Solubility measurement and thermodynamic modeling of pantoprazole sodium sesquihydrate in supercritical carbon dioxide

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Knowing the solubility data of pharmaceutical compounds in supercritical carbon dioxide (ScCO$_2$) is essential for nanoparticles formation by using supercritical technology. In this work, solubility of solid pantoprazole sodium sesquihydrate in ScCO$_2$ is determined and reported at 308, 318, 328 and 338 K and at pressures between 12 and 27 MPa. The solubilities are ranged between 0.0301 $\times 10^{-4}$ and 0.463 $\times 10^{-4}$ in mole fraction. The determined solubilities are modelled with a new model using solid–liquid equilibrium criteria and the required activity coefficient is developed using regular solution theory. The measured solubilities data are also modelled with three recent and four conventional empirical models. The recent models used are, Alwi-Garlapati (AARD = 13.1%), Sodeifian et al. (14.7%), and Tippapa-Garlapati (15.5%) models and the conventional models used are Chrastil (17.54%), reformulated Chrastil (16.30%), Bartle (14.1%) and Mendenz Santiago and Teja (MT) (14.9%) models. The proposed model is correlating the data with less than 14.9% and 16.23% in terms of AARD for temperature dependent and independent cases. Among exiting models, Mendez Santiago and Teja (MT) and Alwi-Garlapati models correlate the data better than other models (corresponding AARD% and AIC$^c$ are 14.9, 13.1 and –518.89, –504.14, respectively). The correlation effectiveness of the models is evaluated in terms of Corrected Akaike's Information Criterion (AIC$^c$). Finally, enthalpy of solvation and vaporization of pantoprazole sodium sesquihydrate are calculated and reported. The new model proposed in this study can be used for the combination of any complex compound with any supercritical fluid.

List of symbols

- $A_0 - A_2$ Eq. (15) parameters
- AARD% Average absolute relative deviation percentage
- AIC Akaike's information criterion
- AIC$^c$ Corrected AIC
- Adj.R$^2$ Statistical parameter
- $B_0 - B_5$ Eq. (16) parameters
- $C_p$ Heat capacity
- $D_0 - D_5$ Eq. (17) parameters
- $E_0 - E_2$ Eq. (18) parameters
- $f^*$ Standard state [fugacity(1 bar)] in Eq. (18)
- $F_0 - F_2$ Eq. (19) parameters
- $G_0 - G_2$ Eq. (20) parameters

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The utilization of carbon dioxide ($\text{CO}_2$) in its supercritical condition (commonly designated as $\text{ScCO}_2$) in drug particle formation is evident in the literature\(^1\)–\(^5\). The implementation of such supercritical technology needs an exact solubility data. The methods of measuring solubility data are well established in the literature and the data are usually available in a limited range\(^6\)–\(^17\). Measuring solubility data at every condition would be cumbersome and appropriate modeling is required to address this task\(^18\)–\(^20\). Solubility modeling is valuable and no single model would serve all the compounds, most of the times, the models are specific to compounds and due to this reason, numbers of models are developed to correlate the solubility data\(^20\). Exact solubilities measurements along with modeling are necessary for selecting the suitable particle micronization method using $\text{ScCO}_2$. Further, it is observed in the literature that there is lack of information about the solubility data of many important drugs in $\text{ScCO}_2$, therefore, the task of estimation of solubility of drugs in $\text{ScCO}_2$ is imperative for the implementation of supercritical technology.

Pantoprazole sodium sesquihydrate is an important drug that is prescribed for the treatment of gastroesophageal reflux disease (GERD) and it proper dosage is critical in its treatment. Drug particle size greatly influences bioavailability of the drug which in turn influences the drug dosage. Currently, maximum of 20 mg per day of pantoprazole sodium sesquihydrate is being used for the treatment of gastroesophageal reflux disease\(^21\). Present study is helpful in the selection of a suitable method for the production of drug nanoparticles or microparticles by using supercritical technology, followed by a reduction in drug dosage. In order to pursue this, experimental solubility information of the drug is essential. However, the solubility of pantoprazole sodium sesquihydrate in $\text{ScCO}_2$ was not reported in the literature, hence, measuring and modeling of its solubility are studied in this work. Pantoprazole sodium sesquihydrate is a typical compound as it has sodium in its structure and due to this, it is not possible to apply the group contribution methods to evaluate the critical properties and vapour pressure data. Thus, the equation of state (EoS) modeling is not applicable for the solubility data and there is need to develop a suitable solubility model to correlate the data. Therefore, in this work a new solubility model is proposed to correlate the solubility of pantoprazole sodium sesquihydrate in $\text{ScCO}_2$. Further, models appeared in recent literature proposed by Alwi-Garlapati\(^22\), Sodeifian\(^23\) and Tippana-Garlapati\(^24\) as well as the conventional models proposed by Chrastil\(^25\), Reformulated Chrastil (R. Chrastil)\(^26\), Bartle\(^27\) and Mendez Santiago and Teja (MT)\(^28\) are explored. The conventional models (Reformulated Chrastil (R. Chrastil), Bartle) are mainly used to obtain necessary thermodynamic information of the solute from its solubility data. Mendez Santiago and Teja (MT) model is used to check its self-consistency. Alwi-Garlapati\(^22\) model is developed based on solid–liquid phase equilibrium criteria and Sodeifian and Tippana-Garlapati models are empirical models developed specifically for correlating solubility data of compounds in $\text{ScCO}_2$. Finally, the correlating ability of different models is evaluated by Akaike’s Information Criterion (AIC).
Experimental section

Chemical details. The CO₂ and Pantoprazole sodium sesquihydrate were obtained from Fadak Company, Kashan (Iran). Pantoprazole sodium sesquihydrate was obtained from Temad Pharmaceutical Company, (Iran) (Table 1).

Experiment. The equipment used for solubility measurement is shown in Fig. 1. The method utilized is considered as the isobaric-isothermal method. Each measurement is performed with high precision, during experiments; temperature is maintained at desired value within ±0.1 K. A known amount of pantoprazole sodium sesquihydrate drug (solute) has been used in the equilibrium cell to measure the solubility data. The capacity of the cell is 70 mL. A magnetic stirrer was mounted with the cell to measure the solubility data. A magnetic stirrer that is mounted with the equilibrium cell helps in attaining equilibrium between the solute and the ScCO₂. To confirm equilibrium attainment, the experiments are done with a fresh sample at specified temperature and pressure at various time intervals (5 min, 10 min, 20 min, 30 min, 40 min, 50 min and 60 min) and the solubility readings are recorded. It is observed that the solubility is independent of time after 30 min. Thus, for correct results after 60 min, samples are considered for analysis. After equilibrium, 600 µL of a saturated sample is collected in dematerialized water (DM water’s conductivity is 1μS/cm) via a 6-way port, two-status valve. More details are readily available elsewhere. This experimental setup has already been validated in the previous work with alpha-tocopherol and naphthalene. Each experiment is carried out in triplicate.

Spectrophotometer (UV–Visible, Model UNICO-4802) is utilized to quantify the pantoprazole sodium sesquihydrate solubility. The drug test samples were prepared by dissolving known weights of drug in known volume of DM water. Pantoprazole sodium sesquihydrate samples were analyzed at 290 nm and calibrations curve was established, indicating R² of 0.99.

The following sets of equations are used to calculate equilibrium mole fraction, y₂, and solubility, S (g/L), in ScCO₂:

![Figure 1. Device used for the measurement of solubility, E1 is the CO₂ cylinder; E-2 is the Filter; E-3 is the Refrigerator unit; E-4 is the Air compressor; E-5 is the Pump; E-6 is the Equilibrium cell; E-7 is the Magnetic stirrer; E-8 is the Needle valve; E-9 is the Back-pressure valve; E-10is the Six-port valve; E-11 is the Oven; E-12 is the Syringe; E13 is the Collection vial; E-14 is the Control panel.](image-url)

Table 1. Chemicals used in the work and its details.

| Compound                      | Formula                                      | Structure                                                                 | M_w (g/mol) | T_m (K) | λ_max (nm) | CAS number       | Minimum purity by supplier |
|-------------------------------|----------------------------------------------|---------------------------------------------------------------------------|-------------|----------|------------|------------------|-----------------------------|
| Pantoprazole sodium sesquihydrate | C₁₆H₁₄F₂N₃NaO₄S × 1.5 H₂O                    | ![Pantoprazole sodium sesquihydrate](image-url)                           | 432.4       | 412      | 290        | 164579-32-2     | 99% (HPLC)                 |
| Carbon dioxide                | CO₂                                          |                                                                           | 44.01       |          |            | 124-38-9        | 99.99% (GC)                |
| Deionized water               | H₂O                                          |                                                                           | 18.01       |          |            |                  |                             |


\[ y_2 = \frac{n_{\text{solute}}}{n_{\text{solute}} + n_{\text{CO}_2}}, \]  
\[ n_{\text{solute}} = \frac{C_s \left( \frac{x}{\text{mol}} \right) V_s (L)}{M_s \left( \frac{x}{\text{mol}} \right)}, \]  
\[ n_{\text{CO}_2} = \frac{V_l (L) \rho \left( \frac{x}{\text{mol}} \right)}{M_{\text{CO}_2} \left( \frac{x}{\text{mol}} \right)} \]  
\[ S \left( \frac{x}{L} \right) = \frac{C_s \left( \frac{x}{\text{mol}} \right) V_l (L)}{V_l (L)} \]

where \( n_{\text{solute}} \) and \( n_{\text{CO}_2} \) are moles of solute (Pantoprazole sodium sesquihydrate) and \( \text{CO}_2 \) in the sampling loop, respectively, \( C_s \) is the solute concentration (g/L), \( M_s \) and \( M_{\text{CO}_2} \) are molecular weights of the solute and \( \text{CO}_2 \) and \( S \) (g/L) is the equilibrium solubility.

**Modeling**

**New solution model.** In this model, \( \text{ScCO}_2 \) is treated as expanded liquid. At equilibrium, the fugacity of the solute in the solid phase is equal to that of liquid phase and the solubility can express as:

\[ y_2 = \frac{1}{\gamma_2^\infty} \frac{f_2^S}{f_2^L} \]  
\[ \ln \left( \frac{f_2^S}{f_2^L} \right) = \frac{\Delta H_m}{RT} \left( \frac{T}{T_m} - 1 \right) - \int_{T_m}^T \left[ \frac{1}{RT^2} \Delta C_p \right] dT \]  
\[ \ln \left( \frac{f_2^S}{f_2^L} \right) = \frac{\Delta H_m}{RT} \left( \frac{T}{T_m} - 1 \right) - \frac{\Delta C_p}{R} \left[ \ln \left( \frac{T}{T_m} \right) - T_m \left( \frac{1}{T_m} - \frac{1}{T} \right) \right] \]

where, \( \Delta C_p \) is known as heat capacity difference of the solute in solid and liquid phases. For constant \( \Delta C_p \), Eq. (6) reduced to Eq. (7).

Combining Eq. (7) with Eq. (5) gives the expression for the solubility model (Eq. (8)).

\[ y_2 = \frac{1}{\gamma_2^\infty} \exp \left[ \frac{\Delta H_m}{RT} \left( \frac{T}{T_m} - 1 \right) - \frac{\Delta C_p}{R} \left[ \ln \left( \frac{T}{T_m} \right) - T_m \left( \frac{1}{T_m} - \frac{1}{T} \right) \right] \right] \]

In order to use Eq. (8), an appropriate model for \( \gamma_2^\infty \) is needed. In this work, the required \( \gamma_2^\infty \) is obtained from regular solution theory and it is represented as Eq. (9).

\[ \gamma_2^\infty = \exp \left[ \frac{V_1 \psi^2}{RT} (\delta_2 - \delta_1)^2 \right] \]

where \( V_1 \psi, R, T, \delta_1 \) and \( \delta_2 \) are molar volume of \( \text{ScCO}_2 \), volume fraction of \( \text{ScCO}_2 \), universal gas constant, system temperature and solubility parameter of \( \text{ScCO}_2 \) (solvent) and solubility parameter of drug (solute), respectively. \( \psi, \delta_1 \) and \( \delta_2 \) are mathematically represented as

\[ \psi = \frac{x_1 \rho_1}{x_1 \rho_2 + x_2 \rho_1} \]  
\[ \delta_1 = \sqrt{a_{11} \rho_1} \]  
\[ \delta_2 = \sqrt{a_{22} \rho_2} \]

Combining Eqs. (10a), (10b), (10c) with Eq. (9) and neglecting the term \( x_2 \rho_1 \) in comparison to \( x_1 \rho_2 \) gives Eq. (11).

\[ \gamma_2^\infty = \exp \left[ \frac{1}{RT} \left( a_{22} + a_{11} \frac{\rho_1}{\rho_2} - 2 \sqrt{a_{11} a_{22}} \left( \frac{\rho_1}{\rho_2} \right)^{0.5} \right) \right] \]

Equation (11) is further reduced in terms of molar volume of solute (\( y_2 \)) as Eq. (12).
\( \gamma_2^\infty = \exp \left[ \frac{1}{RT} \left( a_{22} + a_{11} v_2 \rho_1 - 2\sqrt{a_{11}a_{22}(v_2\rho_1)^{0.5}} \right) \right] \)  \( \text{(12)} \)

Combining Eq. (12) with Eq. (9) gives a new explicit solubility model, (Eq. (13))

\[
y_2 = \exp \left[ \frac{\Delta H_m^m}{RT} \left( \frac{T}{T_m} - 1 \right) - \frac{\Delta C_p}{R} \left[ \ln \left( \frac{T}{T_m} \right) - T_m \left( \frac{1}{T} - \frac{1}{T_m} \right) \right] \right] / \exp \left[ \frac{1}{RT} \left( a_{22} + a_{11} v_2 \rho_1 - 2\sqrt{a_{11}a_{22}(v_2\rho_1)^{0.5}} \right) \right]
\]

Equation (13) indicates that solubility is a function of several quantities, which are melting enthalpy of the solute (\( \Delta H_m^m \)), melting temperature of the solute (\( T_m \)), heat capacity difference of solute between solid and expanded liquid phases (\( \Delta C_p \)), temperature (\( T \)), molar volume of the solute (\( v_2 \)), ScCO\textsubscript{2} density (\( \rho_1 \)), interaction potential of the solvent–solvent molecule (\( a_{11} \)) and interaction potential of the solute–solvent molecule (\( a_{22} \)). In this model, it is assumed that \( \Delta H_m^m, T_m, v_2 \) and \( \rho_1 \) are known/fixed. Therefore, for an isotherm (i.e., known \( T \)) \( \Delta C_p, a_{11} \) and \( a_{22} \) are adjustable parameters; further, over a small temperature range these parameters may be treated as constants. In the case of unavailability of experimental data of \( \Delta H_m^m, T_m \) and \( v_2 \) are estimated with the help of suitable group contribution method. Sometimes, presence of sodium like metals in solute compounds hinders the applicability of group contribution method to evaluate the melting enthalpy and activity coefficient. In such cases, the term \( 6.54(1 - T_m/T) \) is used in place of term \( \Delta H_m^m/RT \left( T/T_m - 1 \right) \) \( ^{36,38} \). Thus, the final expression for the solubility becomes Eq. (14).

\[
y_2 = \exp \left[ 6.54 \left( 1 - \frac{T}{T_m} \right) - \frac{\Delta C_p}{R} \left[ \ln \left( \frac{T}{T_m} \right) - T_m \left( \frac{1}{T} - \frac{1}{T_m} \right) \right] \right] / \exp \left[ \frac{1}{RT} \left( a_{22} + a_{11} v_2 \rho_1 - 2\sqrt{a_{11}a_{22}(v_2\rho_1)^{0.5}} \right) \right]
\]

In Eq. (14), \( \Delta C_p, a_{11} \) and \( a_{22} \) are adjustable constants and thus it is a three parameters model. It is very important to note that proposed solution model essentially requires the solute’s physical property (i.e., melting temperature and density of ScCO\textsubscript{2}). Therefore, the new model proposed in this study cannot be applied to the system whose melting point is not known.

From the literature, it is clear that the solubility is highly a nonlinear function of density, pressure and temperature\(^{34} \). The ability of a particular model in correlating the solubility data is also not clear due to its nonlinearity, so, several models are used for the correlation purpose. The models used are few latest models and conventional models. The other purpose of the conventional models is to estimate the essential thermodynamic information such as total heat, sublimation and solvation enthalpies. More details of the same are presented in the following section.

**Recent models.**  
*Alwi-Garlapati model.*  It is a simple model and its basis is thermodynamic frame work. According to the model, at equilibrium, solute’s chemical potentials in both solid and liquid phases are equal. Further, solid sublimation pressure is assumed to obey Antoine’s equation and sublimation pressure to temperature ratio is negligible when it is compared to total pressure to temperature ratio. Thus, the final expression for the solubility (\( y_2 \)) in terms of reduced density (i.e., \( \rho_1/T_r \)) and reduced temperature (i.e., \( T_r = T/T_c \)) is:

\[
y_2 = \frac{1}{\rho_1/T_r} \exp \left( A_0 + A_1 \frac{T_r}{T} + A_2 \rho_1 T_r \right)
\]

where \( A_0 - A_2 \) are model constants.

*Sodeifian et al., model.* It is a highly nonlinear mathematical model and correlates solubility in terms of pressure, temperature and density as:

\[
\ln \left( y_2 \right) = B_0 + \frac{B_1 P_2}{T} + B_2 \ln \left( \rho_1 T \right) + B_3 \left( \rho_1 \ln \left( \rho_1 \right) \right) + B_4 P \ln \left( T \right) + B_5 \frac{\ln \left( \rho_1 \right) T}{T}
\]

where \( B_0 - B_5 \) are model constants.

*Reddy-Garlapati model.* It is a dimensionless empirical model and correlates solubility in terms of reduced pressure and reduced temperature as:

\[
y_2 = \left( D_0 + D_1 P_r + D_2 P_r^2 \right) T_r^2 + \left( D_3 + D_4 P_r + D_5 P_r^2 \right)
\]

where \( D_0 - D_5 \) are model constants.

**Conventional models.**  
*Chrustil model.* It is the first solvate complex model and correlates solubility as a function of supercritical fluid density and temperature as:

\[
y_2 = \frac{(\rho_1)^{x-1} \exp \left( E_0 + E_1 \frac{T}{T} \right)}{1 + (\rho_1)^{x-1} \exp \left( E_0 + E_1 \frac{T}{T} \right)}
\]

where \( x \) and \( E_0 - E_1 \) are model constants.
Since Eq. (13) is dimensionally inconsistent\cite{24,26,39}, it is dimensionally corrected and known as *Reformulated Chrastil model*:

\[
y_2 = \left( \frac{RT \rho_1}{M_{cmf} \kappa'} \right)^{\kappa' - 1} \exp \left( \frac{F_0 + F_1}{T} \right)
\]

where \( \kappa' \) and \( E_0 - E_1 \) are model constants.

**Bartle et al., model.** It is one of the successful empirical models and correlates solubility as a function of temperature, supercritical fluid density and total pressure as:

\[
\ln \left( \frac{y_2 P}{P_{ref}} \right) = G_0 + G_1 \frac{T}{P} + G_2 (\rho_1 - \rho_{ref})
\]

where \( G_0 - G_2 \) are model constants. From parameter \( G_1 \), the vaporization enthalpy is \( \Delta_{vap} H = -G_1 R \) in which \( R \) is universal gas constant.

**Mendez Santiago and Teja (MT) model.** It is conceptually developed on the statement of enhancement factor. According to this model, solubility is a function temperature, pressure and supercritical fluid density:

\[
T \ln (y_2 P) - H_2 T = H_0 + H_1 P
\]

When solubility data is casted on a plot as “\( T \ln (y_2 P) - H_2 T \) vs. \( \rho_1 \)”, all experimental data points irrespective of temperature collapse on to a single line (which is obtained out of calculated data). This model is usually used to check the generated data’s self-consistency.

**Results and discussion**

The *pantoprazole sodium sesquihydrate* solubility in ScCO\(_2\) is determined at 308, 318, 328 and 338 K and at pressures between 12 and 27 MPa. The measured data is reported in Table 2. The reported ScCO\(_2\) densities are obtained from standard literature\cite{40}. The high operating pressure increases solvent’s density and reduces intermolecular spaces between carbon dioxide molecules which increase interactions between the drug and ScCO\(_2\) molecules. It thus causes an enhancement of ScCO\(_2\)’s solvating power. Also, *pantoprazole sodium sesquihydrate*’s solubility is influenced by the complex effect of operating temperature which has a simultaneous effect on solute’s sublimation pressure, solvent density and obviously intermolecular interactions in the supercritical fluid phase\cite{42,43,44}. From Fig. 2, it is observed that cross over pressure is around 16.0 MPa, further, solubility decreases with increasing temperatures and increases with increasing temperature below and above cross over pressure. The self-consistency is indicated in the Fig. 3. From this figure, it is observed that all measured data fall into a line which indicates that the solubility data in this work is self-consistent.

The new solution model proposed in this work has three adjustable parameters (\( \Delta_C p, a_{11} \) and \( a_{22} \)). For regression, these parameters are treated as temperature dependent and temperature independent. Although conceptually, these parameters are temperature dependent\cite{43,44}; however, in literature, these parameters are handled as temperature independent over a small temperature range\cite{45}. Therefore, both temperature dependent and independent results are reported in this study. For regression, melting temperature and molar volume of *pantoprazole sodium sesquihydrate* are needed. The required melting temperature is obtained from the material’s source and the molar volume of the solid *pantoprazole sodium sesquihydrate* is calculated using Immirzi and Perini method\cite{38}. The material safety data indicates that the melting temperature is 412 K and calculated molar volume is \( 2.8202 \times 10^{-4} \) m\(^3\)/mol. The proposed model correlates the data less than 14.9% and 16.23% in terms of AARD% for temperature dependent and independent cases, respectively. Table 3 shows all the new model correlations. The correlating ability of the new model proposed in this study is indicated in Fig. 4. The correlations of the solubility data with temperature dependent parameters are better than temperature independent parameters. Alwi-Garlapati, Sodeifian et al., and Reddy-Garlapati models correlate the solubility data. The correlation constants are reported in Table 4. The regression ability of the recent models for the solubility prediction is indicated in the Fig. 5. The correlations of the data are quite satisfactory for Alwi-Garlapati model compared to Reddy-Garlapati and Sodeifian models. The correlation constants of conventional models as temperature independent are reported in Table 5. The correlating ability of the recent models is indicated in Fig. 6. From the conventional model constants, the thermodynamic properties, namely total heat of enthalpy of vaporization and solvation are calculated and reported in Table 6. The vaporization enthalpy obtained for Bartle et al., model is 72.18 kJ/mol. From Chrastil model, total heat is \( -59.432 \) kJ/mol (i.e., \( -7147.4 \times R \), where \( R \) is universal gas constant). Solvation enthalpy is obtained from the difference between total and vaporization enthalpies. Solvation enthalpy for Bartle et al., model and Chrastil model combination is \( -15.829 \) kJ/mol and the negative sign is attributed since the solvation enthalpy is exothermic. Similarly, from the reformulated Chrastil and Bartle et al., models combination, solvation enthalpy is \( -35.996 \) kJ/mol.

Statistical comparisons of various models are conveniently carried out with Corrected AICc criterion\cite{38–41}. Mathematically, AIC\(_c\) is represented as:

\[
AIC_c = n \ln(\sigma^2) + 2Q + \frac{2Q(Q + 1)}{n - Q - 1}
\]
### Table 2. Solubility of pantoprazole sodium sesquihydrate in SC\(_2\)O\(_3\) at various temperatures and pressures. The experimental standard deviation was obtained by \(S(\bar{y}_k) = \sqrt{\frac{\sum(y_j - \bar{y})^2}{n-1}}\). Expanded uncertainty (U) = \(k u_{\text{combined}}\) and the relative combined standard uncertainty \(u_{\text{combined}} / y = \sqrt{\sum (P_i u(x_i)/x_i)^2}\). *Standard uncertainty u are \(u(T) = \pm 0.1\) K; \(u(p) = \pm 0.1\) MPa. Also, relative standard uncertainties are obtained below 5% 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.

| Temperature (K) | Pressure (MPa) | Density of SC\(_2\)O\(_3\) (kg/m\(^3\)) | \(y_2 \times 10^4\) (mole fraction) | Experimental standard deviation, \(S(\bar{y}) \times 10^4\) | \(S\) (equilibrium solubility) (g/L) | Expanded uncertainty of mole fraction (10\(^{-4}\) U) |
|-----------------|----------------|-----------------------------------|---------------------------------|-----------------------------------|---------------------------------|----------------------------------|
| 308             | 12             | 769                               | 0.0648                          | 0.001                             | 0.0435                          | 0.0036                           |
|                 | 15             | 817                               | 0.0764                          | 0.003                             | 0.0544                          | 0.0069                           |
|                 | 18             | 849                               | 0.0921                          | 0.004                             | 0.0682                          | 0.0090                           |
|                 | 21             | 875                               | 0.0958                          | 0.004                             | 0.0731                          | 0.0091                           |
|                 | 24             | 896                               | 0.1239                          | 0.006                             | 0.0968                          | 0.0132                           |
|                 | 27             | 914                               | 0.1489                          | 0.006                             | 0.1183                          | 0.0137                           |
| 318             | 12             | 661                               | 0.0548                          | 0.002                             | 0.0316                          | 0.0047                           |
|                 | 15             | 744                               | 0.0580                          | 0.002                             | 0.0377                          | 0.0048                           |
|                 | 18             | 791                               | 0.0990                          | 0.004                             | 0.0682                          | 0.0091                           |
|                 | 21             | 824                               | 0.1192                          | 0.003                             | 0.0856                          | 0.0080                           |
|                 | 24             | 851                               | 0.1436                          | 0.004                             | 0.1064                          | 0.0102                           |
|                 | 27             | 872                               | 0.1930                          | 0.007                             | 0.1467                          | 0.0164                           |
| 328             | 12             | 509                               | 0.0381                          | 0.001                             | 0.0170                          | 0.0026                           |
|                 | 15             | 656                               | 0.0498                          | 0.001                             | 0.0285                          | 0.0030                           |
|                 | 18             | 725                               | 0.1388                          | 0.003                             | 0.0877                          | 0.0086                           |
|                 | 21             | 769                               | 0.1579                          | 0.004                             | 0.1059                          | 0.0106                           |
|                 | 24             | 802                               | 0.2354                          | 0.003                             | 0.1646                          | 0.0120                           |
|                 | 27             | 829                               | 0.3106                          | 0.005                             | 0.2243                          | 0.0170                           |
| 338             | 12             | 388                               | 0.0301                          | 0.001                             | 0.0101                          | 0.0024                           |
|                 | 15             | 557                               | 0.0403                          | 0.002                             | 0.0196                          | 0.0044                           |
|                 | 18             | 652                               | 0.1548                          | 0.002                             | 0.0880                          | 0.0080                           |
|                 | 21             | 710                               | 0.1938                          | 0.004                             | 0.1200                          | 0.0118                           |
|                 | 24             | 751                               | 0.3408                          | 0.006                             | 0.2231                          | 0.0192                           |
|                 | 27             | 783                               | 0.4634                          | 0.003                             | 0.3163                          | 0.0213                           |

**Figure 2.** Pantoprazole sodium sesquihydrate solubility vs. pressure.
Figure 3. Solubility data self-consistency plot based on MT model.

Table 3. Correlation constants of the new model.

| New model, eq | Temperature, K | Correlation parameters | AARD% | R² |
|---------------|----------------|------------------------|-------|----|
| As temperature dependent | 308 | \( a_{11} = 1.0939 \times 10^6 \)  \( a_{22} = 1.3423 \times 10^3 \)  \( \Delta C_p = -7.97 \times 10^3 \) | 6.40 | 0.917 |
| | 318 | \( a_{11} = 1.7124 \times 10^6 \)  \( a_{22} = 1.1794 \times 10^3 \)  \( \Delta C_p = -1.7028 \times 10^3 \) | 11.4 | 0.928 |
| | 328 | \( a_{11} = 1.9675 \times 10^6 \)  \( a_{22} = 2.267 \times 10^3 \)  \( \Delta C_p = -2.4926 \times 10^3 \) | 9.28 | 0.983 |
| | 338 | \( a_{11} = 2.0213 \times 10^6 \)  \( a_{22} = 2.0409 \times 10^3 \)  \( \Delta C_p = -3.3373 \times 10^3 \) | 14.9 | 0.985 |
| As temperature independent | 308–338 | \( a_{11} = 6.6074 \times 10^4 \)  \( a_{22} = 1.7996 \times 10^3 \)  \( \Delta C_p = 21.618 \) | 16.23 | 0.944 |

Figure 4. Pantoprazole sodium sesquihydrate solubility vs. \( \rho_1 \). Lines are new model calculations as temperature independent; dash, dot, dash dot and dash dot dot lines are new model calculations as temperature dependent.
In Eq. (22), $\sigma$, $n$ and $Q$ are variance of deviations, number of experimental data points and number of constants in a particular model, respectively. Table 7 indicates calculated AICc values. From the magnitude of AICc, one can conclude the correlating efficacy of the models and the best model has the least value. From AICc information of various models, MT and Alwi-Garlapati models are able to correlate the data better than the other models. The new model when treated as temperature independent, it correlates the data on par with Sodeifian et al. and Chrastil models.

Table 4. Correlation constants of the recent models.

| Model                        | Correlation parameters | AARD% | $R^2$ | $R^2_{adj}$ |
|------------------------------|------------------------|-------|-------|-------------|
| Alwi-Garlapati model        | $A_0 = 9.0006$         |       | 13.1  | 0.957       |
|                             | $A_1 = -28.013$        |       |       | 0.950       |
|                             | $A_2 = 5.3824$         |       |       |             |
| Sodeifian et al., model     | $B_0 = -12.725$        |       | 14.7  | 0.953       |
|                             | $B_1 = -2.874 \times 10^{-3}$ | | | 0.937 | |
|                             | $B_2 = 3.1435$         |       |       |             |
|                             | $B_3 = 1.3706 \times 10^{-3}$ | | | | |
|                             | $B_4 = -0.02141$       |       |       |             |
|                             | $B_5 = -2201.2$        |       |       |             |
| Reddy and Garlapati model   | $D_0 = -1.2535 \times 10^{-3}$ | | 15.5  | 0.958 |
|                             | $D_1 = 5.5793 \times 10^{-4}$ | | | 0.943 | |
|                             | $D_2 = 1.3763 \times 10^{-3}$ | | | | |
|                             | $D_3 = -5.7085 \times 10^{-4}$ | | | | |
|                             | $D_4 = -2.6286 \times 10^{-4}$ | | | | |

Figure 5. Pantoprazole sodium sesquihydrate solubility vs. $\rho_1$. Lines are Alwi-Garlapati model calculations; dashed lines are Sodeifian et al., model calculations; dash dot lines are Reddy-Garlapati model calculations.

Table 5. Correlation constants of the conventional models.

| Model                        | Correlation parameters | AARD% | $R^2$ | $R^2_{adj}$ |
|------------------------------|------------------------|-------|-------|-------------|
| Chrastil model              | $\kappa = 7.3712$      | 17.54 | 0.933 | 0.923       |
|                             | $E_0 = -29.074$        |       |       |             |
|                             | $E_1 = -7147.4$        |       |       |             |
| Reformulated Chrastil model | $\kappa' = 6.9821$     | 16.30 | 0.955 | 0.948       |
|                             | $F_0 = -58.493$        |       |       |             |
|                             | $F_1 = -4791$          |       |       |             |
| Bartle et al., model        | $G_0 = 23.454$         | 14.10 | 0.950 | 0.942       |
|                             | $G_1 = -9052.4$        |       |       |             |
|                             | $G_2 = 1.226 \times 10^{-2}$ | | | | |
| Mendenz Santiago and Teja model | $H_0 = -13,995$    | 14.90 | 0.975 | 0.918       |
|                             | $H_1 = 4.4779$         |       |       |             |
|                             | $H_2 = 29.372$         |       |       |             |

In Eq. (22), $\sigma$, $n$ and $Q$ are variance of deviations, number of experimental data points and number of constants in a particular model, respectively. Table 7 indicates calculated AICc values. From the magnitude of AICc, one can conclude the correlating efficacy of the models and the best model has the least value. From AICc information of various models, MT and Alwi-Garlapati models are able to correlate the data better than the other models. The new model when treated as temperature independent, it correlates the data on par with Sodeifian et al. and Chrastil models.
Pantoprazole sodium sesquihydrate’s solubility in ScCO₂ is reported at 308, 318, 328, and 338 K in the pressure range of 12–27 MPa, for the first time. The solubilities were ranged between $0.0301 \times 10^{-4}$ and $0.463 \times 10^{-4}$ in mole fraction. For modeling, three recently developed solubility models and four conventional empirical solubility models were used. Further, measured data has been used to develop a new solubility model. Among various models, Alwi-Garlapati model is observed to correlate the data with the least AARD (13.1%). The correlating ability of various equations have been observed in terms of AICc values (ascending) as follows: MT (−518.89), Alwi-Garlapati (−504.14), Sodeifian et al. (−490.05), Reddy-Garlapati model (−492.70), R. Chrastil (−492.42), Bartle et al., model (−495.46), and new model as temperature independent (−487.69). The new model proposed in this study can be used for the combination of any complex compound with any supercritical fluid.

**Figure 6.** Pantoprazole sodium sesquihydrate solubility vs. $\rho_1$. Lines are Chrastil and Reformulated Chrastil model calculations; dashed lines are Bartle et al., model calculations.

**Table 6.** Calculated thermodynamic properties of pantoprazole sodium sesquihydrate. $^d$Magnitude difference between the $\Delta H_{vap}^c$ and $\Delta H_{total}^a$. $^e$Magnitude difference between the $\Delta H_{vap}^c$ and $\Delta H_{total}^b$.

| Model                        | Total enthalpy, $\Delta H_{total}$ (kJ/mol) | Enthalpy of vaporization $\Delta H_{vap}$ (kJ/mol) | Enthalpy of solvation, $\Delta H_{solv}$ (kJ/mol) |
|------------------------------|---------------------------------------------|---------------------------------------------------|--------------------------------------------------|
| Chrastil model              | 59.432$^a$                                  | $-15.829^d$                                       |                                                  |
| Reformulated Chrastil model | 39.832$^b$                                  | $-35.429^e$                                       |                                                  |
| Bartle et al., model        |                                             | 75.261$^c$ (approximate value)                    |                                                  |

**Table 7.** Computed SSE, RMSE and AICc values for various models.

| Model                        | SSE $\times 10^8$ | RMSE $\times 10^5$ | n   | K   | AICc |
|------------------------------|-------------------|--------------------|-----|-----|------|
| New model                    |                   |                    |     |     |      |
| As temperature independent   | 2.65974           | 3.329              | 24  | 3   | −487.69 |
| Recent models                |                   |                    |     |     |      |
| Alwi-Garlapati model         | 1.34046           | 2.36331            | 24  | 3   | −504.14 |
| Sodeifian et al., model      | 1.60651           | 2.58724            | 24  | 6   | −490.05 |
| Reddy–Garlapati model,       | 1.43877           | 2.44844            | 24  | 6   | −492.70 |
| Conventional models          |                   |                    |     |     |      |
| Chrastil model               | 3.56118           | 3.852              | 24  | 3   | −480.69 |
| R. Chrastil model            | 2.1846            | 3.017              | 24  | 3   | −492.42 |
| Bartle model                 | 1.92404           | 2.8314             | 24  | 3   | −495.46 |
| MT model                     | 72.5              | 8.51               | 24  | 3   | −518.89 |

**Conclusion**

Pantoprazole sodium sesquihydrate’s solubility in ScCO₂ is reported at 308, 318, 328, and 338 K in the pressure range of 12–27 MPa, for the first time. The solubilities were ranged between $0.0301 \times 10^{-4}$ and $0.463 \times 10^{-4}$ in mole fraction. For modeling, three recently developed solubility models and four conventional empirical solubility models were used. Further, measured data has been used to develop a new solubility model. Among various models, Alwi-Garlapati model is observed to correlate the data with the least AARD (13.1%). The correlating ability of various equations have been observed in terms of AICc values (ascending) as follows: MT (−518.89), Alwi-Garlapati (−504.14), Bartle (−495.46), Reddy and Garlapati (−492.70), R. Chrastil (−492.42), Sodeifian et al. (−490.05), models, new model as temperature independent (−487.69) and Chrastil model (−480.69). The new model proposed in this study can be used for the combination of any complex compound with any supercritical fluid.
Data availability

All data generated or analyzed during this study are included in this published article.

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G.S. Conceptualization, Methodology, Validation, Investigation, Supervision, Project administration, Writing-review & editing; C.G. Methodology, Investigation, Software, Writing- original draft; F.R. Investigation, Validation, Resources; H.N. Methodology, Validation, measurement. All authors reviewed the manuscript.

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