C. R. Chimie 20 (2017) 559–572

Contents lists available at ScienceDirect

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Novel density-based model for the correlation of solid drugs solubility in supercritical carbon dioxide

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ARTICLE INFO

Article history:
Received 15 June 2016
Accepted 27 September 2016
Available online 29 October 2016

Keywords:
Solubility
Modeling
Density-based models
Solid drugs
Supercritical carbon dioxide

ABSTRACT

A novel density-based model derived by a simple modification of the Jouyban et al. model has been proposed to correlate the solubility of solid drugs in supercritical carbon dioxide. The six-parameter model expresses the solubility only as a function of the solvent density and the equilibrium temperature. This model is in contrast to the Jouyban et al. (J. Superiority. Fluids 24 (2002) 19) model, which gives the solubility as a function of the solvent density and the equilibrium temperature and pressure. The performance of the model has been tested on a database of 100 drugs that account for 2891 experimental data points collected from the literature. The comparison in terms of the mean absolute relative deviation for each solid drug and for the entire database between the proposed model and models that have been suggested to be mostly more accurate demonstrates that the proposed model has the best global correlation performance, exhibiting an overall average absolute relative deviation of 8.13%.

1. Introduction

The level of interest in the technology of supercritical fluids (SCFs) has increased in recent decades because of its economic and environmental impact. Currently, SCF technology has widespread utility ranging from food processing to pharmaceutical applications [1]. Commonly, conventional production processes of many pharmaceuticals comprise a series of separation and purification operations involving a series of organic solvent extraction and precipitation steps and end up very often with the recovery of a large amount of organic solvents. Aside from of being environmentally benign, less energy intensive, and more effective in controlling product specification, SCF processing offers many advantages over conventional methods of extraction, drug particle formation, and drug delivery system design. Reduction of potentially harmful organic solvents and steps required for product fabrication are among the many advantages associated with SCF technology. Being inexpensive, nontoxic, abundant, and environmentally safe, supercritical carbon dioxide ($scCO_2$) can replace toxic and undesirable organic solvents that either require extensive solvent recovery units or remain in very small but still dangerous proportions [1–4].

The importance given to SCF technology is well illustrated by the growing published experimental data on the solubility of solid solutes (e.g., polymers, foods, drugs, nutraceuticals, pesticides, dyes, and metal complexes) in $scCO_2$ with and without cosolvents. Solubility is typically defined as mole fraction (y_2) or weight fraction (c_2) of solute in the SCF, which is in equilibrium with the bulk solute. Various methods to measure solubility in SCFs have been reviewed [4–9]. These methods can be divided into two

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http://dx.doi.org/10.1016/j.crci.2016.09.009
1631-0748/

major categories: static and dynamic. A compilation of most of the published experimental data before 2004 is provided by Gupta and Shim [4]. A series of review articles [5–9] on high-pressure phase equilibria also present a compilation of experimental investigations on the solubility of solid solutes in SCF. This huge enthusiasm for these experimental measurements is because the most important and decisive factor affecting the efficacy and the correspondent technical and economic success of most SCF processes is the accurate knowledge of the equilibrium solubility of the materials to be processed in the selected SCF solvent and/or the solubility of that SCF in those materials.

Attempts at modeling the solubility of solid solutes in the SCF phase for the purpose of correlation and/or prediction have followed suit experimental investigations. However, these modeling efforts have not yet been satisfactory to the desired level of accuracy, which is one reason why it is still a research subject of interest and more experimental data are continuously being published, and new compounds are being investigated. The solubility of a solid solute in an SCF is a problem of phase equilibrium, and as such, the straightforward and obvious modeling method is the use of an equation of state (EoS) or an activity coefficient method. Simple cubic EoS with various mixing rules has been extensively used for calculation of solid solute solubility in $scCO_2$ [10–14]. The use of cubic EoS requires critical properties, the acentric factor, sublimation pressure, and the molar volume of the solute. In the absence of experimental values of these parameters, which is more often the case for complex pharmaceutical compounds, they are estimated using group contribution (GC) methods. Sublimation pressure may also be considered as an adjusted parameter to be fitted to solubility data. The accuracy of the correlation or prediction using the cubic EoS depends considerably on the method used to estimate these solid solute properties [10,11].

More complex and theoretical-sound state of the art EoS, such as nonrandom hydrogen-bonding (NRHB) theory [15] and the statistical associating fluid theory (SAFT) [16–18], have also been used to predict or to correlate the solubility of solids in SCFs. NRHB theory was applied for the modeling of the solubility of six drugs in $scCO_2$ by Tsivintzelis et al. [15]. The solubility of the six drugs in $scCO_2$ was correlated by this EoS with the one temperature-independent binary parameter fitted to the experimental data. For the application of the NRHB model, physical and hydrogen-bonding fluid-specific parameters are optimized using pure fluid properties. For common fluids, such as alkanols, amines, and others, vapor pressures and liquid densities are often used. Furthermore, the hydrogen-bonding parameters can be determined using calorimetric or spectroscopic data. However, for most pharmaceuticals, extended experimental data on physical properties do not exist [15].

Most SAFT-type models require five parameters for each pure associating compound (three for nonassociation ones). The three parameters for nonassociating fluids are the segment number, the interaction energy, and the hard-core segment diameter, which are either calculated using GC methods, such as proposed by Tihic et al. [19] and used by Abdallah El Hadj et al. [18] to correlate the solubility solid drugs in $scCO_2$, or estimated from vapor pressure and liquid-density data over extended temperature ranges. In the absence of such data for specific compounds, such as polymers and pharmaceuticals, GC methods, such as GC-SAFT [20], GC-SAFT variable range (SAFT-VR) [21–23], and GC-SAFT-γ [24], are used for the calculation of required properties.

Activity coefficient models, such as UNIversal Functional Activity Coefficient (UNIFAC), the regular solution theory based models, and more sophisticated models, such as conductor-like screening model (COSMO), cannot be used for high-pressure phase equilibrium calculations without being coupled with another model, namely, an EoS [15]. Activity coefficient models based on the COSMO method [25] such as COSMO–real solvents [26] and COSMO–surface activity coefficient (COSMO-SAC) [27] have been used to predict the thermodynamics in mixtures without data fitting. Shimoyama and Iwai [28] developed a COSMO-vacancy model to extend the range of applicability of predictive COSMO-SAC liquid model to supercritical conditions. The model was successful in predicting the solubility of 16 solid drugs in $scCO_2$, where the melting points and enthalpies of fusion were the only solute properties used, and the molar volume of $scCO_2$ was calculated using an EoS. Recently, Wang and Lin [29] coupled the well-known Peng-Robinson EoS with the COSMO-SAC model (PR + COSMO-SAC) to predict the solubility of 46 drugs in subcritical and supercritical CO_2. In the EoS, the interaction parameter, a, and molecule covolume, b, are determined from the result of first principle solvation calculation instead of using the critical properties and acentric factor of pure substances. Hence, the only experimental data required for drugs are the melting temperature and the melting enthalpy. More recently Wang et al. [30] analyzed the vapor pressure data of 1125 compounds and proposed a modification of the PR + COSMO-SAC model [29] to improve the prediction of saturated pressure that allows the application of the method for the prediction of phase equilibrium containing solid phase, such as solid drugs in supercritical solvents. From this review of the EoS approach in modeling the solubility of solid solutes in supercritical solvents, it is clear that EoS whether predictive or correlative, with the exception of the COSMO model, still rely on experimental data that are required for fitting at least one binary interaction parameter used by mixing rules or the fitting of other required compound properties or for the validation of models. This finding is particularly true for complex multifunctional chemicals, such as pharmaceuticals.

A simpler alternative to EoS models, even if it is also limited to the range of experimental data from which the models are derived, is the use of empirical models based on the density of the SCF, pressure, and/or temperature. The use of empirical and semiempirical models has been extensively reported [31–58]. These models are based on simple error minimization using the least square method to determine the adjustable parameters of the model, and for most of them there is no need to use physical properties of the solute. Since the work of Stahl et al. [31], who proposed a direct linear relationship between the logarithm of the solubility of the solute in a compressed gas and the logarithm of the density of the gas, several models have been proposed by different authors with the aim of improving

the quality of correlation of new experimental data for which previous models may present poor correlation. The main differences between the proposed models may be summarized as follows:

1. The number of adjusted parameters of the models, which vary from 3 to 10.
2. Although most proposed models include a linear relationship between the logarithm of the solubility of the solid solute and the logarithm of the SCF density, we may find, in some models, more complex nonlinear relationships between the logarithm of the solubility of the solid solutes and the density of the SCF and equilibrium temperature and pressure.
3. If one analyzes correlation results from previous works [42,44,47,50,53–56], particularly the work of Tabernero et al. [54], who compared the correlation performance of nine semiempirical equations applied on a solubility data set of 27 pharmaceutical compounds in $scCO_2$-containing 774 experimental data points, and the work of Bian et al. [56], who compared the correlation performance of 15 semiempirical equations applied on a solubility data set of 45 compounds in $scCO_2$-containing 1130 experimental data points, one may clearly note that there is no model that presents the best correlation for all the experimental data of all solutes. However, models with five or six adjustable parameters seem to correlate with experimental data more accurately than models with three adjustable parameters.

The aim of this work is to contribute to the improvement of the quality of density-based correlation of solid drug solubility in $scCO_2$. This contribution will be based on a simple modification of a Jouyban et al. [41] model. The proposed model will then be evaluated on a large experimental data set collected from the literature, by comparison with the literature models that have been suggested in several works [42,44,47,50,54–56], to assess the best correlation performance.

2. Modeling solid-SCF phase equilibrium

The solubility of a nonvolatile pure solid (2) in an SCF (1), y_2, is determined from standard thermodynamic relationships by equating fugacities in the solid phase and in the supercritical phase for each component. This isofugacity criterion for this binary system is reduced to one equation, because the solvent is assumed insoluble in the solid phase:

$$f_2^S = f_2^{SCF} \tag{1}$$

The fugacity of the solid phase is given by

$$f_2^S = P_2^{sub}\phi_2^{sat}\exp\left[\frac{V_2^S}{RT}\left(P - P_2^{sub}\right)\right] \tag{2}$$

Here P_2^{sub}, ϕ_2^{sat}, and V_2^S are the sublimation pressure, molar volume, and the fugacity coefficient of the saturated solid.

The fugacity of solid solute in the supercritical phase is given by

$$f_2^{SCF} = y_2\phi_2^{SCF}P \tag{3}$$

Here ϕ_2^{SCF} is the fugacity coefficient of the solid solute in the supercritical phase.

Combining Eqs. (1)–(3) gives the expression for the mole fraction solubility:

$$y_2 = \frac{P_2^{sub}}{P}\cdot\frac{\phi_2^{sat}}{\phi_2^{SCF}}\exp\left[\frac{V_2^s}{RT}\left(P - P_2^{sub}\right)\right] \tag{4}$$

Eq. (4) shows that the solubility is the product of the ideal solubility (P_2^{sub}/P) and a correction term known as the enhancement factor that reflects the nonideality of the supercritical phase through the ratio ($\phi_2^{sat}/\phi_2^{SCF}$) and the effect of pressure on the fugacity of the solid, as it is known for liquids, through the exponential term known as the Poynting factor. In addition, for solids of very low volatility as is the case with many solid drugs, sublimation pressure is very low and values of the saturated fugacity coefficient of the solid, ϕ_2^{sat}, are very close to one. The expression for the solid solubility of the solute is then reduced to

$$y_2 = \frac{P_2^{sub}}{P}\cdot\frac{1}{\phi_2^{SCF}}\exp\left[\frac{V_2^s}{RT}\left(P - P_2^{sub}\right)\right] \tag{5}$$

In fact, this equation gives the solubility in an implicit form because ϕ_2^{SCF} is a function of y_2, T, P, and Z^{SCF} (the compressibility coefficient of the supercritical phase), itself a function of y_2, T, and P.

$$\phi_2^{SCF} = \phi\left(T, P, Z^{SCF}, y_2\right) \tag{6}$$

$$Z^{SCF} = Z(T, P, y_2) \tag{7}$$

Eqs. (5)–(7) are the basis for calculating the solubility of a solid solute in an SCF by an EoS. The quality of predictions or correlations depends on the EoS, and even for the same EoS, it depends also on the mixing rules. Moreover, this method requires the solute properties, and the calculations are very sensitive to the accuracy of the solute properties [10,11,18].

If one takes the logarithm of Eq. (5),

$$\ln y_2 = \ln P_2^{sub} - \ln P - \ln\phi_2^{SCF} + \frac{V_2^s}{R}\cdot\frac{P}{T} - \frac{V_2^s P_2^{sub}}{R}\cdot\frac{1}{T} \tag{8}$$

For given T and P the volumetric properties of the solvent are governed by Eq. (9):

$$P = ZRT\rho_1 \tag{9}$$

Combining Eqs. (8) and (9), one can relate the solubility of the solute to the density of the solvent and the coefficient of compressibility of the pure solvent at the given temperature and pressure:

$$\ln y_2 = \ln P_2^{sub} - \ln(ZRT\rho_1) - \ln\phi_2^{SCF} + V_2^s Z\rho_1 - \frac{V_2^s P_2^{sub}}{R}\cdot\frac{1}{T} \tag{10}$$

Although Eq. (10) gives the solubility in a complex implicit form as mentioned previously, it shows how the solubility of the solute could be related to the density of the supercritical solvent. A density-based model can be considered a simple empirical approximation to the right-hand side of Eq. (10) that does not require any solute parameter in contrast to EoS models. The next section presents a brief review of density-based modeling.

2.1. Review of density-based modeling

Density-based models for the correlation of the solubility of a solid solute in a dense phase have evolved considerably since the work of Stahl et al. [31]. Table 1 summarizes the density-based models that have been proposed since this work. In this table, y_2 is the solubility of the solid solute in mole fraction, ρ_1 is the density of the SCF (in kg/m^3), T is the temperature (in K), P is the pressure (in bar), a_i represents the characteristic parameters determined by fitting experimental data of the solute/solvent considered. For the Sparks et al. model [42], the solubility is expressed in a dimensionless form, whereas in the Bain et al. model [47] the solute solubility, c_2, is in kilograms per cubic meter. In both models c_2 is related to y_2 by Eq. (27a), in which Mw_1 and Mw_2 are the molecular weights of the solvent and the solute, respectively. It is worth mentioning that some of the models do not relate the solubility explicitly to the density of the SCF solvent. The very few models that require solute parameters whose numerical values are not available for compounds of interest, such as solid drugs, were not included in this work. Literature reviews describing the basis and assumptions upon which these models have been proposed, as well as comparisons of the performance of the correlation of the solubility of a variety of solid solutes between the various models, can be found in Refs. [42,44,47,50,53–56]. Therefore, a brief review is given here only for models that have been suggested to have the best correlating performance.

The first model that established a linear relationship under isothermal conditions between the logarithm of solubility $\ln y_2$ of a solute in an SCF and the logarithm of fluid density $\ln\rho_1$ was proposed by Stahl et al. [31]. On the basis of the theory that at equilibrium a solvato complex is formed between associating solute and solvent molecules, Chrastil [32] added a new term that takes account of the effect of temperature. This led to the model given by Eq. (12) in which a_1 is the average association number, a_2 is a function of the enthalpy of solvation and enthalpy of vaporization, a_0 is a function of the average association number and molecular weight of the solute and solvent.

With the availability of more and newer experimental data, subsequent studies have demonstrated two major drawbacks of Chrastil's equation: it is valid for solubilities less than 100–200 kg/m^3 and for a restricted temperature range [33,34]. To account for the effect of solvent density on solubility, Adachi and Lu [33] correlated the average association number to a second-order polynomial of the solvent density, which led to the model given by Eq. (13), achieving a significant decrease in the error between experimental and calculated solubility data for some systems. The effect of temperature on solubility was taken into consideration in the del Valle and Aguilera [34] modification (Eq. (14)) by adding a reciprocal of squared temperature term to Chrastil's equation.

On the basis of a review of published experimental solubility data in $scCO_2$ and previously presented models, Jouyban et al. [41] suggested the existence of

(1) a nonlinear relationship between $\ln y_2$ and pressure in isothermal conditions,
(2) a nonlinear relationship between $\ln y_2$ and temperature in isobaric conditions, and
(3) a linear relationship between $\ln y_2$ and $\ln\rho_1$ in a certain range of pressure and temperature.

They proposed Eq. (21) as a modification of Chrastil's model in which they introduced the effect of pressure on solubility as a second-order polynomial and a nonlinear relationship that takes account of the combined effect of temperature and pressure. The scarce use of the Jouyban et al. model is the reason why Tabernero et al. [54] excluded it from their comparative study, but Bian et al. [47] recognized the good correlation performance of this model.

Another modification of Chrastil's model was proposed by Sparks et al. [42] (Eq. (22)), in which both the effect of the density in the average association number and the change in the enthalpy of vaporization with the temperature have been considered. In other words, they combined the Adachi and Lu [33] and the del Valle and Aguilera [34] modifications in one model, which improved significantly the results.

On the basis of a review of published experimental solubility data in $scCO_2$ and previously presented models, Garlapati and Madras [44] noted the existence of

(1) a nonlinear relationship between $\ln(y_2)$ and density (ρ_1) in isothermal conditions,
(2) a nonlinear relationship between $\ln(y_2)$ and temperature in isopycnic conditions, and
(3) a linear relationship between $\ln(y_2)$ and $\ln(\rho_1 T)$ in a certain range of density and temperature.

They proposed Eq. (24) in which the average association number is approximated by a linear relation of the solvent density, and they added a term that takes account of remark (3).

In addition to remarks (1) and (2) made by Garlapati and Madras [44], Bian et al. [47] added the following remark.

When the system temperature increases under isobaric conditions, the average association number will certainly decrease because of the increase in the thermal motion of its molecules; on the other hand, when the system pressure increases under isothermal conditions, it will increase as a result of shortening distances and increasing collisions between molecules. Once the average association number changes, the enthalpy of solvation and enthalpy of vaporization will change. Taking account of the latter remark, they proposed Eq. (26) where the average association number is inversely proportional to the logarithm of temperature and linearly proportional to the density of the solvent. They carried a comparison of the correlation

Table 1
Density-based models for the correlation of solid solutes in supercritical fluids.

Model	Equation		Reference
Stahl et al.	$\ln y_2 = a_0 + a_1 \ln \rho_1$	(11)	[31]
Chrastil	$\ln y_2 = a_0 + a_1 \ln \rho_1 + \frac{a_2}{T}$	(12)	[32]
Adachi and Lu	$\ln y_2 = a_0 + (a_1 + a_2\rho_1 + a_3\rho_1^2)\ln \rho_1 + \frac{a_4}{T}$	(13)	[33]
del Valle and Aguilira	$\ln y_2 = a_0 + a_1 \ln \rho_1 + \frac{a_2}{T} + \frac{a_3}{T^2}$	(14)	[34]
Kumar and Johnston	$\ln y_2 = a_0 + a_1\rho_1 + \frac{a_2}{T}$	(15)	[35]
Bartle et al.	$\ln \frac{y_2 P}{P^{\text{ref}}} = a_0 + a_1\left(\rho_1 - \rho_1^{ref}\right) + \frac{a_2}{T}$	(16)	[36]
Yu et al.	$y_2 = a_0 + a_1 P + a_2 P^2 + a_3 PT(1 - y_2) + a_4 T + a_5 T^2$	(17)	[37]
Gordillo et al.	$\ln y_2 = a_0 + a_1 P + a_2 P^2 + a_3 PT + a_4 T + a_5 T^2$	(18)	[38]
Méndez-Santiago and Teja	$T \ln y_2 P = a_0 + a_1\rho_1 + a_2 T$	(19)	[39]
Sung and Shim	$\ln y_2 = \left(a_0 + \frac{a_1}{T}\right)\ln \rho_1 + \frac{a_2}{T} + a_3$	(20)	[40]
Jouyban et al.	$\ln y_2 = a_0 + a_1 P + a_2 P^2 + a_3 PT + a_4 \frac{T}{P} + a_5 \ln \rho_1$	(21)	[41]
Sparks et al.	$c_2^* = \rho_{r,1}^{\left(a_0 + a_1\rho_{r,1} + a_2\rho_{r,1}^2\right)} \exp\left(a_3 + \frac{a_4}{T_r} + \frac{a_5}{T_r^2}\right)$ $c_2^* = \frac{c_2}{\rho_{c,1}};\ \ \rho_{r,1} = \frac{\rho_1}{\rho_{c,1}};\ \ T_r = \frac{T}{T_{c,1}}$	(22)	[42]
Garlapati and Madras (2009)	$\ln y_2 = a_0 \ln(\rho_1 T) + \frac{a_1}{T} + a_2$	(23)	[43]
Garlapati and Madras (2010)	$\ln y_2 = a_0 + (a_1 + a_2\rho_1)\ln \rho_1 + \frac{a_3}{T} + a_4 \ln(\rho_1 T)$	(24)	[44]
Jafari Nedjad et al.	$\ln y_2 = a_0 + a_1 P^2 + a_2 T^2 + a_3 \ln \rho_1$	(25)	[45]
Ch and Madras	$y_2 = \left(\frac{P}{P^{\text{ref}}}\right)^{(a_0 - 1)} \exp\left(\frac{a_1}{T} + a_2\rho_1 + a_3\right)$	(26)	[46]
Bian et al. (2011)	$c_2 = \rho_1^{(a_0 + a_1\rho_1 + a_2/\ln T)} \exp\left(\frac{a_3 + a_4\rho_1}{T} + a_5\right)$	(27)	[47]
	$c_2 = \frac{\rho_1 Mw_2 y_2}{Mw_1(1 - y_2)}$	(27a)	
Haghbakhsh et al.	$y_2 = 10^{-5}(a_0 + a_1 P + a_2\rho + a_3 P^2 + a_4\rho^2 + a_5 P\rho + a_6 P^3 + a_7\rho^3 + a_8 P\rho^2 + a_9 P^2\rho)$	(28)	[48]
Hezave and Lashkarbolooki	$\ln\left(\frac{P(y_2 - a_3 \times T)}{P^{\text{ref}}}\right) = a_0 + \frac{a_1}{T} + a_2\left(\rho - \rho_{\text{ref}}\right)$	(29)	[49]

(*continued on next page*)

Table 1 (*continued*)

Model	Equation		Reference
Keshmiri et al.	$\ln y_2 = a_0 + \frac{a_1}{T} + a_2 P^2 + \left(a_3 + \frac{a_4}{T}\right)\ln \rho_1$	(30)	[50]
Amooey	$\ln y_2 = \left(\frac{a_0 + a_1/\rho + a_2/\rho^2 + a_3 \ln T + a_4(\ln T)^2}{1 + a_5/\rho + a_6 \ln T + a_7(\ln T)^2 + a_8(\ln T)}\right)$	(31)	[51]
Hozhabr et al.	$\ln y_2 = a_0 + \frac{a_1}{T} + \frac{a_2\rho}{T} - a_3 \ln P$	(32)	[52]
Khansary et al.	$\ln y_2 = \frac{a_0}{T} + a_1 P + \frac{a_2 P^2}{T} + (a_3 + a_4 P)\ln \rho_1$	(33)	[53]
Bian et al. (2016)	$\ln y_2 = a_0 + \frac{a_1}{T} + \frac{a_2\rho_1}{T} + (a_3 + a_4\rho_1)\ln \rho_1$	(34)	[56]

performance of their proposed model with 11 previous models, 10 of which correspond to Eqs. (12)–(15),(18),(19),(21),(22),(24),(26), the 11th was a model proposed by Sparks et al. [42] in which the average association number was approximated by a linear relation to solvent density instead of a second-order polynomial as in Eq. (22). The models of Bian et al. [47], Sparks et al. [42], Jouyban et al. [41], and Adachi and Lu [33] were the best at correlating the experimental data of 54 different solid solutes.

On the basis of the same arguments raised by Jouyban et al., Keshmiri et al. [50] proposed, however, a five-parameter model (Eq. (30)), in which the effects of pressure and temperature are assessed differently. Khansary et al. [53] considered that the different empirical linear and nonlinear relationships put forward in previous works could be regarded as rules of thumb for new model developments. They proposed a five adjustable parameters model (Eq. (33)), in which the effects of pressure, temperature, and solvent density on solubility are explicitly expressed.

Recently, Bian et al. [55] proposed a new approach, based on combinations of individual forecasting models in economics, where the proposed model can be viewed as a weighted contribution of models. The models they have selected for combination are those judged from previous works to be the mostly more accurate empirical models (Ch and Madras [46], Garlapati and Madras [44], Adachi and Lu [33], Jouyban et al. [41], Sparks et al. [42], and Bian et al. [47]). They obtained the weights by using the solution of a linear mixed nonnegative programming problem. Bian et al. [55] tested different combinations of two, three, and four models. They found that the three-model combination (Sparks et al. [42], Jouyban et al. [41], and Bian et al. [47]) was the most accurate (average absolute relative deviation [AARD] = 4.37%). However, the difference in the capacity of correlating the 1116 experimental data points between the eight combinations of models tested in terms of AARD was not very significant (4.37% ≤ AARD ≤ 4.77%).

More recently, Bian et al. [56] proposed the five-parameter model (Eq. (34)) shown in Table 1, based on the following empirical observations depending on the system considered:

(1) a linear relationship between $\ln(y_2)$ and $\ln\rho_1$ in isothermal conditions,
(2) a linear relationship between $\ln(y_2)$ and ρ_1/T in isothermal conditions, and
(3) a linear relationship between $\ln(y_2)$ and $\rho_1\ln\rho_1$ in isothermal conditions.

Coelho et al. [58] presented a comparison between seven density-based models (four three-parameter models, one four-parameter model, and two five-parameter models) and the Soave-Kwong-Redlich (SRK) cubic EoS. The comparison concerned a very limited data set of four compounds of interest to the food industry. Although general conclusion cannot be drawn because of the limited data set, the results of Coelho et al. [58] show that the five-parameter models of Garlapati and Madras [44] and Khansary et al. [53] performed better than the other models considered. This study confirmed also the results of previous investigations [10–13,18] that the solubility correlation using the EoS approach is very sensitive to the accuracy of solute properties (critical properties and sublimation pressure) and leads to significantly higher deviations than the density-based models.

2.2. Improved density-based model

Reviewing the previously presented empirical models and the comparative studies [41,47,51,53–56] indicates the following:

1. In most studies, the AARD is used as a criterion of comparison of model performance to correlate the experimental data.
2. The three-parameter models such as [32,35,36,39,43] are the least accurate in correlating experimental data.
3. The models in which the solubility of the solid solute is expressed as a function of temperature, pressure, and the density of the SCF do not take into account the phase rule, because for an SCF only two of these three variables need to be fixed; thus, there is a sort of redundancy in these models.

Table 2
Sources and ranges of solubility data of solid drugs in supercritical carbon dioxide.

No.	Solid drug	Mw (g/mol)	T (K)	P (MPa)	$-\log10(y_2)$	Ni	Reference
1	4-Aminoantipyrine	203.2400	308.20–328.20	10.03–22.04	3.4353–4.9830	21	[60]
2	4-Aminosalicylic acid	153.1350	308.00–328.00	11.00–21.00	4.4449–5.4559	15	[61]
3	5-Fluorouracil	130.0770	308.15–328.15	12.50–25.00	4.8356–5.4202	18	[62]
4	Anastrozole	293.3700	308.00–348.00	12.20–35.50	3.4203–5.4437	45	[63]
5	Aspirin	180.1570	308.15–328.15	12.00–25.00	3.4597–4.2007	24	[64]
6	Atropine	289.3690	308.00–348.00	12.20–35.50	2.7773–4.2218	45	[65]
7	Atorvastatin	558.6400	308.00–348.00	12.16–35.46	2.8398–6.0000	45	[66]
8	Azadirachtin	720.7140	308.15–333.15	10.00–26.00	4.8268–5.9208	54	[67]
9	Azelaic acid	188.2210	313.15–333.15	10.00–30.00	4.9948–6.3768	14	[68]
10	Benzocaine	165.1891	308.00–348.00	12.20–35.50	1.9165–3.5686	40	[68]
11	Bisacodyl	361.4000	308.00–348.00	12.20–35.50	3.2343–5.0458	39	[70]
12	Budesonide	430.5340	338.00–358.00	21.30–38.50	4.5361–5.2269	21	[71]
13	Caffeine	194.1900	313.00–353.00	19.90–34.90	2.9469–3.5482	24	[72]
14	Capecitabine	359.3502	308.00–348.00	15.20–35.40	3.7991–5.5686	40	[73]
15	Carbamazepine	236.26860	308.00–348.00	12.20–35.50	4.0269–5.5229	39	[65]
16	Cefixime trihydrate	507.5000	308.00–328.00	18.30–33.50	6.5200–6.7959	18	[74]
17	Celecoxib	381.3700	323.20–343.20	15.00–30.00	3.8182–4.8182	18	[75]
18	Cetirizine	388.8880	308.15–338.15	16.00–40.00	2.3080–4.9788	28	[76]
19	Chlormezanone	273.7000	308.20–328.20	11.91–23.99	3.2636–5.3010	21	[77]
20	Chlorpheniramine maleate	390.8600	308.00–338.00	20.00–40.00	3.3706–4.8125	24	[78]
21	Cinnarizine	368.5000	308.15–328.15	13.97–24.00	3.6882–5.5376	21	[79]
22	Climbazole	292.7600	313.20–333.20	10.55–39.89	2.3116–3.2076	24	[80]
23	Clobetasol propionate	466.9700	308.00–348.00	12.20–35.50	5.4559–7.0000	44	[81]
24	Clofenamic acid	247.6800	313.00–333.00	12.00–36.00	4.4505–5.8125	24	[82]
25	Clotrimazole	344.8371	308.00–348.00	12.20–35.50	3.9722–6.6990	45	[83]
26	Clozapine	326.8231	318.00–348.00	12.16–35.46	4.3778–5.9208	27	[84]
27	Codeine	299.36420	308.00–348.00	12.20–35.50	2.9101–4.3979	45	[65]
28	Cortisone acetate	402.4800	308.15–373.15	8.24–22.65	5.3830–6.9586	30	[85]
29	Cyproheptadine	278.4000	308.00–338.00	16.00–40.00	2.5100–4.4750	28	[86]
30	Cyproterone acetate	416.9380	308.00–348.00	12.20–35.50	3.5834–4.8861	40	[87]
31	Dexamethasone	392.4610	308.15–328.15	10.00–35.07	5.5513–5.9245	30	[88,89]
32	Diazepam	284.7400	308.00–348.00	12.20–35.50	2.9547–3.7959	45	[65]
33	Diclofenac acid	331.3400	308.15–338.15	12.00–40.00	2.7033–4.6308	32	[90]
34	Diflunisal	250.1980	308.20–328.20	9.10–24.60	5.0930–6.2644	21	[91]
35	Docetaxel	807.8793	308.00–338.00	15.20–35.40	3.2984–4.4318	32	[73]
36	Dutasteride	528.5000	308.00–348.00	12.20–35.50	3.7940–7.0000	45	[92]
37	Exemestane	296.4000	308.00–348.00	12.20–35.50	2.7268–4.8996	45	[63]
38	Finasteride	372.5000	308.00–348.00	12.20–35.50	3.4782–4.4737	45	[92]
39	Fluoxetine hydrochloride	345.7900	308.15–338.15	16.00–40.00	3.0904–4.5768	28	[93]
40	Flurbiprofen	244.2609	303.15–323.15	8.90–24.50	3.7059–4.7768	27	[94]
41	Flutamide	276.1000	308.00–348.00	12.20–35.50	3.2930–5.3372	45	[92]
42	Fluvastatin	411.4700	308.00–348.00	12.16–35.46	3.2211–5.3010	45	[66]
43	Gabapentin	171.2400	308.00–338.00	16.00–40.00	2.1331–4.0472	28	[95]
44	Gemfibrozil	250.3400	308.20–328.20	10.01–22.02	2.3778–4.5317	21	[96]
45	Ibuprofen	206.2808	308.15–318.15	8.00–22.00	2.1675–4.5229	29	[97]
46	Imipramine HCl	316.8700	313.50–323.50	30.00–50.00	5.0044–5.2924	10	[98]
47	Isoniazid	137.1393	308.00–313.00	13.00–18.50	5.2182–6.2757	18	[99]
48	Ketoconazole	531.4310	308.00–348.00	12.20–35.50	3.7582–6.3010	45	[83]
49	Ketoprofen	254.2806	313.15–328.15	9.00–25.00	3.7258–5.4815	15	[100]
50	Lamotrigine	256.0910	318.00–338.00	12.16–35.46	5.3372–6.3979	27	[84]
51	Letrozole	285.3100	308.00–348.00	12.20–35.50	4.0809–6.0000	45	[63]
52	Levonorgestrel	384.5000	308.00–338.00	12.20–35.50	5.5376–6.3979	36	[101]
53	Lovastatin	404.5500	308.00–348.00	12.16–35.46	3.9431–4.9586	45	[66]
54	Mandelic acid	152.1500	308.15–328.15	10.10–23.06	2.5370–4.5686	21	[102]
55	Medroxyprogesterone acetate	386.2460	308.00–348.00	12.20–35.50	2.0458–4.7959	40	[87]
56	Mefenamic acid	241.2900	308.15–338.15	16.00–40.00	2.2262–4.0804	28	[103]
57	Megestrol acetate	312.5000	308.00–338.00	12.20–35.50	4.0600–5.5376	36	[101]
58	Meloxicam sodium salt	373.3800	303.00–323.00	14.90–25.50	4.8941–5.3556	15	[104]
59	Metaxalone	221.3000	308.20–328.20	11.95–24.00	3.8297–6.2366	21	[77]
60	Methimazole	114.1700	308.00–348.00	12.20–35.50	2.7215–4.2676	40	[105]
61	Methocarbamol	241.2000	308.20–328.20	11.99–22.05	3.3125–4.5528	21	[77]
62	Methylparaben	152.1473	308.00–348.00	12.20–35.50	2.9161–3.9666	40	[70]
63	Metronidazole benzoate	275.7600	308.00–348.00	12.20–35.50	2.3420–4.1549	40	[69]
64	Nabumetone	228.3000	308.20–328.20	10.00–22.00	2.5719–4.4056	21	[106]
65	Naproxen	230.2592	313.10–333.10	8.96–19.31	4.4976–5.7212	18	[107]
66	Nicotinic acid	123.1100	313.15–373.15	4.50–30.20	4.9825–6.5086	22	[108]
67	Nifedipine	346.3350	333.15–373.15	12.60–29.60	4.1495–5.8697	29	[109]
68	Niflumic acid	282.2200	313.20–353.20	19.00–31.00	4.6799–5.1487	21	[75]

(*continued on next page*)

Table 2 (*continued*)

No.	Solid drug	Mw (g/mol)	T (K)	P (MPa)	$-\log10(y_2)$	Ni	Reference
69	Nimodipine	418.4403	313.00–333.00	10.00–25.00	4.3737–6.2218	21	[110]
70	Nitrendipine	360.3600	308.00–328.00	8.00–20.00	4.1993–6.0000	15	[111]
71	Norfloxacin	319.3309	313.15–323.15	9.94–30.33	4.6126–5.9136	15	[112]
72	Ofloxacin	361.3675	318.15–323.15	10.11–30.08	5.8729–6.4089	10	[112]
73	*O*-Nitrobenzoic acid	167.1200	308.00–328.00	10.00–21.00	4.4484–5.8182	15	[113]
74	Oxymetholone	332.4770	308.00–328.00	12.10–30.50	3.8268–4.7959	20	[74]
75	Paclitaxel	853.9061	308.15–328.15	10.00–27.50	5.2076–5.9208	21	[62]
76	Penicillin G	334.3901	313.15–333.15	10.00–35.00	4.1986–5.3768	18	[44]
77	Penicillin V	350.3800	314.85–334.85	7.99–28.05	3.2396–4.2636	24	[114]
78	Pentoxifylline	278.3000	308.15–328.15	11.98–24.00	2.8633–4.5229	21	[79]
79	Phenazopyridine	213.2385	308.00–348.00	12.20–35.50	2.6944–4.3565	45	[106]
80	Phenylephrine hydrochloride	203.6660	308.15–338.15	16.00–40.00	2.5391–3.9957	28	[115]
81	Pindolol	248.3210	298.00–318.00	8.00–27.50	3.6498–4.5686	30	[116]
82	Piracetam	142.2000	308.15–328.15	12.00–24.00	4.4283–5.1249	21	[79]
83	Piroxicam	331.3460	308.15–338.15	16.00–40.00	3.2907–4.9318	28	[117]
84	Prednisolone	360.4400	308.15–373.15	8.24–22.65	6.1379–9.0000	28	[85]
85	Prednisone	358.4300	308.15–373.15	8.24–22.65	6.0491–9.0000	28	[85]
86	Propranolol	259.3435	308.00–348.00	12.20–35.50	1.6205–3.4461	45	[105]
87	Pyrocatechol	110.1107	333.15–348.15	10.00–35.00	2.4149–3.9136	22	[118]
88	Rosuvastatin	481.5381	308.00–348.00	12.16–35.46	3.6126–5.5229	45	[66]
89	Salicylamide	137.1361	308.20–328.20	10.00–22.00	3.6778–5.0731	21	[106]
90	Salicylic acid	138.1200	308.15–318.15	9.26–15.79	3.4001–4.0132	20	[119]
91	Simvastatin	418.5662	308.00–348.00	12.16–35.46	3.2716–5.6990	45	[66]
92	Spironolactone	416.5731	308.00–338.00	16.00–40.00	2.3002–4.2041	28	[120]
93	Sulindac	356.4100	308.15–338.15	16.00–40.00	2.0610–4.4377	28	[121]
94	Tetramethylpyrazine	136.2000	318.00–338.00	10.00–30.00	0.8827–2.0000	15	[122]
95	Theobromine	180.1700	313.00–353.00	19.30–34.50	4.3270–5.0555	23	[72]
96	Theophylline	180.1700	313.00–353.00	19.90–34.90	4.4789–4.9872	24	[72]
97	Thymidine	242.2286	308.15–328.15	10.00–30.00	5.0969–5.9208	25	[62]
98	Tolfenamic acid	461.7100	313.00–333.00	12.00–36.00	4.7418–5.7932	24	[82]
99	Triclocarban	315.5800	313.20–333.20	10.93–38.96	3.0605–4.0458	24	[80]
100	Zopiclone	388.8080	313.00–333.00	10.00–25.00	4.6596–5.8239	21	[110]

Considering this, and on the basis of the findings of Jouyban et al. [41], a modification that simplifies their model is proposed based on the following:

1. Previous empirical findings upon which density-based modeling is based.
2. There is a linear relationship between the pressure and density at fixed temperature and a certain range of pressure.
3. Because the volumetric properties (P, T, ρ_1) of $scCO_2$ are governed by the phase rule, only two variables need to be fixed.

Just as the density expansion of the virial EoS is more accurate than the pressure expansion at increased pressures [59], replacing the pressure by density in the Jouyban et al. [41] model would lead, a priori, to better correlation of the solubility.

The proposed model is therefore

$$\ln y_2 = a_0 + a_1\rho_1 + a_2\rho_1^2 + a_3\rho_1 T + a_4\frac{T}{\rho_1} + a_5 \ln \rho_1 \qquad (35)$$

The parameters a_0–a_5 are obtained from regression of the experimental data.

To compare the correlative performance of the proposed model with other models, a set of eight models that have been suggested recently [54–56] to have the best correlation performance, was selected. The solubility data of 100 drugs in $scCO_2$ were collected from the literature and were correlated with the eight models. Table 2 displays 100 binary solute $scCO_2$ systems as well as the experimental temperature and pressure ranges and data sources. It should be noted that all the collected data were assumed correct. The AARD was determined to provide a reliable accuracy criterion to compare the accuracy of the models, possessing different numbers of curve-fitting parameters. The AARD can be written as

$$AARD\ (\%) = \frac{100}{N}\sum_{i=1}^{N}\left|\frac{y_2^{exp} - y_2^{cal}}{y_2^{exp}}\right| \qquad (36)$$

3. Results and discussion

Data from experimental measurements of the solubility of solid solutes in SCFs are reported in the literature, more often by the intensive state variables: temperature, pressure, and solubility. The solubility is expressed either in units of mass of soluble solid solute in a volume of solution in equilibrium with the pure solid solute or in mole fraction of the solute in the supercritical phase. Note that the values of the solubility are very low when expressed in molar fractions. As mentioned previously, the last three decades have been marked by a significant number of studies on the measurement of the solubility of solid solutes in $scCO_2$, including numerous solid drugs.

Table 3
Estimated model parameters (a_i) of the model proposed in this work (Eq. (35)) for the 100 drugs considered.

No.	a_0	a_1	a_2	a_3	a_4	a_5
1	−333.91	−0.07251	1.55×10^{-5}	-6.12×10^{-6}	30.34111	54.33453
2	−300.287	−0.0931	2.22×10^{-5}	4.77×10^{-5}	26.78015	48.91598
3	−2856.04	−1.27481	0.00039	-1.01×10^{-5}	38.36335	538.8038
4	−262.11	−0.08145	1.61×10^{-5}	7.07×10^{-5}	23.3253	41.77072
5	43.83214	0.088543	-4.05×10^{-5}	4.19×10^{-5}	20.38589	−17.3615
6	131.4653	−0.01148	-2.05×10^{-7}	0.000118	−15.8007	−23.1136
7	−275.142	−0.08384	1.60×10^{-5}	8.94×10^{-5}	24.1454	43.38118
8	−222.326	−0.09077	2.42×10^{-5}	5.63×10^{-5}	15.92733	36.9064
9	305.1877	0.013857	-1.66×10^{-6}	0.00013	−37.0519	−51.8162
10	10.05584	−0.01959	6.60×10^{-7}	7.72×10^{-5}	−3.80024	−2.88614
11	77.77971	−0.00529	-9.19×10^{-7}	9.28×10^{-5}	−9.39991	−15.3031
12	1128.914	0.572145	−0.0002	6.81×10^{-5}	−8.13235	−222.418
13	−120.552	−0.0067	-2.79×10^{-6}	2.14×10^{-5}	18.02041	15.99816
14	13.75667	0.071958	-3.30×10^{-5}	6.06×10^{-5}	20.72101	−12.7081
15	135.0307	0.147712	-5.71×10^{-5}	3.51×10^{-5}	26.05973	−36.9962
16	21.93157	−0.01833	4.88×10^{-6}	4.85×10^{-5}	−6.07003	−5.32296
17	−341.078	−0.07899	1.66×10^{-5}	1.99×10^{-5}	31.63075	54.73179
18	−317.281	−0.02262	-6.88×10^{-6}	8.14×10^{-5}	49.47085	43.37128
19	−234.084	−0.00654	-1.22×10^{-5}	5.57×10^{-5}	35.55722	31.4782
20	106.8562	−0.16026	5.22×10^{-5}	0.000204	−57.2256	−7.74003
21	−265.596	0.217796	-9.68×10^{-5}	-4.10×10^{-6}	115.3331	14.7502
22	−154.13	0.029543	-1.69×10^{-5}	-1.48×10^{-5}	29.14851	19.06914
23	287.3706	0.068205	-2.19×10^{-5}	9.25×10^{-5}	−23.9234	−53.2504
24	−293.208	−0.06297	1.13×10^{-5}	2.61×10^{-5}	29.90687	45.82619
25	−217.757	−0.05831	1.05×10^{-5}	5.93×10^{-5}	18.50421	33.48974
26	647.7329	0.110936	-3.43×10^{-5}	0.000181	−62.8639	−111.833
27	118.6692	−0.01346	5.16×10^{-6}	9.36×10^{-5}	−15.2758	−20.5678
28	−108.467	−0.0684	2.98×10^{-5}	2.76×10^{-5}	3.429694	18.37946
29	211.8769	0.106825	-3.94×10^{-5}	0.000108	7.237829	−46.6076
30	238.1777	0.034356	-5.19×10^{-6}	7.32×10^{-5}	−23.4978	−42.0553
31	82.64781	−0.01054	5.20×10^{-6}	4.65×10^{-5}	−14.8406	−14.5072
32	81.45396	0.002502	-1.32×10^{-6}	6.43×10^{-5}	−7.30592	−15.5991
33	−118.329	−0.06704	1.33×10^{-5}	0.000103	6.799404	18.81183
34	117.9632	0.030546	-1.65×10^{-5}	8.32×10^{-5}	−9.32795	−24.2007
35	281.0399	0.116924	-4.38×10^{-5}	8.95×10^{-5}	−1.4997	−56.5648
36	−228.403	−0.04322	4.26×10^{-6}	5.48×10^{-5}	21.95793	33.90646
37	−192.596	−0.08718	1.74×10^{-5}	0.000118	15.73473	30.75498
38	302.8109	0.068543	-2.52×10^{-5}	0.000106	−22.7291	−55.2465
39	−537.598	−0.25983	7.68×10^{-5}	8.41×10^{-5}	9.812528	98.95053
40	−205.394	−0.04717	7.95×10^{-6}	5.91×10^{-5}	28.68469	30.29182
41	186.55	0.023145	-1.09×10^{-5}	0.000102	−20.3335	−33.7139
42	5.167317	−0.00819	-4.40×10^{-6}	9.47×10^{-5}	1.10902	−4.5213
43	−357.553	−0.00124	-1.54×10^{-5}	2.92×10^{-5}	58.05735	49.37206
44	−704.118	−0.23074	7.07×10^{-5}	-1.99×10^{-5}	47.82098	123.2081
45	−256.998	−0.06097	4.92×10^{-6}	6.99×10^{-5}	26.26448	40.30101
46	12,355	6.579034	−0.00187	−0.00068	591.9505	−2467.39
47	−6515.35	−1.28613	0.000329	−0.00068	744.2133	1077.031
48	−167.186	−0.0399	2.64×10^{-7}	0.000101	20.65338	22.94356
49	141.5879	0.083332	-4.05×10^{-5}	7.95×10^{-5}	−3.70116	−31.4735
50	−22.4241	−0.0045	-3.33×10^{-6}	4.30×10^{-5}	1.158043	0.538126
51	35.10967	0.02185	-1.96×10^{-5}	0.0001	2.786269	−11.7478
52	−230.88	−0.06539	1.85×10^{-5}	2.18×10^{-5}	21.602	36.4095
53	−102.45	−0.02195	1.07×10^{-6}	2.79×10^{-5}	9.014762	14.73499
54	−295.747	−0.10019	2.36×10^{-5}	9.01×10^{-5}	28.37983	47.8683
55	−95.8311	−0.03673	1.30×10^{-5}	3.32×10^{-5}	8.151631	14.35616
56	−214.513	−0.06436	1.40×10^{-5}	8.02×10^{-5}	20.48066	32.96468
57	169.579	−0.0092	3.88×10^{-6}	0.000108	−24.798	−28.871
58	−1624.16	−0.90527	0.000281	0.000119	−44.0891	320.7279
59	−35.0598	0.113437	-5.70×10^{-5}	8.54×10^{-5}	40.24724	−10.0175
60	226.5972	0.017148	-4.48×10^{-6}	0.000104	−24.9282	−39.1657
61	−400.299	−0.06815	7.74×10^{-6}	4.59×10^{-5}	51.33682	61.25143
62	−84.0022	−0.0372	7.92×10^{-6}	5.46×10^{-5}	7.562351	12.46796
63	−257.96	−0.06176	1.43×10^{-5}	2.36×10^{-5}	25.55464	41.10095
64	−105.454	−0.06154	1.42×10^{-5}	6.90×10^{-5}	1.362211	18.14281
65	−240.522	−0.07268	1.91×10^{-5}	3.42×10^{-5}	21.20399	38.7047
66	−33.1442	−0.03461	1.01×10^{-5}	5.73×10^{-5}	0.655012	3.899973
67	29.08865	−0.02598	6.47×10^{-6}	8.73×10^{-5}	−5.54546	−6.5935
68	13.75492	−0.02952	8.16×10^{-6}	5.63×10^{-5}	−10.3614	−2.57467

(*continued on next page*)

Table 3 (*continued*)

No.	a_0	a_1	a_2	a_3	a_4	a_5
69	−57.4741	−0.05532	1.21×10^{-5}	9.20×10^{-5}	−1.50031	8.993218
70	−119.148	−0.07376	2.00×10^{-5}	8.41×10^{-5}	5.661167	19.71953
71	1912.328	0.39439	−0.00015	0.000556	−183.351	−330.995
72	−1359.79	−0.43159	0.000132	-2.54×10^{-5}	122.7584	233.9027
73	−388.333	−0.12816	3.04×10^{-5}	6.89×10^{-5}	34.44473	64.19007
74	41.8925	−0.0033	-3.70×10^{-6}	6.54×10^{-5}	−8.25917	−8.88317
75	−1006.32	−0.11918	3.93×10^{-5}	−0.00017	168.8394	155.5943
76	224.6789	0.025636	-1.15×10^{-5}	0.000127	−21.0055	−40.8712
77	−101.416	−0.06353	2.10×10^{-5}	4.66×10^{-5}	4.667168	17.49912
78	−352.552	−0.05179	3.30×10^{-6}	3.26×10^{-5}	41.94947	53.78755
79	−33.1213	−0.01884	1.94×10^{-6}	6.68×10^{-5}	3.847684	3.057963
80	−355.568	−0.17741	4.98×10^{-5}	8.99×10^{-5}	8.975403	64.4528
81	68.74698	0.004456	2.15×10^{-6}	4.08×10^{-5}	−7.00159	−13.5184
82	−343.133	−0.0182	-4.59×10^{-6}	-2.39×10^{-5}	50.39958	50.2686
83	567.2505	0.09314	-2.65×10^{-5}	0.000178	−54.843	−98.5152
84	−193.026	−0.12081	5.31×10^{-5}	4.68×10^{-5}	7.52461	33.68521
85	−152.842	−0.12285	4.76×10^{-5}	0.000122	5.696566	25.7895
86	50.99776	−0.03535	8.35×10^{-6}	0.000119	−7.18326	−9.33889
87	−91.473	−0.02081	3.87×10^{-6}	1.62×10^{-5}	7.186239	13.81712
88	−138.121	−0.02273	-9.61×10^{-7}	4.67×10^{-5}	14.9385	19.30491
89	−146.614	−0.06657	1.62×10^{-5}	5.46×10^{-5}	7.149813	24.518
90	−276.323	−0.05122	8.56×10^{-6}	1.63×10^{-5}	34.43189	42.82894
91	−93.9377	−0.00999	-4.93×10^{-6}	5.92×10^{-5}	11.33474	11.3662
92	522.961	0.077963	-3.12×10^{-5}	0.000217	−41.6145	−91.6123
93	−239.605	−0.02929	-9.98×10^{-6}	0.000132	44.77625	31.26755
94	−266.645	−0.12543	3.07×10^{-5}	9.66×10^{-5}	20.74828	46.44233
95	−54.2958	−0.15951	5.90×10^{-5}	9.94×10^{-5}	−27.1185	17.68296
96	−4.17623	−0.05683	1.86×10^{-5}	5.79×10^{-5}	−13.2033	2.525788
97	−1037.74	−0.43452	0.000143	-2.61×10^{-5}	44.22912	189.9748
98	−99.9916	−0.03954	4.07×10^{-6}	7.86×10^{-5}	9.564865	13.88758
99	−177.147	0.009528	-9.73×10^{-6}	2.50×10^{-6}	31.66024	23.13632
100	−314.429	−0.12333	3.85×10^{-5}	3.21×10^{-5}	21.63374	53.90277

The details of the experimental data used in this work and their references are listed in Table 2. Considering the experimental data collected, it is worth mentioning that there may be some differences between experimental data for a given solute from different sources. With regard to the density of CO_2, we have used the data provided in the experimental solubility data source. Otherwise, the densities of CO_2 for different sets of temperature and pressure were calculated using the carbon dioxide property data available through the National Institute of Standards and Technology web database [123].

Adjustments of the parameters of the selected literature models (Eqs. 13,21,22,24,27,30,33,34) together with the proposed model (Eq. 35) were carried out using genetic algorithms (*ga* MATLAB function) to obtain initial estimates of the parameters. To avoid convergence to local minima, optimization using genetic algorithm is run 20 times. The set of model parameters with best fit is saved and then used as an initial approximation in the least square fitting (*lsqcurvefit* MATLAB function) with the use of the Levenberg–Marquardt algorithm as a computation option. In both cases, Eq. (36) was used as the objective function to be minimized. The results of parameter estimations for the proposed model are shown in Table 3. Parameters of the other models can be accessed in the supplementary material.

The AARDs (%) of each model equation with each drug compound are shown in Table 4, in which the best AARD for the correlation of the solubility data of each binary system is shown in bold.

Table 4 shows that the AARD ranges between 0.61% and 55.77%, but when considering the best AARDs only (bold) they range between 0.61% and 15.38% with an average of 4.83%. The minimum AARD (0.61%) and the maximum AARD (15.38%) are both obtained by the Bian et al. [47] model (Eq. (27)) for the systems 6 ($scCO_2$–atropine) and 16 ($scCO_2$–cefixime trihydrate), respectively. This demonstrates that for the 100 systems considered, empirical modeling as a whole correlates with the experimental data quite satisfactorily. However, the global comparison between the performances of different models indicates that the model proposed in this work gives the best correlating performance, where the AARD ranges between 0.86% and 23.64% with an average of 8.13%. The second best correlating performance is given by the Bian et al. [47] model, where the AARD ranges between 0.61% and 25.57% with an average of 8.40%. The third best correlating performance is given by the Sparks et al. [42] model (Eq. (22)), where the AARD ranges between 0.70% and 29.66% with an average of 8.96%. As shown in Fig. 1, these three models together with the recent model of Bian et al. [56] represent the best correlation of 82% of the 100 systems considered. Beside this, the proposed model for calculating the solubility is simpler as it requires only the temperature and CO_2 density. Furthermore, Table 4 confirms the results of previous comparative studies [41,47,51,53–56], insofar as there is not

Table 4
Average absolute relative deviation (AARD, %) for 100 drugs calculated for each of the 09 studied correlations.

No.	Equation								
	(13)	(21)	(22)	(24)	(27)	(30)	(33)	(34)	(35)
1	**6.33**	7.13	6.38	7.44	7.62	7.59	8.84	7.82	6.73
2	2.42	4.15	5.27	**1.66**	1.73	2.26	3.53	7.83	1.92
3	8.22	6.74	16.95	6.04	**5.76**	7.69	8.17	15.18	6.72
4	7.22	10.15	**3.98**	7.38	7.41	9.26	10.06	5.51	6.97
5	3.00	5.65	**2.68**	4.71	4.45	5.39	5.44	3.43	3.31
6	17.66	19.45	21.54	16.98	**15.38**	16.68	16.80	20.22	16.24
7	4.04	11.94	11.17	5.90	5.44	9.09	10.64	11.16	**3.84**
8	2.67	5.25	9.99	3.36	3.43	**2.60**	3.70	11.02	3.05
9	21.51	17.69	**5.68**	21.86	19.82	16.81	15.80	8.57	17.04
10	11.99	8.33	12.22	11.13	**6.26**	11.05	12.55	15.78	9.67
11	10.85	7.17	**0.70**	12.24	6.10	12.96	15.06	1.95	9.16
12	10.11	8.55	**2.71**	12.07	11.86	8.69	10.04	4.54	9.83
13	3.43	2.88	24.02	2.95	**2.86**	3.20	5.42	18.75	2.90
14	**5.87**	11.71	12.72	9.09	8.56	11.07	11.44	12.43	6.95
15	13.08	15.04	7.40	15.83	15.43	17.63	18.02	**4.58**	11.85
16	2.33	3.01	5.40	0.70	**0.61**	2.11	1.81	4.24	2.22
17	2.25	2.87	13.02	1.80	1.44	1.75	2.93	11.20	**1.42**
18	5.36	8.12	5.91	4.88	4.62	5.84	11.18	7.63	**4.11**
19	**4.12**	4.76	9.15	5.14	4.79	5.61	7.34	10.45	4.13
20	8.83	12.85	**5.16**	6.62	6.08	6.91	6.51	5.40	7.35
21	5.35	4.80	8.13	5.89	5.97	5.63	8.35	6.28	**4.12**
22	4.14	3.72	11.57	3.83	3.37	2.83	5.51	10.86	**2.39**
23	14.38	12.02	**8.53**	15.82	9.59	14.80	16.71	11.86	10.95
24	4.99	6.76	12.95	5.32	5.18	4.97	5.99	12.94	**4.80**
25	**2.83**	8.63	6.91	4.76	4.58	7.03	8.34	5.53	3.71
26	24.09	17.77	**7.61**	24.82	17.13	22.72	25.86	12.68	15.02
27	12.67	10.69	**8.35**	12.26	10.72	14.28	13.31	8.38	12.68
28	14.46	23.84	**3.42**	17.32	12.71	21.66	37.53	10.79	15.40
29	7.24	6.93	**4.02**	8.46	7.60	8.90	9.93	4.95	7.10
30	11.04	10.25	3.74	10.69	7.67	10.32	9.70	**3.62**	5.55
31	7.72	4.39	**4.20**	8.29	7.50	6.48	5.89	5.78	7.42
32	7.47	5.00	14.28	7.54	**3.42**	7.93	8.11	12.24	3.53
33	6.60	13.19	5.10	5.31	**4.22**	5.81	5.84	5.84	5.01
34	12.47	10.05	**9.30**	13.29	10.60	15.54	14.52	14.85	11.05
35	6.14	6.34	**2.94**	8.34	6.40	8.33	9.09	3.82	5.83
36	3.98	10.80	3.81	7.23	6.72	10.01	10.26	**3.74**	5.05
37	18.16	26.38	21.16	10.85	**10.16**	19.91	17.71	19.37	20.60
38	16.43	15.28	**7.38**	18.85	12.01	19.00	21.22	7.68	11.57
39	9.67	13.63	29.66	10.24	10.13	10.45	**9.48**	13.59	9.82
40	**5.15**	5.85	8.83	5.39	5.36	6.19	5.97	9.00	5.23
41	19.77	13.39	**2.85**	19.65	13.11	15.90	18.84	3.77	15.63
42	8.28	6.87	3.83	10.09	4.40	11.42	12.19	**3.00**	3.71
43	10.31	11.77	16.65	10.82	10.49	10.19	12.58	10.85	**9.61**
44	10.67	15.42	**7.42**	11.79	11.11	13.98	16.48	7.55	11.35
45	8.40	11.35	15.82	11.90	11.69	10.63	9.73	13.22	**6.22**
46	12.95	7.20	**6.45**	13.00	11.36	7.37	7.64	7.44	7.67
47	8.33	6.51	**3.18**	6.89	5.21	5.70	6.73	7.00	5.37
48	9.32	18.40	**2.69**	11.91	11.53	18.89	14.67	3.57	12.20
49	8.49	6.20	**3.61**	10.84	8.38	9.31	9.86	**3.61**	6.18
50	**2.97**	7.32	6.38	11.68	6.60	24.60	23.47	9.59	4.31
51	14.86	18.75	**7.42**	19.87	18.27	19.84	19.50	9.22	13.96
52	9.64	11.02	**2.30**	9.99	10.08	9.51	10.52	3.37	9.54
53	**4.08**	7.90	13.88	4.95	4.82	4.88	4.25	23.63	4.29
54	3.90	4.49	5.95	3.58	**3.36**	7.57	7.75	5.48	3.56
55	24.13	26.21	**4.75**	25.69	22.49	27.77	26.21	6.04	23.64
56	3.61	5.96	5.70	3.82	3.49	3.89	6.98	6.05	**3.42**
57	22.38	23.88	**3.05**	20.04	20.80	19.99	18.96	3.97	21.10
58	4.29	4.95	7.73	5.71	5.73	4.89	5.74	7.53	**3.20**
59	22.96	11.68	**4.10**	23.93	25.57	22.18	19.93	4.97	22.89
60	14.05	**9.08**	23.69	14.12	10.10	12.43	13.49	22.59	9.46
61	4.01	5.96	4.02	4.36	4.12	4.28	5.13	4.21	**3.82**
62	5.85	5.02	10.21	5.15	**3.72**	7.24	7.47	10.45	5.21
63	15.55	14.43	**7.19**	9.96	9.62	14.80	19.48	7.51	12.86
64	2.89	9.02	4.17	3.72	3.47	5.59	5.68	5.43	**1.75**
65	3.83	4.94	**1.56**	4.08	3.67	3.84	4.34	2.29	3.77
66	21.41	16.02	14.61	21.28	14.11	18.83	26.28	**12.48**	17.68
67	16.11	**10.00**	19.77	16.36	11.15	13.15	17.14	17.54	12.16

(*continued on next page*)

Table 4 (*continued*)

No.	Equation								
	(13)	(21)	(22)	(24)	(27)	(30)	(33)	(34)	(35)
68	1.91	3.21	4.08	1.17	1.04	0.93	1.87	6.94	**0.86**
69	7.38	8.45	16.35	8.08	6.48	6.65	10.14	13.14	**4.80**
70	7.79	9.11	7.67	9.38	8.44	**7.55**	9.68	8.70	8.25
71	29.32	13.42	1.18	31.33	12.87	19.66	27.33	**1.05**	14.93
72	8.85	10.50	1.80	9.17	8.43	7.80	8.42	**1.74**	6.64
73	3.66	6.06	19.62	**3.07**	3.52	4.10	5.23	21.31	3.12
74	3.83	3.87	10.03	3.74	**2.54**	2.92	3.79	9.65	2.83
75	16.86	16.77	6.71	16.52	7.92	12.49	16.95	**6.54**	8.92
76	23.00	11.04	**3.41**	22.63	16.49	24.05	19.19	4.11	15.57
77	3.76	5.42	**2.63**	9.07	9.13	7.10	8.30	4.65	4.97
78	5.69	6.54	8.39	5.99	6.04	5.75	6.61	8.41	**5.61**
79	7.43	7.20	14.30	8.31	**6.59**	11.08	10.89	13.60	6.67
80	10.81	13.14	22.30	11.35	11.20	11.25	11.57	16.32	**10.41**
81	8.64	14.08	10.75	8.21	9.19	16.36	13.76	11.67	**7.67**
82	4.27	3.37	2.92	3.23	3.24	3.66	5.28	3.24	**2.75**
83	16.03	15.17	5.32	14.04	13.60	14.42	14.40	**5.26**	13.86
84	19.60	38.04	**3.75**	29.75	25.26	29.66	55.77	4.61	19.03
85	27.04	36.81	**6.25**	33.86	24.71	22.91	48.31	7.65	21.04
86	15.83	**7.47**	15.23	15.74	10.73	14.05	15.17	18.33	11.29
87	6.58	10.34	10.75	8.34	7.14	9.94	8.52	17.05	**6.57**
88	**3.71**	7.69	8.38	7.20	6.92	8.84	9.83	8.85	3.82
89	2.75	7.69	9.80	3.55	3.43	5.01	4.31	12.29	**1.78**
90	3.61	3.70	25.74	3.64	**3.41**	3.83	3.87	24.97	3.63
91	6.57	9.38	10.24	9.73	8.98	11.29	12.95	8.62	**5.92**
92	12.01	20.04	16.36	9.84	**7.61**	11.41	13.75	14.49	9.69
93	8.44	12.69	**3.69**	8.84	6.74	9.46	10.97	9.11	6.70
94	2.90	10.54	17.97	**2.74**	2.83	2.99	2.90	30.38	3.63
95	4.48	4.41	12.14	4.43	4.43	3.83	3.28	21.31	**3.17**
96	5.34	**4.19**	26.64	5.33	4.24	4.82	5.09	35.29	4.61
97	23.02	22.89	**3.31**	14.59	14.50	22.41	22.11	3.37	22.88
98	4.53	7.91	5.82	4.71	3.70	4.31	4.81	5.34	**3.60**
99	5.83	**3.56**	5.01	5.88	4.71	5.17	6.05	5.04	5.15
100	5.96	5.32	4.48	6.56	5.28	5.45	7.26	**3.70**	5.77
Minimum AARD	1.91	2.87	0.70	0.70	**0.61**	0.93	1.81	1.05	0.86
Maximum AARD	29.32	38.04	29.66	33.86	25.57	29.66	55.77	35.29	**23.64**
Average	9.57	10.44	8.96	10.17	8.40	10.47	11.94	9.61	**8.13**

a model that can best correlate all of the systems of the experimental data set.

Validation and performance of the models selected in this study are shown as scatter plots for the 2891 experimental points of the database. Fig. 2 shows the scatter plot of the proposed model. These plots are generated using the

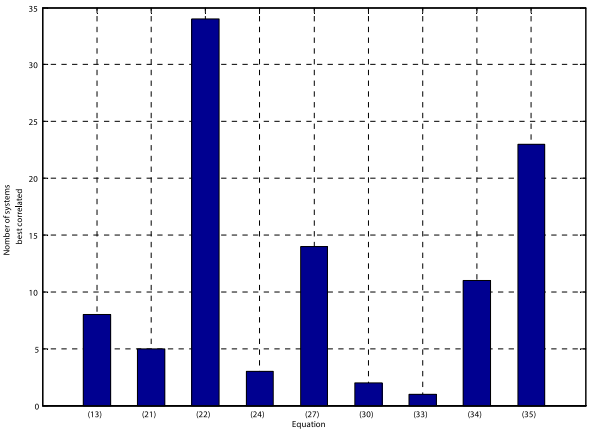

Fig. 1. The number of systems best correlated by each model equation.

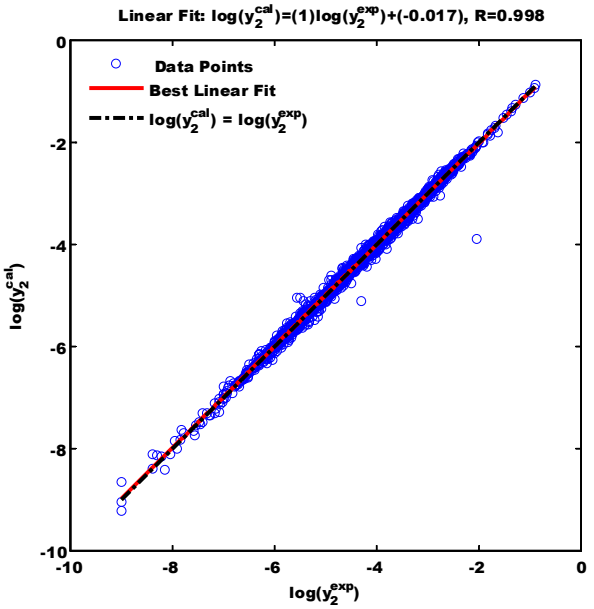

Fig. 2. Scatter plot of the entire data set of the drug solubility calculated using the model proposed in this work (Eq. (35)) versus experimental solubility.

Table 5
Validation agreement vector (α [slope], β [y intercept], and R [correlation coefficient]) calculated for the nine studied models.

Validation agreement vector	Equation								
	(13)	(21)	(22)	(24)	(27)	(30)	(33)	(34)	(35)
α	0.9949	0.9947	0.9953	0.9946	0.9960	0.9947	0.9936	0.9951	0.9960
β	−0.0219	−0.0226	−0.0199	−0.0232	−0.0172	−0.0228	−0.0274	−0.0209	−0.0171
R	0.9974	0.9974	0.9977	0.9973	0.9980	0.9973	0.9966	0.9976	0.9980

postreg function of MATLAB, in which the calculated solubility in logarithmic scale is plotted against experimental solubility. The scatter plot shows the dispersion of the cloud of points of the whole data set around the first bisector ($\log(y^{cal}) = \log(y^{exp})$), the degree of dispersion can be evaluated from the equation for the best linear fit ($\log(y^{cal}) = \alpha$. $\mathrm{Log}(y^{exp}) + \beta$), where α is the slope and β is the intercept, which together with the correlation coefficient R are used as a validation agreement vector. The ideal performance is achieved when [$\alpha = 1$, $\beta = 0$, and $R = 1$]. The values of α, β, and R for the seven selected models and the proposed model are summarized in Table 5. According to the α value close to 1, the β value close to 0, and R close to 1, clearly the proposed model has the best validation agreement vector and as such the best overall correlation performance.

4. Conclusions

The novel density-based model proposed in this work has been derived by simple modification of the six-parameter Jouyban's model to correlate the solubility of solid drugs in $scCO_2$. The modification considers the phase rule insofar as the solubility of the solid solute in the supercritical phase is expressed only as a function of the solvent density and the equilibrium temperature, in contrast to Jouyban's model that gives the solubility as a function of the solvent density and the equilibrium temperature and pressure. The performance of the model has been tested on a database of 100 drugs that account for 2891 experimental data points collected from the literature. The correlative performance of the proposed model has been compared with that of seven previous models that have been selected on the basis of being suggested in previous works to possess the best correlating performance. This study demonstrates that for the data set considered, empirical modeling as a whole correlates with the experimental data quite satisfactorily with an AARD range of 0.61%–15.38% and an overall average of 4.83%. The global comparison between the performances of different models indicates that the model proposed in this work gives the best correlating performance, where the AARD ranges between 0.86% and 23.64% with an average of 8.13%.

Acknowledgments

The authors gratefully acknowledge the Algerian Ministry of Higher Education and Scientific Research (CNEPRU Projects: No. J0102620110007 and No. J0102620140015) and the University Yahia Fares of Medea.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.crci.2016.09.009.

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