 = 62.052\) | 8.78  | 0.929   |
| Tippana–Garlapati model      | \(J_1 = 8.334 \times 10^{-3}; J_2 = 1.3157 \times 10^{-3}; J_3 = -3.3583 \times 10^{-3}; J_4 = 5.6805 \times 10^{-3}; J_5 = -3.913 \times 10^{-3}; J_6 = 7.7236 \times 10^{-2}\) | 7.57  | 0.951   |
| Mahesh–Garlapati model       | \(K_1 = -14.614; K_2 = -2.4145; K_3 = 3.3127\) | 17.9  | 0.797   |
corrected AIC (AICc) is used for identifying the best model. The model that gives lowest AICc value is the best model. Table 8 indicates computed AIC and AICc values. The least AICc value − 678.88 is seen for Reddy–Garlapati model; therefore, it is considered as the best model, however, the new cluster model has also comparable performance with the best model, the corresponding AICc value is − 678.59. The highest AICc value is seen for Alwi-Garlapati model. Hence, it is treated as a poor model for clemastine fumarate.

**Conclusion**

Solubilities of clemastine fumarate in ScCO₂ at temperatures (T = 308–338 K) and pressures (P = 12–27 MPa) were reported for the first time. The measured solubilities were successfully correlated with several models; however, Tippana–Garlapati model is observed to be the best model in correlating the solubility data. The correlating ability in ascending order of various models in terms of lowest AICc values are as follows: Reddy–Garlapati model, new cluster model, PR EoS as temperature independent, K.-W. Chen et al., model, Sodefian et al., model, Mahesh–Garlapati model, Chrastil model, Reformulated Chrastil model, Garlapati–Madras model, Mendez–Teja model, Bartel et al., model, Alwi-Garlapati model. The new cluster model proposed in this work may be useful for correlating solids solubility in any SCF.

### Table 5. Correlation constants of PR EoS + VdW2 combination.

| Model | Correlation parameters | AARD% | R² |
|-------|------------------------|-------|----|
| New model | κ = 0.10756; aᵣ = 443,590; bᵣ = 1357.1; cᵣ = − 9115.7 | 10.3 | 0.936 |
| K.-W. Chen et al., model | κ = 0.10794; aᵣ = 6093.7; bᵣ = − 70.319 | 12.1 | 0.913 |

### Table 6. Correlation constants of cluster models.

| Model | Property | Total enthalpy, ΔH_total (kJ/mol) | Enthalpy of sublimation, ΔH_sub (kJ/mol) | Enthalpy of solvation, ΔH_sol (kJ/mol) |
|-------|----------|---------------------------------|----------------------------------|----------------------------------|
| Chrastil model | 40.798 | − 18.896; − 12.282 |
| Reformulated Chrastil Model | 35.056 | − 24.638; − 6.54 |
| Bartel et al., model | 59.694 | (approximate value) |
| PR EoS + vdW2 model | 28.516 | (average value) |

**Table 7. Summary of thermodynamic properties.** a Obtained as a result of difference between the ΔH_sub and ΔH_total. b Obtained as a result between the ΔH_sub and ΔH_total. c Obtained as a result between the ΔH_sub and ΔH_total. d Obtained as a result of difference between the ΔH_sub and ΔH_total. e Obtained as a result of difference between the ΔH_sub and ΔH_total.
Figure 5. Solubility of clemastine fumarate in ScCO₂. Symbols are experimental points; lines are calculated with three parameter models.

Figure 6. Solubility of clemastine fumarate in ScCO₂. Symbols are experimental points; lines are calculated with five parameter models.
Figure 7. Solubility of clemastine fumarate in ScCO$_2$. Symbols are experimental points; lines are calculated with six parameter models.

Figure 8. Solubility of clemastine fumarate in ScCO$_2$. Symbols are experimental points; lines are calculated with PREoS models.
Figure 9. Solubility of clemastine fumarate in ScCO₂. Symbols are experimental points; lines are calculated with cluster models.

| Model                          | SSE.10¹¹ | Np | N | AIC  | AICc  |
|-------------------------------|----------|----|---|------|------|
| **Existing density models**    |          |    |   |      |      |
| Alwi–Garlapati model          | 2.41888  | 3  | 24| -636.5 | -635.30 |
| Bartel et al., model          | 3.29465  | 3  | 24| -649.54 | -648.34 |
| Bian et al., model            | 94.47    | 5  | 24| -675.52 | -672.19 |
| Chrastil model                | 2.69392  | 3  | 24| -654.37 | -653.17 |
| Reformulated Chrastil model   | 2.70787  | 3  | 24| -654.25 | -653.05 |
| Garlapati–Madras model        | 2.36986  | 5  | 24| -653.45 | -650.11 |
| Mendez–Teja model             | 3.2662   | 3  | 24| -649.75 | -648.55 |
| Sodeñan et al., model         | 1.03868  | 6  | 24| -671.24 | -666.30 |
| Reddy–Garlapati model         | 61.5158  | 6  | 24| -683.82 | -678.88 |
| Mahesh–Garlapati model        | 2.64529  | 3  | 24| -654.81 | -653.61 |
| **Cluster models**            |          |    |   |      |      |
| New cluster model             | 82.7593  | 4  | 24| -680.70 | -678.59 |
| K.-W. Chen et al., model      | 1.10632  | 3  | 24| -675.73 | -674.53 |
| **EoS model**                 |          |    |   |      |      |
| PR EoS model + vdW2 Mixing Rule | 84.4568 | 5  | 24| -678.21 | -674.88 |

Table 8. Computed AIC and AICc values.

Received: 14 June 2021; Accepted: 7 December 2021
Published online: 21 December 2021

References
1. Mina, J. G. M. et al. Antileishmanial chemotherapy through clemastine fumarate mediated inhibition of the leishmania inositol phosphoryl ceramide synthase. ACS Infect. Dis. 7, 47–63. https://doi.org/10.1021/acsinfectdis.0c00546 (2021).
2. Subramaniam, B., Rajewski, R. A. & Snavely, K. Pharmaceutical processing with supercritical carbon dioxide. J. Pharm. Sci. 86, 885–890. https://doi.org/10.1021/jp9700661 (1997).
8. Sodeifan, G., Sajadian, S. A. & Daneshyan, S. Preparation of Aprepitant nanoparticles (efficient drug for coping with the effects of cancer treatment) by rapid expansion of supercritical solution with solid cosolvent (RESS-SC). J. Supercrit. Fluids 133, 239–252. https://doi.org/10.1016/j.supflu.2017.10.015 (2018).

9. Zordi, N. D., Kikic, I., Moneghini, M. & Solinas, D. Solubility of pharmaceutical compounds in supercritical carbon dioxide. J. Supercrit. Fluids 66, 16–22. https://doi.org/10.1016/j.supflu.2011.09.018 (2012).

10. Reddy, T. A. & Garlapati, C. Dimensionless empirical model to correlate pharmaceutical compound solubility in supercritical carbon dioxide. Chem. Eng. Technol. 42, 2621–2630. https://doi.org/10.1007/ceat.201900283 (2019).

11. Mahesh, G. & Garlapati, C. Modelling of solubility of some parabens in supercritical carbon dioxide and new correlations. Arab. J. Sci. Eng. https://doi.org/10.1007/s13369-021-05500-2 (2021).

12. Sodeifan, G., Razimanesh, F., Sajadian, S. A. & Panah, H. S. Solubility measurement of an antihistamine drug (loratadine) in supercritical carbon dioxide: Assessment of qCPA and PCP-SAFT equations of state. Fluid Phase Equilib. 472, 147–159. https://doi.org/10.1016/j.fluid.2018.05.018 (2018).

13. Sodeifan, G., Nasri, L., Razimanesh, F. & Abadian, M. Measuring and modeling the solubility of an antihypertensive drug (losartan potassium, Cozaar) in supercritical carbon dioxide. J. Mol. Liq. 331, 115745. https://doi.org/10.1016/j.molliq.2021.115745 (2021).

14. Sodeifan, G., Garlapati, C., Razimanesh, F. & Sodeifan, F. Solubility of anamolide besylate (calcium channel blocker drug) in supercritical carbon dioxide: Measurement and correlations. J. Chem. Eng. Data. 66, 1119–1131. https://doi.org/10.1021/acs.jced.0c00913 (2021).

15. Sodeifan, G., Razimanesh, F., Ardestani, N. S. & Sajadian, S. A. Experimental data and thermodynamic modeling of solubility of Atazanavir, as an immunosuppressive and anti-cancer drug, in supercritical carbon dioxide. J. Mol. Liq. 299, 112179. https://doi.org/10.1016/j.molliq.2019.112179 (2020).

16. Sodeifan, G., Alwi, R. S., Razimanesh, F. & Tamura, K. Solubility of quetiapine hemifumarate (antipsychotic drug) in supercritical carbon dioxide: Experimental, modeling and hansen solubility parameter application. Fluid Phase Equilib. 537, 113003. https://doi.org/10.1016/j.fluid.2021.113003 (2021).

17. Sodeifan, G., Sajadian, S. A. & Ardestani, N. S. Determination of solubility of Aprepitant (an antiemetic drug for chemotherapy) in supercritical carbon dioxide: Empirical and thermodynamic models. J Supercrit. Fluids 128, 102–111. https://doi.org/10.1016/j.supflu.2017.05.019 (2017).

18. Sodeifan, G., Sajadian, S. A. & Razimanesh, F. Solubility of an antihypertensive drug (amiodarone hydrochloride) in supercritical carbon dioxide: Experimental and modeling. Fluid Phase Equilib. 450, 149–159. https://doi.org/10.1016/j.fluid.2017.07.015 (2017).

19. Sodeifan, G., Sajadian, S. A., Razimanesh, F. & Havaei, S. M. Solubility of Ketoconazole (antifungal drug) in SC-CO2 for binary and ternary systems: Measurements and empirical. Sci. Rep. 11, 7546. https://doi.org/10.1038/s41598-021-87243-6 (2021).

20. Sodeifan, G., Garlapati, C., Razimanesh, F. & Sodeifan, F. The solubility of Sulfabenzamide (an antibacterial drug) in supercritical carbon dioxide: Evaluation of a new thermodynamic model. J. Mol. Liq. 335, 116446. https://doi.org/10.1016/j.molliq.2021.116446 (2021).

21. Peper, S., Fonseca, J. M. S. & Dohrn, R. High-pressure fluidphase equilibria: Trends, recent developments, and systems investigated (2009–2012). Fluid Phase Equilib. 484, 126–224. https://doi.org/10.1016/j.fluid.2018.10.007 (2019).

22. Alwi, R. S. & Garlapati, C. A new semi empirical model for the solubility of dyestuffs in supercritical carbon dioxide. Chem. Pap. 75, 2585–2595. https://doi.org/10.1007/s11696-020-01482-x (2021).

23. Barfie, K. D., Cliford, A. A., Jafar, S. A. & Shilstone, G. F. Solubilities of solids and liquids of low volatility in supercritical carbon dioxide. J. Phys. Chem. Ref. Data 20, 713–756. https://doi.org/10.1063/1.553893 (1991).

24. Bian, X.-Q., Zhang, Q., Du, Z.-M., Chen, J. & Iauber, J. N. A five-parameter empirical model for correlating the solubility of solid compounds in supercritical carbon dioxide. Fluid Phase Equilib. 411, 74–80. https://doi.org/10.1016/j.fluid.2015.12.017 (2016).

25. Chrusti, J. Solubilities of solids and liquids in supercritical gases. J. Phys. Chem. 86, 3016–3021. https://doi.org/10.1021/jc100412a (1982).

26. Garlapati, C. & Madras, G. Solubilities of Palmitic and steric fatty acids in supercritical carbon dioxide. J. Chem. Thermodyn. 42, 193–197. https://doi.org/10.1016/j.jct.2009.08.001 (2010).

27. Garlapati, C. & Madras, G. Solubilities of solids in supercritical fluids using dimensionally consistent modified solvate complex models. Fluid Phase Equilib. 283, 97–101. https://doi.org/10.1016/j.fluid.2009.05.013 (2009).

28. Garlapati, C. & Madras, G. New empirical expressions to correlate solubilities of solids in supercritical carbon dioxide. Thermochim. Acta 500, 123–127. https://doi.org/10.1016/j.tca.2009.12.004 (2010).

29. Méndez-Santiago, J. & Te Ta, A. S. solubility of solids in supercritical fluids. Fluid Phase Equilib. 158, 501–510. https://doi.org/10.1016/S0378-3812(99)00154-5 (1999).

30. Sodeifan, G., Razimanesh, F. & Sajadian, S. A. Solubility measurement of a chemotherapeutic agent (Imatinib mesylate) in supercritical carbon dioxide: Assessment of new empirical model. J. Supercrit. Fluids 146, 89–99. https://doi.org/10.1016/j.supflu.2019.01.006 (2019).

31. Sandler, S. I. Chemical, Biochemical and Engineering Thermodynamics 664–666 (Wiley, 1996).

32. Peng, D. Y. & Robinson, D. B. A new two-constant equation of state. Ind. Eng. Chem. Fundam. 15, 59–64. https://doi.org/10.1021/i160057a011 (1976).

33. Prausnitz, J. M., Lichtenthaler, R. N. & De Azevedo, E. G. Molecular Thermodynamics of Fluid-Phase Equilibria 33–34 (Mcgraw-Hill, 2001).

34. Garlapati, C. & Madras, G. Temperature independent mixing rules to correlate the solubilities of antibiotics and anti-inflammatory drugs in SCCO₂. Thermochim. Acta 496, 54–58. https://doi.org/10.1016/j.tca.2009.06.022 (2009).

35. Sodeifan, G., Garlapati, C., Razimanesh, F. & Sodeifan, F. Solubility of 2,4,7-Triamino-6-phenylpteridine (triateriune, diuretic drug) in supercritical carbon dioxide: Experimental data and modeling. J. Chem. Eng. Data 65, 4406–4416. https://doi.org/10.1021/acs.jced.5c02628 (2020).

36. Chen, K.-W., Tang, M. & Chen, Y.-P. Calculation of solid solubility in supercritical fluids using a simplified cluster salvation model. Fluid Phase Equilib. 234, 169–186. https://doi.org/10.1016/S0378-3812(03)00350-9 (2003).

37. Zong, M., Han, B., Ke, J., Yan, H. & Peng, D. Y. A model for correlating solubility of of solids in supercritical CO₂. Fluid Phase Equilib. 146, 93–102. https://doi.org/10.1016/S0378-3812(98)00207-6 (2000).
38. Lemert, R. M. & Johnston, K. P. Chemical complexing agents for enhanced solubilities in supercritical fluid carbon dioxide. Ind. Eng. Chem. Res. 30, 1222–1231. https://doi.org/10.1021/ie00054a024 (1991).
39. Rajaram, J. & Kuriacose, J. C. Chemical Thermodynamics Classical, Statistical and Irreversible 218–219 (Pearson Dorling Kindersley, 2013).
40. Fedors, R. F. A relationship between chemical structure and the critical temperature. Chem. Eng. Commun. 16, 149–151. https://doi.org/10.1080/00986448208911092 (1982).
41. Reid, R. C., Prausnitz, J. M. & Poling, B. E. The Properties of Gases and Liquids (McGraw-Hill, 1988).
42. Immirzi, A. & Perini, B. Prediction of density in organic crystals. Acta Crystall. A-Cryst. 33, 216–218. https://doi.org/10.1107/S0567739477000448 (1977).
43. Lyman, W. J., Reese, W. F. & Rosenblatt, D. H. Handbook of Chemical Property Estimation Methods (McGraw-Hill, 1982).
44. Valderrama, J. O. & Alvarez, V. H. Correct way of reporting results when modelling supercritical phase equilibria using equations of state. Can. J. Chem. Eng. 83, 578–581. https://doi.org/10.1002/cjce.5450830323 (2005).
45. Kletting, P. & Glatting, G. Model selection for time-activity curves: The corrected Akaike information criterion and the F-test. Zeitschrift für medizinische Physik 19, 200–206. https://doi.org/10.1016/j.zemedi.2009.05.003 (2019).
46. Burnham, K. P. & Anderson, D. R. Multimodel inference understanding AIC and BIC in model selection. Sociol. Methods Res. 33, 261–304. https://doi.org/10.1177/0049124104268644 (2004).
47. Deepitha, J., Pitchaiah, K. C., Rao, C. V. S. R., Madras, G. & Sivaraman, N. Solubilities of dialkylhydrogen phosphonates in supercritical carbon dioxide and their correlation using semi-empirical equations. Sep. Sci. Technol. 54, 1650–1660. https://doi.org/10.1080/01496395.2018.1538244 (2019).
48. Pitchaiah, K. C. et al. Experimental measurements and correlation of the solubility of N, N-dialkylamides in supercritical carbon dioxide. J. Supercrit. Fluids 143, 162–170. https://doi.org/10.1016/j.supflu.2018.09.007 (2019).
49. Lamba, N., Narayan, R. C., Modak, J. & Madras, G. Solubilities of 10-undecenoic acid and geranium in supercritical carbon dioxide. J. Supercrit. Fluids 107, 384–391. https://doi.org/10.1016/j.supflu.2015.09.026 (2016).
50. National Institute of Standards and Technology U.S. Department of Commerce, NIST ChemistryWebBook, in, 2018, October. https://webbook.nist.gov/chemistry/ (23 March 2021).

Acknowledgements
Corresponding authors would like to thank the research deputy of university of Kashan (Grant # Pajoohaneh-1400/16) for the financial support of this project. Authors also appreciate Amin Pharma Company for providing the required drug.

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; M.G.: Methodology, Investigation, Validation.

Competing interests
The authors declare no competing interests.

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

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, and indicate if changes were made. If material is not included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021