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# An association model for the solubilities of pharmaceuticals in supercritical carbon dioxide

Rajasekhar Ch, Giridhar Madras*

*Department of Chemical Engineering, Indian Institute of Science, Bangalore 560012, Karnataka, India*

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ABSTRACT

The equilibrium solubility of a pharmaceutical compound, 1,5-dimethyl-2-phenyl-4-propan-2-ylpyrazol-3-one (propyphenazone, isopropylantipyrine) in supercritical carbon dioxide ($SCCO_2$) was experimentally determined by a saturation method at 308, 318 and 328 K, over the pressure range of 9.0–19.0 MPa. The solubility data satisfied the self-consistency test, proposed by Méndez-Santiago and Teja. A new association model was derived to correlate the solubilities of pharmaceutical compounds in $SCCO_2$. Solubility data from 54 different pharmaceutical compounds including steroids, antibiotics, anti-inflammatory, antioxidants, statins and specific functional drugs were collected from literature. The model successfully correlated the experimental results for the solubilities of all these compounds in $SCCO_2$ within 12% AARD.



## 1. Introduction

Supercritical fluid technology has emerged as an important technique for various applications including production of controlled drug delivery systems, chemical reactions and a variety of extractions [1]. This is due to the solvent power, high diffusivity and low viscosity of the supercritical fluids (SCFs). Carbon dioxide is the most common SCF that is used in the food and pharmaceutical industries because of non-toxicity and near ambient critical temperature [2].

SCFs are used in the extraction of active ingredients from herbal plants for avoiding thermal or chemical degradation, and in the elimination of residual solvents from the products [3]. SCFs have been used in synthesis of drugs [4] and several methods of drug synthesis in supercritical carbon dioxide ($SCCO_2$) have been reported [1,5]. The knowledge of the equilibrium solubility of the drugs in $SCCO_2$ is a critical parameter in the design of both extraction and synthetic processes.

The solubilities of various pharmaceutical compounds in $SCCO_2$ have been determined. However, the solubilities of propyphenazone, which is a derivative of phenazone, in $SCCO_2$ have not been reported. Propyphenazone belongs to the family of non-steroidal anti-inflammatory drugs. Due to its analgesic, antipyretic and anti-inflammatory properties, propyphenazone is commonly used to reduce pain, fever, inflammation [6].

Because the experimental determination of the solubilities of solids in SCFs at various temperatures and pressures is time consuming, modeling of solubilities in SCFs is essential. Both equation of state (EOS) based models and semi-empirical models are commonly used for the correlation of solids in $SCCO_2$. EOS based models require parameters such as the critical constants, sublimation pressures of the complex pharmaceutical compounds, which are normally not available. Therefore semi-empirical models are often utilized in correlating solubilities of solids in $SCCO_2$ [7–10]. Although there are several semi-empirical equations in the literature, the best equation to correlate the solubilities of pharmaceutical compounds in SCFs varies from study to study.

Recently, in an extensive work, Tabernero et al. [11] have compared the solubilities of 27 pharmaceutical compounds with 9 most used semi-empirical equations. These nine models are the Chrastil model [7], Méndez-Santiago and Teja model [8], Bartle model [9], Gordillo model [10], del Valle and Aguilera (VA) model [12], Adachi and Lu (AL) model [13], Sparks model [14], Kumar and Johnston (KJ) model [15], and Yu model [16]. The best correlation was obtained by the use of Gordillo and Sparks model. While Sparks and other equations are density based models, the equation proposed by Gordillo includes pressure and temperature as parameters. This is because the solubility shows a curvilinear behavior with pressure at constant temperature and with temperature at constant pressure [16]. The model proposed in this work has pressure, temperature and density as parameters. However, unlike the above models in the lit-

* Corresponding author. Tel.: +91 80 22932321; fax: +91 80 23600683.
*E-mail addresses:* giridhar@chemeng.iisc.ernet.in, giridharmadras@gmail.com (G. Madras).

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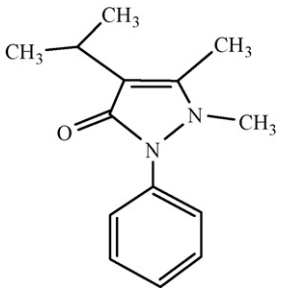
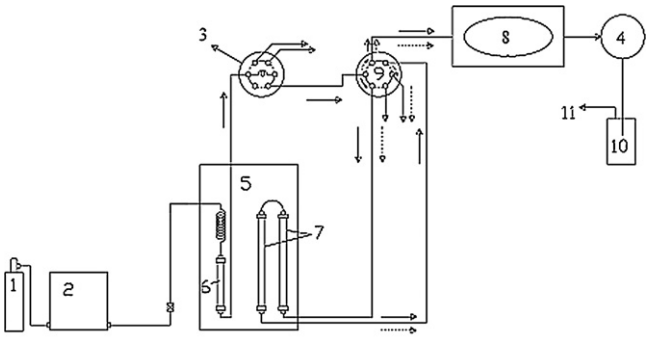


**Fig. 1.** Chemical structure of propyphenazone.




1. Carbon dioxide gas cylinder; 2. Carbon dioxide pump; 3. Injector port; 4. Back pressure regulator; 5. Thermostat; 6. Accumulator; 7. Packed column; 8.UV Detector; 9. Switching valve; 10. Collector; 11. Gas vent.

**Fig. 2.** Schematic drawing of the apparatus.

erature that have six adjustable parameters, the model developed in this work has only four parameters.

The objectives of this work are twofold. First, the solubilities of propyphenazone were experimentally determined at 308, 318, and 328 K over the pressure range of 9.0–19.0 MPa in $SCCO_2$. The solubilities were correlated by Méndez-Santiago and Teja model to check the data consistency. Secondly, a new semi-empirical equation with four parameters based on chemical association of solute molecules with $SCCO_2$ was developed and used to correlate the solubility data of 55 pharmaceutical compounds.

## 2. Experimental

### 2.1. Materials

Carbon dioxide (CAS 124-38-9) (99.9% mass fraction) was purchased from Bhoruka Gases (India). Propyphenazone (CAS 479-92-5; 99.5% mass purity; its molecular weight is 230.31 g mol$^{-1}$) was purchased from Vani Pharma Labs Ltd. (India). The chemical structure of this compound is shown in Fig. 1. Acetonitrile (CAS 75-05-8) (HPLC grade) was purchased from Merck (India) and was used for analysis.

### 2.2. Solubility measurement

The solubility measurements of propyphenazone were carried out using a flow apparatus described in detail in previous studies [17–20]. A schematic diagram of the apparatus is shown in Fig. 2. The solubility measurements were conducted in the pressure range of 9.0–19.0 MPa at temperatures of 308, 318 and 328 K. The experimental uncertainties of temperatures and pressures were ±0.1 K and ±0.2 MPa, respectively.

Carbon dioxide was pressurized with a pump (Jasco model PU-1580-$CO_2$), which was operated in a constant flow mode. Carbon dioxide passed through two columns (300 mm × 14 mm) in series packed with about 35 g of pure solute. The ends of the columns were fitted with 2 μm filters and packed with glass wool to avoid entrainment of the solute. The columns were placed in a constant temperature oven. To ensure that the exiting $SCCO_2$ stream is saturated with the solute, experiments were operated with a flow rate of 0.2 mL min$^{-1}$ of $SCCO_2$ (flow rates are based on pump head). The flow rates of operation and time for collection of samples to ensure saturation were fixed after extensive trails, as described in our previous studies [19,20]. Samples from the exiting fluid phase were collected by a quick depressurization and expansion into a small glass trap. These samples were dissolved in acetonitrile. The analysis of the samples was performed by a UV–vis spectrophotometer (1700 Shimadzu) to determine the solubilities. A suitable wavelength for UV determination was determined by scanning the UV spectrum between 200 and 600 nm and the observed maximum wavelength was at 282 nm for propyphenazone. The calibration was obtained by using standard samples of concentrations between 4 and 14 ppm (parts per million). The calibration curve obtained (with a regression coefficient better than 99.6%) was used to establish the concentration of propyphenazone in the glass trap. The solubilities in mole fraction were determined by the concentration of the sample and the total flow of the $SCCO_2$. Each measurement was carried out at least thrice and the relative uncertainty in the determination of the solubility in mole fraction was less than ±5%.

## 3. Theoretical model for solubilities of solids in SCF

If one molecule of a solute A associates with $\kappa$ molecules of B to form one molecule of a solvate complex $AB_\kappa$ in equilibrium with the gaseous system,

$$A + \kappa B \Leftrightarrow AB_\kappa \tag{1}$$

The equilibrium constant for the process in terms of fugacities is

$$K_f = \frac{(\hat{f}_{AB_\kappa}/f^*_{AB_\kappa})_{SCP}}{(\hat{f}_A/f^*_A)_S((\hat{f}_B/f^*_B)^\kappa)_{SCP}} \tag{2}$$

where SCP represents the supercritical phase, S represents the solute phase and $f^*$ is reference fugacity. The fugacity for each component can be calculated with the following equations

$$\hat{f}_A = y_A\hat{\phi}_A P \tag{3}$$

$$\hat{f}_B = y_B\hat{\phi}_B P \tag{4}$$

$$\hat{f}_{AB_\kappa} = y_{AB_\kappa}\hat{\phi}_{AB_\kappa} P \tag{5}$$

$$f^*_{AB_\kappa} = \phi^*_{AB_\kappa} P^* \tag{6}$$

$$f^*_A = \phi^*_A P^* \tag{7}$$

$$f^*_B = \phi^*_B P^* \tag{8}$$

We assumed that the fluid-phase component does not dissolve in the solid, i.e., the solid is pure. Solute A exists in an associated state in SCP

$$y_B + y_{AB_\kappa} = 1 \tag{9}$$

where $y_B$, $y_{AB_\kappa}$ are mole fraction of each component in supercritical fluid phase.

Because the solute A mainly exists in an associating state, the solubility of solute A is

$$y = y_{AB_\kappa} \tag{10}$$

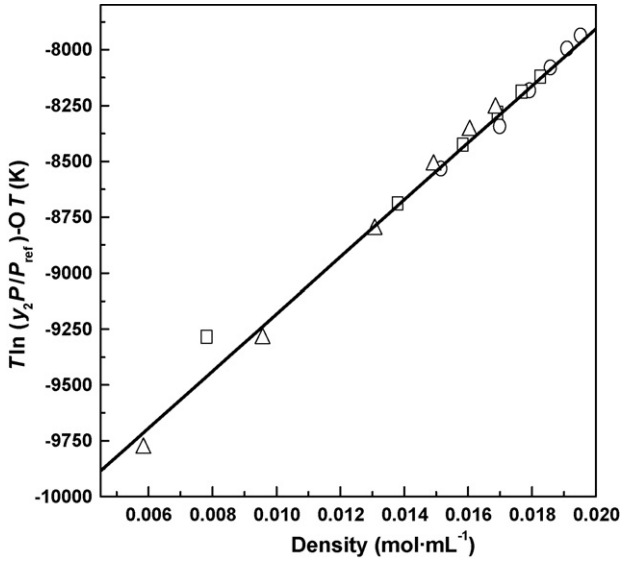



**Fig. 3.** Experimental solubility data (Table 1) in mole fraction ($y_2$) of propyphenazone in $SCCO_2$ at (○) 308 K; (□) 318 K; (△) 328 K. The solid lines are model correlations based on the Méndez-Santiago and Teja model. All the correlation parameters are given in Table 2.

**Table 1**
Propyphenazone solubility in mole fraction ($y_2 \times 10^4$) in $SCCO_2$ at temperatures of 308, 318 and 328 K and a pressure range of 9.0–19.0 MPa.

| $P$ (MPa) | $T$ (K) | | |
|---|---|---|---|
| | 308 | 318 | 328 |
| 9.0 | 3.19 | 0.72 | 0.38 |
| 11.0 | 4.84 | 3.83 | 1.40 |
| 13.0 | 6.92 | 7.40 | 5.23 |
| 15.0 | 8.34 | 10.05 | 10.92 |
| 17.0 | 9.70 | 11.94 | 15.43 |
| 19.0 | 10.53 | 13.21 | 18.82 |

Supposing that the standard state of the solute A is the pure solute under system pressure and temperature, then

$$\hat{f}_A = f_A \tag{11}$$

The fugacity of pure solute can be written as [21],

$$f_A = P_A^{sub} \exp\left(\frac{V_A(P - P_A^{sub})}{RT}\right) \tag{12}$$

where $P_A^{sub}$ is the sublimation pressure of the pure solid, $V_A$ is the molar volume of the pure solid, at system temperature, $T$, and pressure, $P$. Substituting Eqs. (3)–(12) in Eq. (2)

$$K_f = \frac{(y\hat{\phi}_{AB_\kappa}P/\phi^*_{AB_\kappa}P^*)}{((P_A^{sub}\exp(V_A(P - P_A^{sub})/RT))/\phi^*_A P^*)(y_B\hat{\phi}_B P/\phi^*_B P^*)^\kappa} \tag{13}$$

$$\ln(K_f) = \ln(y) + \ln\left(\frac{\hat{\phi}_{AB_\kappa}}{\phi^*_{AB_\kappa}}\right) + \ln\left(\frac{P}{P^*}\right) + \ln(\phi^*_A) - \ln\left(\frac{P_A^{sub}}{P^*}\right) - \frac{V_A(P - P_A^{sub})}{RT} - \kappa\ln(y_B) - \kappa\ln\left(\frac{\hat{\phi}_B}{\phi^*_B}\right) - \kappa\ln\left(\frac{P}{P^*}\right) \tag{14}$$

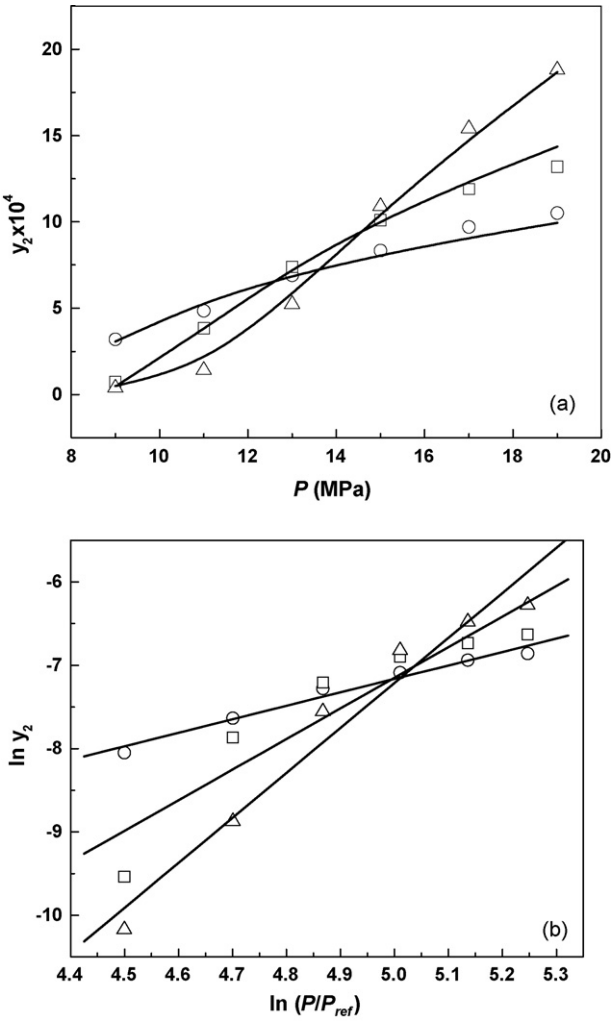



**Fig. 4.** Experimental solubility data (Table 1) in mole fraction ($y_2$) of propyphenazone in $SCCO_2$ (a) in normal scale and (b) in log–log scale at (○) 308 K; (□) 318 K; (△) 328 K. The solid lines are model correlations based on the new association model (Eq. (19)). All the correlation parameters are given in Table 2.

The equilibrium constant, $K_f$, may be expressed as $\ln(K_f) = \Delta H_s/RT + q_s$ where $\Delta H_s$ is the heat of solvation and $q_s$ is a constant. The term, $V_A P/RT$, may be expressed as $ZV_A\rho/M$ where $\rho$ is the density of the supercritical phase. Thus Eq. (14) may be expressed as

$$\ln(y) - \kappa\ln(y_B) + (1-\kappa)\ln\left(\frac{P}{P^*}\right) = \ln\left(\frac{\hat{\phi}_{AB_\kappa}}{\phi^*_{AB_\kappa}}\right) + \ln(\phi^*_A)$$

$$-\ln(P_A^{sub}) + \ln(P^*) - \frac{ZV_A\rho}{M} + \frac{V_A P_A^{sub}}{RT} - \kappa\ln\left(\frac{\hat{\phi}_B}{\phi^*_B}\right) + \frac{\Delta H_s}{RT} + q_s \tag{15}$$

The sublimation pressure of the solid solute may expressed as

$$\ln(P_A^{sub}) = A_1 - \frac{B_1}{T} \tag{16}$$

where $A_1$ and $B_1$ are temperature-independent parameters. The term $(V_A P_A^{sub}/RT)$ ($\sim 10^{-9}$) can be neglected because the sublima-

**Table 2**
Correlation parameters for solubilities of propyphenazone in $SCCO_2$.

| Model | Correlation parameters | AARD (%) |
|---|---|---|
| Méndez-Santiago and Teja model | $M$ (K) = −10 450; $N$ (K mol$^{-1}$ mL) = 127 600; $O$ = 24.15 | 10.1 |
| New association model | $\kappa$ = 0.3923; $a/K$ = −8201; $b$ (m$^3$ kg$^{-1}$) = 0.00846; $c$ = 15.631 | 8.3 |

**Table 3**
Physical properties and data references for the pharmaceutical compounds considered in this study.

| SN | Compound | Formula | $M_w$ (g/mol) | $T_m$ (K) | $T$ (K) | $P$ (bar) | $N$ | Ref. |
|---|---|---|---|---|---|---|---|---|
| 1 | Acetanilide | $C_8H_9NO$ | 135.17 | 387.5 | 308–328 | 104–225 | 24 | [22] |
| 2 | Amical-48 | $C_8H_8O_2SI_2$ | 422.02 | 453.2 | 318–338 | 100–300 | 18 | [23] |
| 3 | Anastrazole | $C_{17}H_{19}N_5$ | 293.37 | 354.2 | 308–348 | 120–355 | 45 | [24] |
| 4 | Antipyrine | $C_{12}H_{12}N_2O$ | 188.20 | 385.6 | 308–328 | 100–220 | 21 | [25] |
| 5 | Artemisinin | $C_{15}H_{22}O_5$ | 282.33 | 429.6 | 310–338 | 100–270 | 36 | [26] |
| 6 | Aspirin | $C_9H_8O_4$ | 180.16 | 407.4 | 308–328 | 120–250 | 24 | [27] |
| 7 | Atorvastatin | $C_{33}H_{33}FN_2O_4$ | 540.60 | 432.2 | 308–348 | 120–355 | 45 | [28] |
| 8 | BDP | $C_{28}H_{37}ClO_7$ | 521.01 | 391.2 | 338–358 | 210–390 | 21 | [29] |
| 9 | Benzocaine | $C_9H_{11}NO_2$ | 165.19 | 363.1 | 308–318 | 80–250 | 20 | [30] |
| 10 | Benzoin | $C_{14}H_{12}O_2$ | 212.15 | 410.2 | 308–328 | 100–230 | 21 | [31] |
| 11 | BUD | $C_{25}H_{34}O_6$ | 430.59 | 499.5 | 338–358 | 210–385 | 21 | [29] |
| 12 | Cholesterol | $C_{27}H_{46}O$ | 386.65 | 421.2 | 313–333 | 100–250 | 24 | [32,33] |
| 13 | Cholesterol benzoate | $C_{34}H_{50}O_2$ | 490.76 | 421.8 | 308–328 | 120–270 | 20 | [32] |
| 14 | Climbazole | $C_{15}H_{17}ClN_2$ | 292.76 | 371.5 | 313–333 | 100–400 | 24 | [34] |
| 15 | Clofibric acid | $C_{10}H_{11}ClO_3$ | 214.60 | 394.2 | 308–328 | 100–220 | 21 | [35] |
| 16 | Codeine | $C_{18}H_{21}NO_3$ | 299.36 | 429.4 | 308–348 | 120–360 | 45 | [36] |
| 17 | Diazepam | $C_{16}H_{13}ClN_2O$ | 284.74 | 401.9 | 308–348 | 120–360 | 45 | [36] |
| 18 | DDT | $C_{14}H_9Cl_5$ | 354.48 | 381.6 | 313–333 | 100–210 | 18 | [37] |
| 19 | 4-Dimethylaminoantipyrine | $C_{13}H_{17}N_3O$ | 231.30 | 381.2 | 308–328 | 100–220 | 21 | [25] |
| 20 | Flurbiprofen | $C_{15}H_{13}FO_2$ | 244.30 | 383.9 | 303–323 | 80–250 | 27 | [38] |
| 21 | Fluvastatin | $C_{24}H_{26}FNO_4$ | 411.4 | 467.0 | 308–348 | 120–355 | 45 | [28] |
| 22 | Ibuprofen | $C_{13}H_{18}O_2$ | 206.30 | 349.2 | 308–318 | 80–220 | 29 | [39] |
| 23 | Ketoprofen | $C_{16}H_{14}O_3$ | 254.28 | 367.2 | 313–332 | 90–250 | 10 | [40] |
| 24 | Lamotrigine | $C_9H_7Cl_2N_5$ | 256.94 | 491.0 | 318–348 | 120–355 | 36 | [41] |
| 25 | Lovastatin | $C_{24}H_{36}O_5$ | 404.50 | 447.5 | 308–348 | 120–355 | 45 | [28] |
| 26 | Lycopene | $C_{40}H_{56}$ | 536.87 | 450.0 | 313–333 | 200–420 | 19 | [42] |
| 27 | Mandelic acid | $C_8H_8O_3$ | 152.15 | 394.4 | 308–328 | 100–235 | 21 | [31] |
| 28 | Methimazole | $C_4H_6N_2S$ | 114.17 | 418.8 | 308–348 | 120–360 | 40 | [43] |
| 29 | 2-Methyl-acetanilide | $C_9H_{11}NO$ | 149.19 | 383.2 | 308–328 | 120–225 | 21 | [22] |
| 30 | 4-Methyl-acetanilide | $C_9H_{11}NO$ | 149.19 | 421.7 | 308–328 | 120–225 | 21 | [22] |
| 31 | Nabumetone | $C_{15}H_{16}O_2$ | 228.30 | 353.2 | 308–328 | 100–220 | 21 | [44] |
| 32 | Naproxen | $C_{14}H_{14}O_3$ | 230.26 | 427.2 | 313–333 | 80–200 | 18 | [45] |
| 33 | Nimesulide | $C_{13}H_{12}N_2O_5S$ | 308.31 | 421.6 | 313–333 | 120–220 | 8 | [40] |
| 34 | 2-Nitroanisole | $C_7H_7NO_3$ | 153.14 | 282.6 | 313–333 | 80–200 | 18 | [46] |
| 35 | Pencillin V | $C_{16}H_{18}N_2O_5S$ | 350.39 | 397.2 | 313–335 | 80–300 | 24 | [47] |
| 36 | Paraxetin | $C_{19}H_{20}FNO_3$ | 329.30 | 402.2 | 308–328 | 80–220 | 24 | [48] |
| 37 | Phenacetin | $C_{10}H_{13}NO_2$ | 179.21 | 407.1 | 308–328 | 90–190 | 16 | [20] |
| 38 | Phenazopyridine | $C_{11}H_{11}N_5$ | 213.24 | 412.2 | 308–348 | 120–360 | 45 | [43] |
| 39 | Phenyl butazone | $C_{19}H_{20}N_2O_2$ | 308.30 | 378.6 | 308–328 | 100–220 | 21 | [44] |
| 40 | Piroxicam | $C_{15}H_{13}N_3O_4S$ | 331.35 | 469.2 | 313–331 | 100–220 | 9 | [40] |
| 41 | Procaine | $C_{13}H_{20}N_2O_2$ | 236.31 | 334.2 | 308–318 | 80–250 | 18 | [30] |
| 42 | Pyrocatechol | $C_6H_6O_2$ | 110.11 | 378.2 | 308–338 | 120–400 | 32 | [49] |
| 43 | Resorcinol | $C_6H_6O_2$ | 110.11 | 383.2 | 308–338 | 120–400 | 18 | [49] |
| 44 | Rosuvastatin | $C_{22}H_{28}FN_3O_6S$ | 481.50 | 435.0 | 308–348 | 120–355 | 45 | [28] |
| 45 | Salicylamide | $C_7H_7NO_2$ | 137.10 | 413.6 | 308–328 | 100–220 | 21 | [44] |
| 46 | Salicylic acid | $C_7H_6O_3$ | 138.12 | 432.2 | 313–328 | 90–250 | 11 | [50] |
| 47 | Sulfamethazine | $C_{12}H_{14}N_4O_2S$ | 278.30 | 177.5 | 313–333 | 130–480 | 20 | [51] |
| 48 | Triclocarban | $C_{13}H_9Cl_3N_2O$ | 315.58 | 528.2 | 313–333 | 100–400 | 24 | [52] |
| 49 | α-Tocopherol | $C_{29}H_{50}O_2$ | 430.70 | 276.2 | 313–353 | 190–350 | 24 | [52] |
| 50 | Vitamin A | $C_{20}H_{30}O$ | 286.44 | 336.2 | 313–353 | 200–350 | 20 | [52] |
| 51 | Vitamin E | $C_{29}H_{50}O_2$ | 430.70 | 276.2 | 313–353 | 190–350 | 24 | [52] |
| 52 | Vitamin D2 | $C_{28}H_{44}O$ | 396.66 | 389.6 | 313–353 | 200–320 | 19 | [52] |
| 53 | Vitamin K1 | $C_{31}H_{46}O_2$ | 450.7 | 253.2 | 313–353 | 200–350 | 24 | [52] |
| 54 | Zopiclone | $C_{17}H_{17}ClN_6O_3$ | 388.81 | 451.2 | 313–333 | 100–250 | 21 | [53] |

tion pressures ($\sim 10^{-4}$) and molar volume of solid solutes ($\sim 10^{-4}$) are very small. Thus the contribution of the term in overall value of Eq. (15) is negligible and thus can be neglected. Therefore, Eq. (15) becomes

$$\ln(y) - \kappa \ln(y_B) + (1-\kappa)\ln\left(\frac{P}{P^*}\right) = \frac{a}{T} + b\rho + c \tag{17}$$

where $a = (\Delta H_s/R) - B_1$, $b = ZV_A/M$ and $c = \ln((\phi_A^*)(\hat{\phi}_{AB_\kappa}/\phi_{AB_\kappa}^*)/(\hat{\phi}_B/\phi_B^*)^\kappa) - \ln P^* + q_s + A_1$

Eq. (17) may be written as

$$y = (y_B)^\kappa \left(\frac{P}{P^*}\right)^{(\kappa-1)} \exp\left(\frac{a}{T} + b\rho + c\right) \tag{18}$$

Because the solubilities of drugs in $SCCO_2$ are very dilute, therefore, for a binary system we may assume $Y_B$ is unity. Then Eq. (18) becomes

$$y = \left(\frac{P}{P^*}\right)^{(\kappa-1)} \exp\left(\frac{a}{T} + b\rho + c\right) \tag{19}$$

## 4. Results and discussion

### 4.1. Solubility data

The solubilities of propyphenazone (in mole fraction) at 308, 318 and 328 K, over the pressure range from 9 to 19 MPa in $SCCO_2$ were in the range of $3.19 \times 10^{-4}$ to $18.82 \times 10^{-4}$, as shown in Table 1.

**Table 4**
Correlation parameters for solubilities of pharmaceutical compounds in $SCCO_2$ using the association model.

| SN | Compound | $\kappa$ | $a$ (K) | $b$ ($kg^{-1}\ m^3$) | $c$ | AARD (%) |
|---|---|---|---|---|---|---|
| 1 | Acetanilide | 1.1066 | −7677 | 0.00689 | 9.760 | 7.0 |
| 2 | Amical-48 | 0.8897 | −4984 | 0.00456 | 2.647 | 11.7 |
| 3 | Anastrazole | 0.2228 | −11 000 | 0.01106 | 19.437 | 6.9 |
| 4 | Antipyrine | 0.1337 | −6587 | 0.00895 | 10.542 | 3.9 |
| 5 | Artemisinin | 0.7814 | −4013 | 0.00612 | 2.469 | 6.3 |
| 6 | Aspirin | 0.2672 | −7798 | 0.00827 | 13.154 | 5.0 |
| 7 | Atorvastatin | 0.3032 | −12 490 | 0.01593 | 20.512 | 6.4 |
| 8 | BDP | 2.3847 | −4236 | 0.00365 | −9.716 | 11.1 |
| 9 | Benzocaine | 3.7526 | 4580 | −0.00278 | −36.330 | 9.9 |
| 10 | Benzoin | 0.5514 | −6124 | 0.00787 | 7.021 | 5.7 |
| 11 | BUD | 3.5522 | −2537 | 5.6e−4 | −19.022 | 10.7 |
| 12 | Cholesterol | 0.3479 | −7386 | 0.01018 | 8.928 | 5.0 |
| 13 | Cholesterol benzoate | 0.5437 | −8370 | 0.01087 | 9.193 | 8.5 |
| 14 | Climbazole | 0.0770 | −4709 | 0.01052 | 5.169 | 5.6 |
| 15 | Clofibric acid | 0.3176 | −6083 | 0.00779 | 9.104 | 5.5 |
| 16 | Codeine | 1.0583 | −6156 | 0.00669 | 5.122 | 11.9 |
| 17 | Diazepam | 1.6067 | −3736 | 0.00353 | −2.547 | 9.2 |
| 18 | DDT | 0.2697 | −7381 | 0.00995 | 11.715 | 7.2 |
| 19 | 4-Dimethylaminoantipyrine | 0.3418 | −7181 | 0.00846 | 12.819 | 4.6 |
| 20 | Flurbiprofen | 1.3258 | −7261 | 0.00652 | 6.857 | 6.5 |
| 21 | Fluvastatin | 0.1054 | −11 000 | 0.01427 | 17.587 | 11.7 |
| 22 | Ibuprofen | 0.1328 | −12 560 | 0.01172 | 29.733 | 10.2 |
| 23 | Ketoprofen | 0.4505 | −9325 | 0.01094 | 13.986 | 7.0 |
| 24 | Lamotrigine | 0.1264 | −5748 | 0.00774 | 3.332 | 3.8 |
| 25 | Lovastatin | 0.2583 | −5252 | 0.00606 | 5.410 | 4.8 |
| 26 | Lycopene | 1.6464 | −2308 | −0.00194 | −8.965 | 4.6 |
| 27 | Mandelic acid | 1.5145 | −10 230 | 0.01254 | 12.598 | 10.4 |
| 28 | Methimazole | 0.8181 | −6168 | 0.00822 | 3.539 | 9.4 |
| 29 | 2-Methyl-acetanilide | 0.9908 | −11 940 | 0.01258 | 18.887 | 6.8 |
| 30 | 4-Methyl-acetanilide | 0.4996 | −11 500 | 0.01179 | 20.800 | 8.3 |
| 31 | Nabumetone | 0.5342 | −7195 | 0.00865 | 11.776 | 7.7 |
| 32 | Naproxen | 1.0808 | −5630 | 0.00650 | 1.505 | 4.9 |
| 33 | Nimesulide | 2.2225 | −5083 | 0.00598 | −5.006 | 11.0 |
| 34 | 2-Nitroanisole | 0.6864 | 2904 | 0.00327 | −15.528 | 7.7 |
| 35 | Pencillin V | 1.4607 | −2822 | 0.00193 | −3.146 | 11.2 |
| 36 | Paraxetin | 0.8379 | −6310 | 0.00614 | 8.544 | 4.7 |
| 37 | Phenacetin | 0.6703 | −5412 | 0.00618 | 3.590 | 5.6 |
| 38 | Phenazopyridine | 0.7812 | −7040 | 0.00898 | 5.761 | 7.7 |
| 39 | Phenyl butazone | 0.5094 | −6597 | 0.00970 | 9.237 | 9.2 |
| 40 | Piroxicam | 2.0940 | −3288 | 0.00719 | −11.632 | 5.4 |
| 41 | Procaine | 1.5142 | −1942 | 5.9e−4 | −5.894 | 3.6 |
| 42 | Pyrocatechol | 0.8608 | −5073 | 0.00380 | 6.958 | 3.3 |
| 43 | Resorcinol | 1.5488 | −4606 | 0.00180 | 1.831 | 3.5 |
| 44 | Rosuvastatin | 0.2041 | −7926 | 0.01098 | 10.236 | 5.0 |
| 45 | Salicylamide | 0.7300 | −6346 | 0.00643 | 7.296 | 6.1 |
| 46 | Salicylic acid | 0.4860 | −7683 | 0.00729 | 13.163 | 4.4 |
| 47 | Sulfamethazine | 1.8842 | −850 | −7.4e−4 | −14.928 | 5.4 |
| 48 | Triclocarban | 0.4510 | −5278 | 0.00965 | 3.904 | 7.0 |
| 49 | α-Tocopherol | 0.7426 | −4113 | 0.00906 | 0.382 | 3.3 |
| 50 | Vitamin A | 1.2417 | −3004 | 0.00648 | −3.411 | 7.2 |
| 51 | Vitamin E | 0.7426 | −4113 | 0.00906 | 0.382 | 3.3 |
| 52 | Vitamin D2 | 0.8928 | −6030 | 0.00790 | 5.018 | 10.6 |
| 53 | Vitamin K1 | 1.3408 | −3390 | 0.00950 | −5.670 | 5.9 |
| 54 | Zopiclone | 0.8429 | −5498 | 0.00484 | 2.513 | 8.3 |

### 4.2. Méndez-Santiago and Teja model

It is based on the theory of dilute solutions and relates the solute solubility, $y_2$, with the density of $SCCO_2$ (mol $mL^{-1}$).

$$T \ln\left(\frac{y_2 P}{P^*}\right) = M + N\rho + OT \tag{20}$$

While Eq. (19) is derived on the basis of solvate complex theory, Eq. (20) is based on the dilution theory (Henry's law). In Eq. (20), $M$, $N$ and $O$ are temperature-independent parameters. These parameters are obtained by correlating the experimental data with Eq. (20) and are shown in Table 2 along with AARD (%). This is defined as

$$\text{AARD}\,(\%) = \frac{100}{N_i}\sum_{i=1}^{N_i}\frac{|y_2^{\text{calc}} - y_2^{\text{exp}}|}{y_2^{\text{exp}}}$$

where $N_i$ is the number of data points, $y_2$ is the molar solubility of the solute and superscripts calc and exp denotes the calculated and experimental values, respectively. After determining $M$, $N$, $O$ by nonlinear regression, a plot of $T\ln(y_2P/P^*) - OT$ vs $\rho$ is drawn and verified to be linear. The data consistency is verified by the Méndez-Santiago and Teja model wherein experimental data at different temperatures collapse onto a single straight line, as shown in Fig. 3. The density of $SCCO_2$ was calculated from the Span and Wagner equation of state [54].

### 4.3. Association model

The solubilities of propyphenazone (in mole fraction) were correlated by the association model (Eq. (19)) and the correlations along with the experimental data are shown in Fig. 4. The solid solubilities of 54 pharmaceutical compounds containing steroids,

**Table 5**
Comparison of AARDs of the new association model with the models discussed by Tabernero et al. [11].

| Compound | Chrastil | VA | AL | Sparks | MST | KJ | Bartle | Yu | Gordillo | New model |
|---|---|---|---|---|---|---|---|---|---|---|
| Fluvastatin | 14.73 | 14.59 | 9.31 | 10.64 | 14.30 | 11.81 | 11.42 | 56.85 | 20.47 | 11.7 |
| Lovastatin | 5.90 | 5.78 | 4.38 | 4.27 | 5.37 | 9.80 | 4.19 | 8.55 | 12.53 | 4.8 |
| Methimazole | 12.69 | 12.34 | 10.43 | 10.95 | 10.99 | 9.56 | 12.43 | 15.29 | 11.90 | 9.4 |
| Naproxen | 9.77 | 9.74 | 8.93 | 8.58 | 10.41 | 11.36 | 11.80 | 6.27 | 15.63 | 4.9 |
| Nimesulide | 14.08 | 14.06 | 6.35 | 5.63 | 12.59 | 8.59 | 14.58 | 4.72 | 14.51 | 11.0 |
| Pencillin V | 18.17 | 18.13 | 5.99 | 6.24 | 16.59 | 11.49 | 16.17 | 6.68 | 16.10 | 11.2 |
| Phenazopyridine | 15.46 | 15.71 | 21.40 | 20.92 | 9.21 | 8.14 | 10.94 | 17.97 | 13.09 | 7.7 |
| Vitamin K1 | 6.68 | 5.98 | 3.69 | 3.64 | 5.05 | 5.23 | 6.54 | 3.75 | 8.56 | 5.1 |
| Mean | 12.18 | 12.04 | 8.81 | 8.86 | 10.56 | 9.50 | 11.00 | 15.01 | 14.10 | 8.22 |
| S.D. | 4.35 | 4.51 | 5.62 | 5.59 | 4.03 | 2.20 | 3.94 | 17.64 | 3.51 | 3.00 |

antioxidants, antibiotics and statin drugs in $SCCO_2$ were correlated with the association model (Eq. (19)). Table 3 shows the physical properties of these compounds. The correlation of the experimental solubility data requires an optimization process where the constants for the association model were determined by using the nonlinear regression. The correlated results are shown in Table 4 along with AARD (%). The same definition of AARD (as used for the Méndez-Santiago and Teja model) was used and the density was calculated from the Span and Wagner equation of state. It is observed that the new proposed equation has successfully correlated the solubilities of all the compounds within 12%. Tabernero et al. [11] have compared the solubilities of 27 pharmaceutical compounds with various equations and have shown that the best correlations are obtained by the use of Sparks or Gordillo equation. Even in these cases, the AARD are quite high and vary between 10 and 40% though the average AARD is around 15%. However, the equation developed in this study is able to correlate a wide variety of pharmaceutical compounds with lesser AARD. The average AARD of 54 pharmaceutical compounds for the new model is 7%. Table 5 shows the comparison of AARDs obtained by the new association model and the AARDs obtained by various models discussed by Tabernero et al. [11]. This again indicates the current association is superior in correlating the solubilities. Further, unlike the above models that have six adjustable parameters, the model proposed in this work has only four parameters. Thus the current model may be an alternative to the existing semi-empirical equations that are present in the literature.

## 5. Conclusions

The equilibrium solubilities of propyphenazone in $SCCO_2$ at 308, 318 and 328 K, over the pressure range from 9 to 19 MPa were determined. The mole fraction of propyphenazone ranges from 0.38 to $18.82 \times 10^{-4}$. The experimental solubility data satisfied the self-consistency test. A new association model was developed for correlating the solubilities of drugs in supercritical fluids. Solubility data from 54 different pharmaceutical compounds were taken from literature. The model proposed in this work required only 4 parameters and successfully correlated the experimental results for the solubilities of drugs in $SCCO_2$ within 12% (AARD).

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