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Measurement and Modeling of *Clemastine Fumarate* (Antihistamine Drug) Solubility in Supercritical Carbon Dioxide

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ABSTRACT

The solubilities of *clemastine fumarate* in supercritical carbon dioxide (ScCO₂) 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 fraction and it is ranged from 1.61×10^{-6} to 9.41×10^{-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., cluster salvation model, equation of state (EoS) model and few density models. Among density models, Tippana and Garlapati model was observed to be the best model and corresponding AARD% was 7.57 (corresponding AIC_c is -678.88). The Peng-Robinson equation of state as temperature independent was able to correlate the data and deviation was 8.25% in terms of AARD% (corresponding AIC_c is -674.88). Moreover, thermodynamic enthalpies of *clemastine fumarate* were estimated.

Keywords: Clemastine fumarate, Solubility, Empirical models, New cluster solvation model.

1. Introduction

Supercritical fluid technology (SFT) applications in process industry have gained significant importance. The application of carbon dioxide as supercritical fluid has several advantages over conventional techniques¹ and it is designated as ScCO₂. ScCO₂ poses attractive physical properties. ScCO₂ has gas like diffusivity and liquid like density with low viscosity and surface tension¹⁻². Adjusting pressure and temperatures one can tune the density of ScCO₂ as desired and it is exploited in various applications. Due to this tunable nature ScCO₂ has been used as a solvent in various process applications. ScCO₂ major applications include drug particle micronization, extraction, reactions, food processing, textile dyeing, ceramic coating, and many more³⁻⁷. To implement SFT one needs to have basic phase equilibrium information such as saturation solubility. The solubility is one of the basic information that is essential for the design and development of SFT. Drug particle micronization requires exact solubility information and in literature solubility of many drug solids in the ScCO₂ is readily available, however, the solubility of *clemastine fumarate* is not reported^{8,9}, therefore for the first time the solubility of *clemastine fumarate* in ScCO₂ is reported in this work. We believe that this study may be useful in particle micronization using ScCO₂. The molecular formula of *clemastine fumarate* is C₂₁ H₂₆ Cl NO.C₄H₄O₄ and its molecular weight is 459.97. The chemical structure is shown in figure 1.

The *clemastine fumarate* is a special drug and it is having 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 leishmania infection¹⁰. 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 size¹⁰. Therefore, present study may be useful in particle micronization using ScCO₂. Experimental solubility data at each pressure and temperature is very difficult therefore we need a proper model to generate the solubility data. Solubility models are classified into five types. Among them quite simple and useful are equation of state models, density models and mathematical models¹¹.

The main objectives of the present work are in two stages, in the first stage we determine solubility of *clemastine fumarate* and in the second stage we developed a new cluster solubility

model. The proposed model is compared with existing cluster salvation model. furthermore, few density models and equation of state model are evaluated.

2. Experimental

2.1. Materials

Gaseous CO₂ (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 > 99.9%) was obtained from Sigma Aldrich company. Table 1 indicates all the information about the chemicals utilized in this work.

2.2. 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 studies¹²⁻³⁰. However, a brief outline of the same is presented in this section. This measuring methodology may be classified as an isobaric-isothermal method³¹. Each reading was reported by controlling temperature and pressures at desired values within ± 0.1 K and ± 0.1 MPa precision, respectively. For each experiment about 1g of *clemastine fumarate* drug was used. The attainment of equilibrium was observed in 60 min. After equilibrium saturated ScCO₂ sample (600 μ L) was collected via 2-status 6-way port valve in a methanol preloaded vial. Once sample was collected, the port valve was washed with 1ml methanol. Thus, the total saturation solution obtained was 5 ml. Each measurement was repeated thrice and average readings were reported. For calculations the following formulas were used [12-30].

$$y_2 = \frac{n_{drug}}{n_{drug} + n_{CO_2}} \quad (1)$$

where n_{solute} is the moles of the drug, and n_{CO_2} is the moles of CO₂ in the sampling loop.

Further, we quantify moles of drug and moles of CO₂ as

$$n_{solute} = \frac{C_s \cdot V_s}{M_s} \quad (2)$$

$$n_{CO_2} = \frac{V_1 \cdot \rho}{M_{CO_2}} \quad (3)$$

where C_s is the drug concentration in saturated sample vial in g/L. The volume of sampling loop is $V_s(L) = 5 \times 10^{-3} \text{ m}^3$ and vial collection is $V_1(L) = 600 \times 10^{-6} \text{ m}^3$. The M_s and M_{CO_2} are the molecular weight of drug and CO_2 , respectively. Solubility is also described as

$$S = \frac{C_s V_s}{V_1} \quad (4)$$

The relation between S and y_2 is explained as

$$S = \frac{\rho M_s}{M_{CO_2}} \frac{y_2}{1 - y_2} \quad (5)$$

A UNICO-4802 (model) spectrophotometer (UV-Visible) (Model UNICO-4802) has been used for the measurements of *clemastine fumarate* solubility. Samples collected for analysis in methanol solvent was analyzed at 270 nm.

3. Models

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

3.1 Existing empirical and semi-empirical models

3.1.1. Alwi-Garlapati model³². 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

$$y_2 = \frac{1}{\rho_r T_r} \exp \left(A_1 + \frac{A_2}{T_r} + A_3 \rho_r \right) \quad (6)$$

Where $A_1 - A_3$ are model constants.

3.1.2. Bartel et al., model³³. 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

$$\ln\left(\frac{y_2 P}{P_{ref}}\right) = B_1 + \frac{B_2}{T} + B_3(\rho - \rho_{ref}) \quad (7)$$

Where $B_1 - B_3$ 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.

3.1.3. Bian et al., model³⁴. It is a five parameter model. It is an empirical model and it is mathematically stated as

$$y_2 = \rho_1^{(D_1 + D_{23}\rho_1)} \exp(D_3/T + D_4 \rho_1/T + D_5) \quad (8)$$

Where $D_3 - D_5$ are model constants.

3.1.4. Chrastil model³⁵. It is a three parameter model. It is a semi empirical model and it is mathematically stated as

$$c_2 = \rho_1^\kappa \exp\left(E_1 + \frac{E_2}{T}\right) \quad (9)$$

Where κ, E_1 and E_2 are model constants.

In terms of mole fraction it is mathematically stated as

$$y_2 = \frac{(\rho_1)^{\kappa-1} \exp\left(E_1 + \frac{E_2}{T}\right)}{\left[1 + (\rho_1)^{\kappa-1} \exp\left(E_1 + \frac{E_2}{T}\right)\right]} \quad (9a) \quad (9a)$$

3.1.5. Reformulated Chrastil model^{36,37}. It is also a three parameter model. It is a semi-empirical model and it is mathematically stated as

$$y_2 = \left(\frac{RT\rho_1}{M_{CF} f^\bullet}\right)^{\kappa'-1} \exp\left(F_1 + \frac{F_2}{T}\right) \quad (10)$$

Where κ', F_1 and F_2 are model constants.

3.1.6. Garlapati-Madras model³⁸. It is a five parameter model. It is a mathematical model and it is mathematically stated as

$$\ln(y_2) = G_1 + (G_2 + G_3\rho_1)\ln(\rho_1) + \frac{G_4}{T} + G_5\ln(\rho_1T) \quad (11)$$

Where $G_1 - G_5$ are model constants

3.1.7. Mendez-Teja model (MT model)³⁹. It is a semi-empirical model and it has three parameters. It is mathematically stated as

$$T \ln(y_2P) = H_1 + H_2\rho + H_3T \quad (12)$$

Where $H_1 - H_3$ are model constants.

Eq. (12) is used in checking self-consistency of the measured solubility data. Accordingly, all the data points lie on a line when they plotting $T \ln(y_2P) - H_3T$ vs. ρ_1 .

3.1.8. Sodefian et al., model⁴⁰. It is a mathematical model and it has six parameters and it is mathematically stated as

$$\ln(y_2) = I_1 + \frac{I_2P^2}{T} + I_3\ln(\rho_1T) + I_4(\rho_1\ln(\rho_1)) + I_5P\ln(T) + I_6\frac{\ln(\rho_1)}{T} \quad (13)$$

Where $I_1 - I_6$ are model constants

3.1.9. Tippiana-Garlapati model⁹. It is based on degree of freedom. It is a six parameter model. It is an empirical model and it is mathematically stated as

$$y_2 = (J_1 + J_2P_r + J_3P_r^2)T_r^2 + (J_4 + J_5P_r + J_6P_r^2) \quad (14)$$

Where $J_1 - J_6$ are model constants.

3.1.9. Mahesh-Garlapati model¹¹. It is based on degree of freedom. It is a three parameter model. It is an empirical model and it is mathematically stated as

$$y_2 = \exp(K_1 + K_2\rho_rT_r + K_3\rho_rT_r^3) \quad (15)$$

3.2. Equation of state (EoS) model

The solubility of *clemastine fumarate* drug, i (solute), in a supercritical carbon dioxide, j (solvent), is expressed as⁴¹

$$y_i = \frac{p_i^s \hat{\phi}_i^s}{P \hat{\phi}_i^{ScCO_2}} \exp \left[\frac{(P - p_i^s) V_i}{RT} \right] \quad (16)$$

Where p_i^s is solute sublimation pressure; T , P are system temperature and pressures, respectively; V_i is solute molar volume; R is the universal gas constant. The fugacity coefficient of the pure solute at saturation ($\hat{\phi}_i^s$) is usually taken to be unity. In this work, $\hat{\phi}_i^{ScCO_2}$ is the fugacity coefficient of the solute in the solvent phase. $\hat{\phi}_i^{ScCO_2}$ is calculated using Peng-Robinson (PR) EoS along with two parameter van der Waals mixing rule (vdW2)⁴². The expression used for calculation of $\hat{\phi}_i^{ScCO_2}$ is obtained from the following basic thermodynamic relation⁴³.

$$\ln(\hat{\phi}_i^{ScCO_2}) = \frac{1}{RT} \int_v^\infty \left[\left(\frac{\partial P}{\partial N_i} \right)_{T, V, N_j} - \frac{RT}{v} \right] dv - \ln Z \quad (17)$$

The general PREoS form [42] is

$$P = \frac{RT}{V - b} - \frac{a(T)}{V(V + b) + b(V - b)} \quad (18)$$

Where P is the pressure, R is the universal gas constant, T is the temperature and V is the molar volume. The pure component parameters a and b are

$$a(T) = 0.45724 \frac{R^2 T_c^2}{P_c} \alpha(T_r, \omega) \quad (19)$$

$$\alpha(T_r, \omega) = \left[1 + \left(0.37464 + 1.5422\omega - 0.26992\omega^2 (1 - \sqrt{T_r}) \right) \right]^2$$

$$b = 0.07780 \frac{RT_c}{P_c} \quad (20)$$

The expression for $\hat{\phi}_i^{ScCO_2}$ is:

$$\ln(\hat{\phi}_i^{ScF}) = \frac{\hat{b}}{b} (Z-1) - \ln \left[Z \left(1 - \frac{b}{v} \right) \right] + \frac{a}{(2\sqrt{2})bRT} \left[\frac{\hat{a}}{a} - \frac{\hat{b}}{b} \right] \ln \left(\frac{Z-0.414b}{Z+2.414b} \right) \quad (21)$$

$$\hat{a} = \frac{1}{n} \frac{\partial n^2 a}{\partial n_i} = 2 \sum x_i a_{ij} ; \hat{b} = \frac{\partial nb}{\partial n_i} = 2 \sum x_i b_{ij} - b$$

3.2.1. The expressions for VdW2

$$a = \sum_i \sum_j x_i x_j a_{ij} \quad (22)$$

$$b = \sum_i \sum_j x_i x_j b_{ij} \quad (23)$$

$$a_{ij} = (1 - k_{ij}) \sqrt{a_{ii} a_{jj}} \quad (24)$$

$$b_{ij} = (1 - l_{ij}) \frac{(b_{ii} + b_{jj})}{2} \quad (25)$$

The PREoS regression may be carried out either temperature independent or temperature dependent. For temperature independent regression a suitable sublimation expression is used. The general form^{44,45} used for the regression purpose is

$$R \ln(p_{sub}) = \beta + \frac{\gamma}{T} + \Delta_{sub} \delta \ln \left(\frac{T}{298.15} \right) \quad (26)$$

The regression directly results in binary interaction parameters along with sublimation pressure expression coefficients (β/R , γ/R and $\Delta_{sub}\delta/R$) and from parameters γ and $\Delta_{sub}\delta$ we can estimate sublimation pressure. The expression for sublimation enthalpy is

$$\Delta_{sub}H = -\gamma + \Delta_{sub}\delta T \quad (27)$$

3.3. New cluster model

This model is an extension to K.-W. Chen et al., model⁴⁶. According to the model the formation of solvate complex AB_κ is a due to the equation reaction mention in eq.(28), where A is solute and B is supercritical fluid.

It is an equilibrium reaction and at equilibrium the following condition is satisfied.

$$\sum \nu_i \bar{F}_i(T, P, z_i) = 0 \quad (29)$$

Where $\sum$ is summation; ν and $\bar{F}$ are stoichiometric coefficient and partial molar Gibbs energy, respectively.

In general the partial molar Gibbs energy for species is written as

$$\bar{F}_i(T, P, z_i) = \bar{F}_i^o(T, P^o, z_i^o) + (\bar{F}_i(T, P, z_i) - \bar{F}_i^o(T, P^o, z_i^o)) \quad (30)$$

Where P^o and z_i^o are reference state pressure and composition of species i. In this work, similar to that of K.-W. Chen et al. model, reference pressure is taken as critical pressure of the supercritical fluid. Similar to K.-W. Chen et al., model⁴⁶, the expression for the equilibrium in terms of fugacity coefficients is

$$\ln\left(\frac{z_{AB_\kappa}}{z_B^{\kappa''}}\right) = k \ln\left(\frac{\hat{\phi}_B(T, P, z_B)P}{\phi_B(T, P_{c,scf})P_{c,scf}}\right) + \frac{V_s(P - P_{c,scf})}{RT} - \ln\left(\frac{\hat{\phi}_{AB_\kappa}(T, P, z_{AB_\kappa})P}{\phi_{AB_\kappa}(T, P_{c,scf})P_{c,scf}}\right) - \frac{\Delta F^{rxn}(T, P_{c,scf})}{RT} \quad (31)$$

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

The model has two parameters κ'' and $\Delta F^{rxn}(T, P_{c,scf})$. In this work we have used the following temperature dependent general from⁴⁷ in place of $\Delta F^{rxn}(T, P_{c,scf})$

$$\Delta F^{rxn}(T, P_{c,scf}) = a' + b'T \ln(T) + c'T \quad (32)$$

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

The eq.(31) is further simplified with the help of Taylor series on left hand side

$$\ln\left(\frac{z_{AB_\kappa}}{1 - \kappa'' z_{AB_\kappa}}\right) = k \ln\left(\frac{\hat{\phi}_B(T, P, z_B)P}{\phi_B(T, P_{c,scf})P_{c,scf}}\right) + \frac{V_s(P - P_{c,scf})}{RT} - \ln\left(\frac{\hat{\phi}_{AB_\kappa}(T, P, z_{AB_\kappa})P}{\phi_{AB_\kappa}(T, P_{c,scf})P_{c,scf}}\right) - \frac{\Delta F^{rxn}(T, P_{c,scf})}{RT} \quad (33)$$

The experimental solubility and cluster mole fractions are related as⁴⁸ follows

$$y = z_{AB_\kappa} / (1 + \kappa'' z_{AB_\kappa}) \quad (34)$$

The fugacity coefficient of the components and mixtures are evaluated with any cubic equation of state. However, in this work we have followed the K.-W. Chen et al., model, where PREoS had shown good results. For fugacity coefficient calculations we need mixture properties and they are calculated with the help of cluster and supercritical fluids. More details about these can be seen elsewhere⁴⁹.

The cluster obeys the following mixing rules for volume and energy parameters

$$b_{AB_\kappa} = \kappa'' b_B + b_A \quad (35)$$

$$a_{AB_\kappa} = \left[\kappa'' (a_B b_B)^{0.5} + (a_A b_A)^{0.5} \right]^2 / b_{AB_\kappa} \quad (36)$$

More details about PREoS, fugacity coefficient of pure component and mixture can be seen in section 3.2 and literature^{48,49}

The final expression for the solubility is

$$y = \frac{\exp \left[\kappa'' \ln \left(\frac{\hat{\phi}_B(T, P, z_B)P}{\phi_B(T, P_{c,scf})P_{c,scf}} \right) + \frac{V_s(P - P_{c,scf})}{RT} - \ln \left(\frac{\hat{\phi}_{AB_\kappa}(T, P, z_{AB_\kappa})P}{\phi_{AB_\kappa}(T, P_{c,scf})P_{c,scf}} \right) - \frac{(a' + b'T \ln(T) + c'T)}{RT} \right]}{1 + 2\kappa'' \exp \left[\kappa'' \ln \left(\frac{\hat{\phi}_B(T, P, z_B)P}{\phi_B(T, P_{c,scf})P_{c,scf}} \right) + \frac{V_s(P - P_{c,scf})}{RT} - \ln \left(\frac{\hat{\phi}_{AB_\kappa}(T, P, z_{AB_\kappa})P}{\phi_{AB_\kappa}(T, P_{c,scf})P_{c,scf}} \right) - \frac{(a' + b'T \ln(T) + c'T)}{RT} \right]} \quad (37)$$

Hereafter it may be called as cluster model by sodeifian et al.

3.3.1. K.-W. Chen et al., model

Cluster model proposed by K.-W. Chen et al., is⁴⁶

$$y = \frac{\exp \left[\kappa''' \ln \left(\frac{\hat{\phi}_B(T, P, z_B)P}{\phi_B(T, P_{c,scf})P_{c,scf}} \right) + \frac{V_s(P - P_{c,scf})}{RT} - \ln \left(\frac{\hat{\phi}_{AB_\kappa}(T, P, z_{AB_\kappa})P}{\phi_{AB_\kappa}(T, P_{c,scf})P_{c,scf}} \right) - \frac{(a'' - b''T)}{RT} \right]}{1 + 2\kappa''' \exp \left[\kappa''' \ln \left(\frac{\hat{\phi}_B(T, P, z_B)P}{\phi_B(T, P_{c,scf})P_{c,scf}} \right) + \frac{V_s(P - P_{c,scf})}{RT} - \ln \left(\frac{\hat{\phi}_{AB_\kappa}(T, P, z_{AB_\kappa})P}{\phi_{AB_\kappa}(T, P_{c,scf})P_{c,scf}} \right) - \frac{(a'' - b''T)}{RT} \right]} \quad (38)$$

Where κ''' , a'' and b'' are three adjustable parameters.

All the models mentioned in sections 3.1, 3.2 and 3.3 are evaluated with the following objective function⁵⁰.

$$OF = \sum_{i=1}^N \left| y_i^{\text{exp}} - y_i^{\text{cal}} \right| / y_i^{\text{exp}} \quad (39)$$

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

$$AARD\% = 100/N \sum_{i=1}^N \left| y_i^{\text{exp}} - y_i^{\text{cal}} \right| / y_i^{\text{exp}} \quad (40)$$

Where N is number of experimental data points; y_i is mole fraction; the superscripts *cal* and *exp* denotes the calculated and measured mole fractions, respectively.

4. 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 data base. Fig. 3 indicates the effect of pressure on various isotherms and no cross over region observed, such solubility behavior is observed for some other pharmaceutical compounds in our earlier studies²³. Fig. 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 methods⁵¹⁻⁵⁴. Table.3 indicates all computed data. 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, Tippana-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^{23, 30, 35}. 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 where as 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 the new cluster model is superior to exiting K.-W. Chen et al., model. The new model parameters ‘ a' ’ and ‘ b' ’ directly results in enthalpy change and entropy change of the cluster formation 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 are represented in Figs.(4)-(9).

The models used in correlation exercise are having varying number of parameters and the best model is obtained with the help of Akaike’s information criterion (AIC)⁵⁵⁻⁵⁹. The data used in this exercise is small ($N < 40$), hence corrected AIC (AIC_c) is used for the identifying the best model.

$$AIC_c = AIC + \frac{2N_p(N_p + 1)}{N - N_p - 1} \quad (41)$$

Where AIC is $N \ln(SSE/N) + 2Q$; N is number of experimental data points; N_p is model parameters; SSE is error sum of squares. According to AIC_c test, each model gives least value that model would be considered as the best model. Table 8 indicates computed AIC and AIC_c values. The least AIC_c value -678.88 is seen for Tippiana-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 AIC_c value is -678.59. The highest AIC_c value is seen for Bartel et al., model hence it is treated as poor model for *clemastine fumarate*.

Conclusion

Solubilities of *clemastine fumarate* in $ScCO_2$ 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, Tippiana-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 AIC_c values are as follows: Tippiana-Garlapati model, new cluster model, PREoS as temperature independent, K.-W. Chen et al., model, Bian et al., model, Sodefian et al., model, Alwi-Garlapati model, Mahesh-Garlapati model, Chrastil model, Reformulated Chrastil model, Garlapati-Madras model, Mendez-Teja model, Bartel et al., model. The new cluster model proposed in this work may be useful for correlating solids solubility in any SCF.

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Nomenclature

$A_1 - A_3$	Alwi-Garlapati parameters
$B_1 - B_3$	Bartel model parameters
$D_1 - D_5$	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
$J_1 - J_6$	Tippiana-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_{sol}	Salvation enthalpy
H_{sub}	Sublimation enthalpy
H_{Total}	Total enthalpy
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
$\hat{\phi}_i^S$	Fugacity coefficient of the pure substance at saturation
$\hat{\phi}_i^{scCO_2}$	Solute fugacity in supercritical carbon dioxide (scCO ₂)
ϖ	Acentric factor
ρ	Density
ρ_r	Reduced density
κ_{ji}	Correlation parameter
l_{ji}	Correlation parameter
$\kappa \kappa' \kappa'' \kappa'''$	Association numbers in respective eqs.

Sub and

Supercriticals

exp	Experimental
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cal	Calculated
j	Solvent/ScCO ₂
i	Solute/drug
c	Critical
r	Reduced

REFERENCES

1. Subramaniam, B., Rajewski, R.A. & Snavely, K. Pharmaceutical processing with supercritical carbon dioxide, *J. Pharmaceutical. Sci.* **86**, 885-890. [https://doi.org/10.1021/js9700661\(1997\)](https://doi.org/10.1021/js9700661(1997)).
2. Hitchen, S. & Dean, J. Properties of supercritical fluids. in: *Applications of Supercritical Fluids in Industrial Analysis*, 1-11 (Springer, 1993).
3. Reverchon, E., De Marco, I. & Torino, E. Nanoparticles production by supercritical antisolvent precipitation: a general interpretation, *J. Supercrit. Fluids* **43**, 126-138. <https://doi.org/10.1016/j.supflu.2007.04.013> (2007).
4. Sodeifan, G. & Sajadian, S. A. Solubility measurement and preparation of nanoparticles of an anticancer drug (Letrozole) using rapid expansion of supercritical solutions with solid cosolvent (RESS-SC). *J. Supercrit. Fluids* **133**, 239–252. <https://doi.org/10.1016/j.supfu.2017.10.015> (2018).
5. Sodeifan, G., Ardestani, N. S., Sajadian, S. A. & Panah, H. S. Experimental measurements and thermodynamic modeling of Coumarin-7 solid solubility in supercritical carbon dioxide: Production of nanoparticles via RESS method. *Fluid Phase Equilib.* **483**, 122–143. <https://doi.org/10.1016/j.fuid.2018.11.006> (2019).
6. Ardestani, N.S., Sodeifan, G. & Sajadian, S.A preparation of phthalocyanine green nano pigment using supercritical CO₂ gas antisolvent (GAS): Experimental and modeling, *Heliyon*, **6**, e049476. [https://doi.org/10.1016/j.heliyon.2020.e04947\(2020\)](https://doi.org/10.1016/j.heliyon.2020.e04947(2020))
7. 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* **140**, 72–84. <https://doi.org/10.1016/j.supfu.2018.06.009> (2018).
8. 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).
9. 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/10.1002/ceat.201900283> (2019).
10. Mina, J. G. M et al. Antileishmanial Chemotherapy through Clemastine Fumarate Mediated Inhibition of the Leishmania Inositol Phosphorylceramide Synthase: *ACS Infect. Dis.* **7**, 47–63. <https://doi.org/10.1021/acsinfecdis.0c00546> (2021).
11. Mahesh G & Garlapati, C., Modelling of solubility of some parabens in supercritical carbon

- dioxide and new correlations, *Arab. J. Sci. Eng.*, 1-13
<https://doi.org/10.1007/s13369-021-05500-2> (2021).
12. Sodeifan, G., Ardestani, N. S. & Sajadian, S. A. Solubility measurement of a pigment (Phthalocyanine green) in supercritical carbon dioxide: Experimental correlations and thermodynamic modeling. *Fluid Phase Equilib.* **494**, 61–73. <https://doi.org/10.1016/j.fuid.2019.04.024> (2019).
 13. Sodeifan, G., Drakhsheshpoor, R. & Sajadian, S. A. Experimental study and thermodynamic modeling of Esomeprazole (protonpump inhibitor drug for stomach acid reduction) solubility in supercritical carbon dioxide. *J. Supercrit. Fluids* **154**, 104606. <https://doi.org/10.1016/j.supfu.2019.104606> (2019).
 14. Sodeifan, G., Hazaveie, S. M., Sajadian, S. A. & Saadati Ardestani, N. Determination of the solubility of the repaglinide drug in supercritical carbon dioxide: Experimental data and thermodynamic modeling. *J. Chem. Eng. Data* **64**, 5338–5348. <https://doi.org/10.1021/acs.jced.9b00550> (2019).
 15. Sodeifan, G., Sajadian, S. A. & Ardestani, N. S. Optimization of essential oil extraction from *Launaea acanthodes* Boiss: Utilization of supercritical carbon dioxide and cosolvent. *J. Supercrit. Fluids* **116**, 46–56. <https://doi.org/10.1016/j.supfu.2016.05.015> (2016).
 16. Sodeifan, G., Sajadian, S. A. & Ardestani, N. S. Experimental optimization and mathematical modeling of the supercritical fluid extraction of essential oil from *Eryngium billardieri*: Application of simulated annealing (SA) algorithm. *J. Supercrit. Fluids* **127**, 146–157. <https://doi.org/10.1016/j.supfu.2017.04.007> (2017).
 17. Sodeifan, G. & Sajadian, S. A. Investigation of essential oil extraction and antioxidant activity of *Echinophora platyloba* DC. using supercritical carbon dioxide. *J. Supercrit. Fluids* **121**, 52–62. <https://doi.org/10.1016/j.supfu.2016.11.014> (2017).
 18. 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* **140**, 72–84. <https://doi.org/10.1016/j.supfu.2018.06.009> (2018).
 19. Sodeifan, G., Sajadian, S. A., Razmimanesh, F. & Ardestani, N. S. A comprehensive comparison among four different approaches for predicting the solubility of pharmaceutical solid compounds in supercritical carbon dioxide. *Korean J. Chem. Eng.* **35**, 2097–2116. <https://doi.org/10.1007/s11814-018-0125-6> (2018).
 20. Sodeifan, G., Sajadian, S. A. & Derakhsheshpour, R. Experimental measurement and thermodynamic modeling of Lansoprazole solubility in supercritical carbon dioxide: Application of SAFT-VR EoS. *Fluid Phase Equilib.* **507**, 112422. <https://doi.org/10.1016/j.fuid.2019.112422> (2020).
 21. Sodeifan, G., Razmimanesh, 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.fuid.2018.05.018> (2018).
 22. Sodeifan, G., Nasri, L., Razmimanesh, 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).
 23. Sodeifan, G., Garlapati, C., Razmimanesh, F. & Sodeifan, F. Solubility of amlodipine 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).
24. Sodeifan, G., Razmimanesh, F., Ardestani, N. S. & Sajadian, S. A. Experimental data and thermodynamic modeling of solubility of Azathioprine, 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).
 25. Sodeifan, G., Alwi, R. S., Razmimanesh, 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).
 26. Sodeifan, G. & Sajadian, S. A. Experimental measurement of solubilities of sertraline hydrochloride in supercritical carbon dioxide with/without menthol: Data correlation. *J. Supercrit. Fluids* **149**, 79–87. <https://doi.org/10.1016/j.supfu.2019.03.020> (2019).
 27. 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.supfu.2017.05.019> (2017).
 28. Sodeifan, G., Sajadian, S. A. & Razmimanesh, F. Solubility of an antiarrhythmic 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).
 29. Sodeifan, G., Sajadian, S. A., Razmimanesh, F., & Hazaveie, S.M. Solubility of Ketoconazole (antifungal drug) in SC-CO₂ for binary and ternary systems: measurements and empirical. *Scientific Reports* **11**, 7546. <https://doi.org/10.1038/s41598-021-87243-6> (2021).
 30. Sodeifan, G., Garlapati, C., Razmimanesh, 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).
 31. Peper, S., Fonseca, J.M.S. & Dohrn, R. High-pressure fluid phase 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).
 32. 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).
 33. Bartle, K. D., Clifford, 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/10.1063/1.555893> (1991).
 34. Bian, X.-Q., Zhang, Q., Du, Z.-M., Chen, J. & Jaubert, 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).
 35. Chrastil, J. Solubilities of solids and liquids in supercritical gases, *J. Phys. Chem.* **86**, 3016–3021. <https://doi.org/10.1021/j100212a041> (1982).
 36. Garlapati, C. & Madras, G. Solubilities of Palmitic and steric fatty acids in supercritical carbon dioxide, *J. Chem. Thermodyn.* **42**, 193–197. <http://dx.doi.org/10.1016/j.jct.2009.08.001> (2010).
 37. 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).
38. Garlapati, C. & Madras, G. New empirical expressions to correlate solubilities of solids in supercritical carbon dioxide, *Thermochimica Acta* **500**, 123-127. <https://doi.org/10.1016/j.tca.2009.12.004>(2010).
 39. Méndez-Santiago, J. & Teja, A. S. Te solubility of solids in supercritical fluids. *Fluid Phase Equilib.* **158**, 501–510. [https://doi.org/10.1016/S0378-3812\(99\)00154-5](https://doi.org/10.1016/S0378-3812(99)00154-5) (1999).
 40. Sodeifan, G., Razmimanesh, 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.supfu.2019.01.006> (2019).
 41. Sandler, S.I. *Chemical, Biochemical and Engineering Thermodynamics*, 664-666 (Wiley, 1996).
 42. 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).
 43. Prausnitz, J. M., Lichtenthaler, R. N. & De Azevedo, E. G. *Molecular thermodynamics of fluid-phase equilibria*, 33-34 (McGraw-Hill, 2001).
 44. Garlapati, C. & Madras, G. Temperature independent mixing rules to correlate the solubilities of antibiotics and anti-inflammatory drugs in SCCO₂, *Thermochimica Acta* **496**, 54-58. <https://doi.org/10.1016/j.tca.2009.06.022> (2009).
 45. Sodeifan, G., Garlapati, C., Razmimanesh, F. & Sodeifan, F. Solubility of 2,4,7-Triamino-6-phenylpteridine (Triamterene, Diuretic Drug) in Supercritical Carbon Dioxide: Experimental Data and Modeling. *J. Chem. Eng. Data* **65**, 4406-4416. <https://doi.org/10.1021/acs.jced.0c00268> (2020).
 46. 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](https://doi.org/10.1016/S0378-3812(03)00350-9)(2003).
 47. Rajaram, J. & Kuriacose, J.C. *Chemical thermodynamics Classical, statistical and irreversible*, 218-219 (Pearson Dorling Kindersley, 2013).
 48. Zong, M., Han, B. Ke, J., Yan, H. & Peng, D.Y. A model for correlating solubility of solids in supercritical CO₂, *Fluid Phase Equilib.* **146**, 93-102. [https://doi.org/10.1016/S0378-3812\(98\)00207-6](https://doi.org/10.1016/S0378-3812(98)00207-6) (1998).
 49. 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).
 50. 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).
 51. 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)
 52. Reid, R.C., Prausnitz, J.M. & Poling, B.E. *The properties of gases and liquids* (McGraw-Hill, 1988)
 53. Immirzi, A. & Perini, B. Prediction of density in organic crystals, *Acta Crystall. A-Crys.* **33**, 216-218. <https://doi.org/10.1107/S0567739477000448> (1977).
 54. Lyman, W.J., Reehl, W.F. & Rosenblatt, D.H. *Handbook of chemical property estimation methods*, (McGraw-Hill, 1982).
 55. 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)
56. 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).
 57. Deepitha, J., Pitchaiah, K.C., Rao, C.V.S.B., 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).
 58. 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.2018.08.007> (2019).
 59. Lamba, N., Narayan, R.C., Modak, J. & Madras, G. Solubilities of 10-undecenoic acid and geraniol in supercritical carbon dioxide, *J. Supercrit. Fluids* **107**, 384-391. <https://doi.org/10.1016/j.supflu.2015.09.026> (2016).

Figure 1

Line diagram of the solubility measurement device, 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.

Figure 3

Clemastine fumarate solubility in ScCO₂ and effect of pressure on isotherms.

Figure 4

Self-consistency plot of clemastine fumarate solubility in ScCO₂. Symbols are experimental points; line is calculated with MT Model.

Figure 5

Solubility of clemastine fumarate in ScCO_2 . Symbols are experimental points; lines are calculated with three parameter models.

Figure 6

Solubility of clemastine fumarate in ScCO_2 . Symbols are experimental points; lines are calculated with five parameter models.

Figure 7

Solubility of clemastine fumarate in ScCO₂. 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.

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