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A comprehensive comparison among four different approaches for predicting the solubility of pharmaceutical solid compounds in supercritical carbon dioxide

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Abstract−Supercritical technologies have been developed in the food, environmental, biochemical and pharmaceutical product processing during the recent decades. Obtaining accurate experimental solubilities of pharmaceutical compounds in supercritical carbon dioxide (SC-CO_2) and their correlations are highly important and essential for the design of industrial operating units. In this study, the solubilities of six pharmaceutical compounds (Anti-HIV, Anti-inflammatory and Anti-cancer) in SC-CO_2 were correlated using four different models: cubic equation of state (EoS) model (SRK and modified-Pazuki EoSs), empirical and semi-empirical models (Chrastil, Mendez-Santiago-Teja, Spark et al. and Bian et al. models), regular solution model coupled with the Flory-Huggins equation, and an artificial neural network-based (ANN-based) model. In EoS calculations, twin-parametric van der Waals (vdW2) and Panagiotopoulos-Reid (mrPR) mixing rules were used for estimating the supercritical solution properties, with three different sets employed for obtaining critical and physicochemical properties of the solid compounds. To evaluate the capabilities of various approaches, a comprehensive comparison was carried out among the four models based on several statistical criteria, including AARD, R_{adj} and *F*-value. Results of the analysis of variance (ANOVA) indicated that the ANN-based model provided the best results in terms of correlating the experimental solubility of the pharmaceutical compounds in SC-CO_2.

Keywords: Supercritical Carbon Dioxide (SC-CO_2), Pharmaceutical Compounds Solubility, Cubic Equations-of-state (EoS), Empirical and Semi-empirical Models, Artificial Neural Network (ANN)

INTRODUCTION

The medical and pharmaceutical industries are focused on advanced technologies to achieve ultra-purity products. For this purpose, supercritical fluid technology (SFT) provides a new and interesting approach in chemical, biochemical, pharmaceutical and food processing industries [1-7]. Supercritical fluids (SCFs) exhibit interesting characteristics such as diffusivities between those of gases and liquids, compressibilities comparable to gases, densities comparable to liquids, low surface tension, and high selectivity. These characteristics make the species suitable solvents for industrial applications, especially in the extraction and purification of pharmaceuticals, food supplements and natural products, particle formation/micronization/drug delivery systems, polymerization, and energy production-related processes [8-17].

Reportedly, thanks to its convenient critical temperature and pressure, low cost, chemical stability, non-flammability and nontoxicity, supercritical carbon dioxide (SC-CO_2) is the best solvent for such purpose [18-20].

The equilibrium solubility of a compound in SCFs at operational temperature and pressure is a fundamental requirement for any SCF-based process design. However, accurate data on solubility in SCFs is yet to become available for most pharmaceutical products, due to complexity, time-intensiveness, and cost-intensiveness of the required experimental apparatus and test methods [21]. As a workaround, mathematical modeling can be used to come with estimates of the solubility of solid compounds in SCFs. Being required for proper process design, solubility data of complex pharmaceutical compounds and their correlations have received much attention in recent years [22].

There are different approaches for calculating the solubility data, e.g., equations of state (EoS), empirical and semi-empirical models based on density, pressure and temperature, solution models and artificial neural networks (ANN) [23]. Several EoSs (cubic and non-cubic) can be used in the solubility calculations. Cubic EoSs from the van der Waals family (e.g., Peng-Robinson (PR) [24], Soave-Redlich-Kwong (SRK) [25], Patel-Teja-Valderrama (PTV) [26], and Pazuki [27]) with several mixing rules (e.g., classical van der Waals (vdW), Panagiotopoulos-Reid (mrPR) and Wong-Sandler (WS) mixing rules) have been the most commonly used approaches for correlating the solubility of solid compounds [21]. Given the pool of various EoSs and mixing rules in the literature, researchers should select the most appropriate set of EoS and mixing rule for any particular system according to the system specifications and their pre-

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Table 1. The details of solubility of pharmaceutical solutes in SC-CO_2

Component	Formula	M_w/g/mol	T range/K	P range/bar	Data points	T_m/K	Data references
2-Phenyl-4*H*-1,3-benzoxazin-4-one	$C_{14}H_9NO_2$	223.233	308-328	100-275	23	397	[58]
Azodicarbonamide	$C_2H_4N_4O_2$	116.08	308-328	100-300	26	497	[58]
Propyphenazone	$C_{14}H_{18}N_2O$	230.31	308-328	90-190	18	376	[59]
Sulindac	$C_{20}H_{17}FO_3S$	356.41	308-338	160-400	28	456	[60]
Thymidine	$C_{10}H_{14}N_2O_5$	242.23	308-328	100-275	20	460	[58]
Capecitabine	$C_{15}H_{22}FN_3O_6$	359.35	308-348	152-354	40	362	[61]

vious experiences [21]. The EoS-based models not only suffer from complex computations, but also require such data as critical and physicochemical properties of solutes (acentric factor, sublimation pressure, molar volumes and vapor pressure of the solids), which are unavailable in many cases, especially for pharmaceutical compounds and biomolecules. On the other hand, these properties can be estimated by several group-contribution methods which results are known to be erroneous [21]. Empirical and semi-empirical models not only have provided good accuracy, but also are simpler than the EoS-based models, making those popularly used in literature. Empirical and semi-empirical models work based on a number of independent variables (e.g., SCF density, pressure, and temperature) and several constants obtained by correlating the experimental solubility data for each pure compound [28-35]. Solution models are feasible methods for correlating the solubilities of complex pharmaceutical compounds in SC-CO_2. In this method, SC-CO_2 is considered as a liquid solvent with the so-called infinite dilution activity coefficient applied for considering the non-ideal behavior of solid-liquid equilibrium [36,37]. Previous studies have indicated that a regular solution model coupled with a Flory-Huggins term can correlate solubilities of biological and pharmaceutical compounds at satisfactory accuracy [22,36].

As an effective technique for comparing and modeling complex nonlinear problems, artificial neural networks (ANN) can be used to estimate solutions for such problems. Combining feed-forward output computation with back-propagation learning abilities, these networks mimic the human neurological system. ANNs can learn well from experimental data and create input-output relationships for nonlinear processes. Being a nonlinear parameter, solubility can be modeled adequately using the ANN method. Accordingly, many researchers have studied the application of ANN for modeling the solubility of different compounds in SC-CO_2 [38-42].

Sodeifian et al. [43] investigated three of the main approaches--semi-empirical density-based models, equations of state (EoSs), and regular solution models, for correlating the Amiodarone hydrochloride solubility in SC-CO_2. Also, Sodeifian et al. [44] applied quadrupolar cubic plus association theory (qCPA EoS) and the perturbed-chain polar statistical associating fluid theory (PCP-SAFT EoS) to correlate the solubility of solid drug compounds in SC-CO_2. Ardjmand et al. [45] compared seven semi-empirical models and seven cubic EoSs for the correlation of ibuprofen solubility in SC-CO_2. Coimbra et al. [21] investigated the accuracy of different EoSs with different mixing rules for correlating the solubility of several anti-inflammatory drugs in SC-CO_2. They further examined the importance of solid properties estimation methods. Mehdizadeh and Movagharnejad [40] compared the accuracies of seven semi-empirical ANN-based models for the estimation of solubility in SC-CO_2. Gharagheizi et al. [39] studied a feed-forward ANN-based method to predict the solubility of solid compounds in SC-CO_2. Su and Chen [36] used the regular solution model with Flory-Huggins equation to correlate the solubility of solid pharmaceutical compounds in SC-CO_2. Accuracy of the solution model was then compared with commonly utilized semi-empirical models.

We performed a comprehensive comparison among four approaches, namely EoS, empirical and semi-empirical, solution models and ANN method, for correlating solubilities of different pharmaceutical compounds (Thymidine and Capecitabine as anti-cancer drugs, 2-phenyl-4*H*-1,3-benzoxazin-4-one and Azodicarbonamide as anti-HIV drugs, and Propyphenazone and Sulindac as anti-inflammatory drugs) in SC-CO_2 (Table 1). To the best of authors' knowledge, the present research provides the first report on modeling the solubility data for Thymidine, 2-phenyl-4*H*-1,3-benzoxazin-4-one and Azodicarbonamide. On the other hand, only empirical models have been exploited to correlate solubilities of the other three compounds. Given the importance of finding the best approach to solubility correlation for different compounds, a comprehensive comparison is herein presented to address the issue. Such a comparison among four different models has been rarely reported in previous studies. In this research, two EoSs (Soave-Redlich-Kwong (SRK) and modified-Pazuki equations) with twin-parametric van der Waals and mrPR mixing rules, four semi-empirical models (Chrastil, Mendez-Santiago-Teja (MST), Spark et al. and Bian et al. models), and regular solution model coupled with a Flory-Huggins term were used to undertake the solubility calculations. Moreover, a multilayer feed-forward neural network with a tangent sigmoid transfer function (Tansig) at hidden layers and a linear transfer function (pure line) at the output layer was used. The back-propagation methodology was used to have the network trained based on experimental data which were further utilized to train, test and validate the model.

Outcomes of correlating the EoSs were compared and discussed on the basis of the applied EoSs and mixing rules. Significance of the results obtained from the estimation methods (group-contribution method) based on critical and physical properties of the drugs was further discussed.

Accuracy of each model was investigated by evaluating the deviation of the calculated results from the corresponding experimental solubility data in terms of such statistical criteria as average absolute relative deviation (AARD, %), adjusted correlation coefficient (R_{adj}), and *F*-value. Finally, the results were devised to determine

Table 2. Summary of the cubic EoSs used in this work

Name	Equation of state	a	b
Soave-Redlich-Kwong (SRK)	$P=\frac{RT}{\upsilon-b}-\frac{a(T)}{\upsilon(\upsilon+b)}$	$0.42747\frac{R^2T_c^2}{P_c}\times\alpha(T_r,\omega)$ $\alpha(T_r,\omega)=[1+m(1-\sqrt{T_r})]^2$ $m=0.480+1.574\omega-0.176\omega^2$	$0.08664\frac{RT_c}{P_c}$
Modified-Pazuki	$P=\frac{RT}{\upsilon-b(T)}\cdot\frac{\upsilon+2b(T)}{\upsilon}-\frac{a(T)}{\upsilon(\upsilon+b(T))}$	$0.51301\frac{R^2T_c^2}{P_c}\times\alpha(T_r,\omega)$ $\alpha^{1/2}(T_r,\omega)=1+m_1(1-T_r^{0.5})+m_2(1-T_r^{0.5})+m_3(1-T_r^{0.5})^3$ $m_1=0.4690+0.709\omega-0.2660\omega^2$ $m_2=-0.6548-1.2625\omega-1.9727\omega^2$ $m_3=0.9553+5.0064\omega+0.4159\omega^2$	$b(T)=0.058743\frac{RT_c}{P_c}\times\beta(T_r,\omega)$ $\beta(T_r,\omega)^{1.2}=1+n(1-T_r)$ $n=0.1723-0.3858\omega-0.1683\omega^2$

Table 3. Summary of the mixing and combining rules used in this work

Designation	Parameters	a	b	c
Van der Waals-2 parameter (vdW2)	k_{ij}, l_{ij}	$a=\sum_i^n\sum_j^n y_iy_ja_{ij}$	$b=\sum_i^n\sum_j^n y_iy_jb_{ij}$	$c=\sum_i^n\sum_j^n y_iy_jc_{ij}$
		$a_{ij}=(1-k_{ij})(a_{ii}a_{jj})^{0.5}$	$b_{ij}=\frac{b_{ii}+b_{jj}}{2}(1-l_{ij})$	$c_{ij}=\frac{c_i+c_j}{2}$
Panagiotopoulos-Reid (mrPR)	k_{ij}, k_{ji}	$a=\sum_i^n\sum_j^n y_iy_ja_{ij}$	$b=\sum_i^n\sum_j^n y_iy_jb_{ij}$	$c=\sum_i^n\sum_j^n y_iy_jc_{ij}$
		$a_{ij}=(a_ia_j)^{0.5}[1-k_{ij}+(k_{ij}-k_{ji})y_i]$	$b_{ij}=\frac{b_{ii}+b_{jj}}{2}$	$c_{ij}=\frac{c_i+c_j}{2}$

the best method among the models mentioned above.

THEORETICAL BACKGROUND

1. Equation of State (EoS) Model

1-1. Phase Equilibrium and Cubic EoSs with Mixing Rules

The solubility of solid solute (2) in SCF (1), y_2, is derived as follows:

$$y_2=\frac{P_2^{sub}\Phi_2^{sub}\left(\exp\frac{\upsilon_2^s}{RT}(P-P_2^{sub})\right)}{P\ \Phi_2^{SCF}} \quad (1)$$

This equation is obtained by setting equal the fugacities of solute in two phases (stationary phase and mobile phase). In Eq. (1), v_2^s is pure solid molar volume, T and P are the equilibrium temperature and pressure, respectively, the effect of pressure on partial molar volume of pure solute is ignored, Φ_2^{sub} is fugacity coefficient of the pure solid at its sublimation pressure, P_2^{sub} (equal to 1 for P_2^{sub} values below 0.1 MPa at a particular temperature), and Φ_2^{SCF} is the fugacity coefficient of the pure solid in supercritical phase, which can be calculated through any EoS using the following thermodynamic relationship [21]:

$$RT\ln\Phi_i^{SCF}=-RT\ln Z+\int_V^\infty\left[\left(\frac{\partial P}{\partial n_i}\right)_{T,V,n_j\neq n_i}-\frac{RT}{V}\right]dV \quad (2)$$

As of the present, no single EoS can perfectly correlate solubilities of all of the considered compounds; as such, there is a need to find the best EoS and mixing rule for any particular system based on previous results on similar cases. For this purpose, according to previous works [21,45], Soave-Redlich-Kwong (SRK) and modified-Pazuki equations with twin-parametric van der Waals and Panagiotopoulos-Reid (mrPR) mixing rules were selected in this study. Tables 2 and 3 present the cubic EoSs and the corresponding mixing rules. Each EoS needs one or more interaction parameters that can be obtained by correlating the results to the corresponding experimental solubility data.

1-2. Estimation of Critical and Physicochemical Properties of Drugs (Group-contribution Method)

Three different group contribution methods were used to estimate critical and other physicochemical properties of the compounds examined in this research, ending up with different results depending on the particular method used. Table 4 reports estimated values of the drug properties and physical characteristics of SC-CO_2.

2. Empirical and Semi-empirical Models

There are several empirical and semi-empirical models for estimating the solubility data. In this study, four empirical and semi-empirical models with three, four and five constants were used for this purpose.

Chrastil [28] presented a semi-empirical model with three constants that is based on the assumption that one molecule A (sol-

Table 4. Different sets of estimated critical and physicochemical properties of drugs and physical properties of SC-CO_2

Component		T_c/K	P_c/MPa	ω	υ_2^s/ (cm^3/mol)[e]	P_2^{sub}/Pa[f]				
						308	318	328	338	348
2-Phenyl-4*H*-1,3-benzoxazin-4-one	Set1	881.62[a]	2.9274[a]	0.6167[b]	151.7	$6.4937*10^{-3}$	$2.0656*10^{-2}$	$6.0452*10^{-2}$	-	-
	Set2	876.59[c]	3.5473[c]	0.7489[b]	151.7	$1.1422*10^{-3}$	$4.1453*10^{-3}$	$1.3701*10^{-2}$		
	Set3	876.59[c]	3.5473[c]	0.7721[d]	151.7	$7.8261*10^{-4}$	$2.9117*10^{-3}$	$9.8475*10^{-3}$		
Azodicarbonamide	Set1	740.0	5.9479	0.8946	45	0.1869	0.5801	1.6531	-	-
	Set2	737.68	4.8766	0.7946	45	0.1716	0.5301	1.5031		
	Set3	737.68	4.8766	0.9175	45	0.1327	0.4178	1.2057		
Propyphenazone	Set1	847.06	2.3131	0.7101[b]	200	0.0053	0.0175	0.0527	-	-
	Set2	853.04	2.4580	0.7801[b]	200	0.0043	0.0144	0.0438		
	Set3	853.04	2.4580	0.7314[d]	200	0.0031	0.0106	0.0329		
Sulindac	Set1	1014.9	1.7346	0.9099	242	$2.0242*10^{-8}$	$1.2054*10^{-7}$	$6.3281*10^{-7}$	$2.9626*10^{-6}$	-
	Set2	990.5	2.0965	1.1810	242	$2.9604*10^{-10}$	$2.3640*10^{-9}$	$1.6286*10^{-8}$	$9.8132*10^{-8}$	
	Set3	990.5	2.0965	1.3305	242	$1.1633*10^{-11}$	$1.1288*10^{-10}$	$9.3222*10^{-10}$	$6.6495*10^{-9}$	
Thymidine	Set1	983.47	3.2043	1.2565	141.4	$1.4513*10^{-10}$	$1.2525*10^{-9}$	$9.2729*10^{-9}$	-	-
	Set2	943.53	3.3126	1.5770	141.4	$4.0702*10^{-12}$	$4.6382*10^{-11}$	$4.4408*10^{-10}$		
	Set3	943.53	3.3126	1.8313	141.4	$2.3034*10^{-14}$	$3.6080*10^{-13}$	$4.6452*10^{-12}$		
Capecitabine	Set1	1088.60	2.0474	1.5533	225.2	$2.2606*10^{-17}$	$4.1119*10^{-16}$	$6.1155*10^{-15}$	$7.5746*10^{-14}$	$7.9410*10^{-13}$
	Set2	1102.14	1.8904	1.3529	225.2	$1.4013*10^{-15}$	$1.9758*10^{-14}$	$2.3184*10^{-13}$	$2.3020*10^{-12}$	$1.9632*10^{-11}$
	Set3	1102.14	1.8904	1.5857	225.2	$2.7480*10^{-18}$	$5.4961*10^{-17}$	$8.9344*10^{-16}$	$1.2029*10^{-14}$	$1.3641*10^{-13}$
CO_2		304.18	7.38	0.274	-	-	-	-	-	-

[a]Wilson and Jasperson first order method [62]
[b]Definition method[63]
[c]Joback method [62]
[d]Lee and Kesler Relation [64]
[e]Estimated by Fedors method [49]
[f]Estimated by the Ambrose-Walton corresponding states method [62]

ute) is associated with k molecules B (solvent) for the formation of solvated complex.

$$c = \rho^k \exp\left(\frac{a}{T} + b\right) \tag{3}$$

where c (g/L) is the solubility of solute, ρ (g/L) is the pure density of SC-CO_2, k is an association number, and a and b are model constants.

Also, Méndez-Santiago and Teja (MST) [34] offered a semi-empirical model with three constants, that was derived based on the theory of dilute solution:

$$T \ln(y_2 P) = A + B\rho + CT \tag{4}$$

where A, B and C are model constants.

Sparks et al. [35] introduced an empirical model with four constant parameters:

$$c_2^* = \rho_{r,1}^{e_0 + e_1\rho_{r,1}} \exp\left(\alpha + \frac{\beta}{T_r}\right) \tag{5}$$

where:

$$c_2^* = \frac{c_2}{\rho_{c,1}} \tag{6}$$

$$\rho_{r,1} = \frac{\rho_1}{\rho_{c,1}} \tag{7}$$

$$T_r = \frac{T}{T_{c,1}} \tag{8}$$

For the purpose of the above equations, critical density of carbon dioxide ($\rho_{c,1}$) is 467.6 kg·m^{-3}, and its critical temperature ($T_{c,1}$) is 304.18 K.

Recently, Bian et al. [33] suggested the following empirical model with five constant parameters (e_0–e_4):

$$y_2 = \rho^{(e_0 + e_1\rho)} \exp\left(\frac{e_2}{T} + \frac{e_3\rho}{T} + e_4\right) \tag{9}$$

They compared their model with the 14 important empirical models and concluded that the model was superior to the others. Accordingly, the model was used as a good alternative in the present study.

3. Regular Solution Model with the Flory-Huggins Equation

In this method, SC-CO_2 is considered as an expanded liquid and equilibrium solubilities of solid compounds (y_2) in SC-CO_2 are obtained from the following equation [36]:

$$y_2 = \frac{f_2^s}{\gamma_2^\infty f_2^l} \tag{10}$$

where f_2^s and f_2^l are fugacities of pure solute in solid phase and supercritical phase, respectively, and γ_2^∞ is activity coefficient of the solid solute at infinite dilution. The ratio of these fugacities is ob-

tained as follows [36]:

$$\ln\left(\frac{f_2^s}{f_2^l}\right)=\frac{\Delta H_2^f}{R}\left(\frac{1}{T_{2,m}}-\frac{1}{T}\right) \tag{11}$$

where $T_{2,m}$ is the melting temperature of the solid compound, ΔH_2^f is its molar heat of fusion and R is the universal gas constant. The parameter γ_2^∞ is calculated by modified regular solution model coupled with the Flory-Huggins term, as follows:

$$\ln\gamma_2^\infty=\left(\frac{v_2}{RT}\right)(\delta_1-\delta_2)^2+1-\left(\frac{v_2}{v_1}\right)+\ln\left(\frac{v_2}{v_1}\right) \tag{12}$$

where v is the molar volume and δ is the solubility parameter calculated as follows:

$$\delta_i=\left(\frac{\Delta U_i^{vap}}{v_i}\right)^{0.5} \tag{13}$$

ΔU_i^{vap} is the molar internal energy of vaporization. The equilibrium solubility of the solid in SC-CO_2 is calculated using Eqs. (10)-(12):

$$\ln y_2=\frac{\Delta H_2^f}{R}\left(\frac{1}{T_{2,m}}-\frac{1}{T}\right)-\left(\frac{v_2}{RT}\right)(\delta_1-\delta_2)^2-1+\left(\frac{v_2}{v_1}\right)-\ln\left(\frac{v_2}{v_1}\right) \tag{14}$$

where ΔH_2^f and δ_1 are estimated by the methods proposed by Yalkowsky [46] and Pang and McLaughlln [47] methods, respectively, molar volume of SC-CO_2 (v_1) is estimated by the EoS proposed by Huang et al. [48] with 27 constants, and δ_2 is determined using Eq. (15) [49]:

$$\delta_2=\delta_2^0\left(\frac{v_2}{v_2^0}\right)^{1.13} \tag{15}$$

where δ_2^0 and v_2^0 are estimated by the group-contribution method developed by Fedors [49] at 298 K. In this relationship, v_2 is an adjustable parameter. Previous studies have shown a linear relationship between ln v_2 and ln ρ_1 where ρ_1 is the density of SC-CO_2 [36,37].

$$\ln v_2=\alpha\ln\rho_1+\beta \tag{16}$$

where α and β are temperature-independent parameters corresponding to different solid compounds.

4. ANN Methodology

ANN is a powerful mathematical tool with nonlinear learning capabilities. It is generally used for designing and modeling complex processes in science and engineering applications. Basically, an ANN is grounded on training with experimental data rather going through mathematical functions. The artificial neural networks (ANNs), simulating human brain analytical function, have an inherent ability to learn and recognize highly non-linear and complex relationships by experience and experiment. The ability to solve complex problems has made ANNs successfully applied in numerous applications and recently in applications of chemical engineering. In fact, the ANN approach has a good capability to learn from experimental data and to create the input-output relationships for nonlinear processes. When the input is given to the network, its output is compared with the target, and then the learning modules are used to adjust the weights and biases [50,51]. As a nonlinear and complex algorithm, multilayer perception (MLP) is a typical ANN with a wide spectrum of applications in many research fields. Being composed of a multilayer feed-forward neural network with a single hidden layer, it can provide solutions with a given degree of accuracy. A MLP-ANN consists basically of three layers, namely input, hidden and output layers, with each of the layers containing one or more neurons connected to one another via weighting factors ω_i and biases θ_i across in a specified network. Resembling nodes, input signals x_i are fed into the input layer from where those proceed to the hidden layer and further to the output layer (target) once subjected to a so-called transfer function [40,51]. Output of the neurons can be mathematically expressed using Eq. (17) [52]:

$$\left[Y_i=\sum_{i=1}^{n}x_i\omega_i+\theta_i\right] \tag{17}$$

where Y_i is the net input to the node i in a hidden or the output layer, ω_i (i=1, n) are weights, θ_i is bias and x_i is input parameter. The weights and biases were adjusted according to reduce error caused by the contrast between the values of the simulated data and the experimental data. Two different transfer functions were used to train the feed-forward network. A linear transfer function was applied to the neurons in the input and output layers, and a nonlinear sigmoid transfer function was used to transfer the neurons in the hidden layer. The linear transfer function (pure line) used in the output layer is expressed by Eq. (18) [52].

$$[F(x)=x] \tag{18}$$

where F(x) is liner function between $-1<F(x)<1$ and x is input parameter.

The sigmoid transfer function was given by the following equation [52]:

$$\left[F(x)=\frac{1}{1-e^{-x}}\right] \tag{19}$$

where F(x) is sigmoid function between $0<F(x)<1$ and x is input parameter.

ANN tries to improve the performance of the neural network by reducing the total error by changing the weights along its gradient. The learning of ANN is a procedure of modifying the weights. The error for each neuron is the difference squared between the expected output and the actual output. The relation $e_j(n)=d_j(n)-y_j(n)$ defines error signal at the neuron *j*'s output for the *n*th iteration. $d_j(n)$ is the actual output for each neuron and $y_j(n)$ is the expected output. However, neuron *j*'s error is defined by the following equation [52]:

$$\left[E(n)=\frac{1}{2}\sum ej^2(n)\right] \tag{20}$$

First, the network was trained using some 70% of the input data (training dataset). Among the several methods already proposed for training and optimizing the neural network connections, the most common approach for training a multilayer feed-forward neural network is the back-propagation method. An appropriate neural network for a particular purpose can be obtained only after an appropriate training step. Once trained, the network was evaluated using 15% of the original data, provided the evaluation dataset was not used in the training step, ending up with a trained, evaluated network to be tested on the remaining 15% of the original dataset [41].

Performance of the models was examined by measuring the corresponding average absolute relative deviation (AARD), as defined below [21,31,53-55]:

$$\text{AARD\%} = \frac{100}{N_i}\sum_{i=1}^{N_i}\frac{\left|y_2^{calc} - y_2^{exp}\right|}{y_2^{exp}} \quad (21)$$

where N_i is the number of data points for each solute, y_2 denotes molar fraction solubility of the solute, and superscripts calc and exp indicate the calculated and experimental values, respectively. Adjustable parameters were optimized using a simulated annealing (SA) technique where the objective function is minimized through the statistical measure of AARD between the experimental solubility and those obtained from the EoS [15,43].

In addition, for comparing the models comprehensively, ANOVA was used, where several statistical criteria such as adjusted correlation coefficient (R_{adj}) and *F*-value were calculated and compared among different models. To this end, R_{adj} was defined as follows [31,53]:

$$R_{adj} = \sqrt{\left|R^2 - (Q(1-R^2)/(N-Q-1))\right|} \quad (22)$$

where N is the number of data points for each solute, Q is the number of independent variables in each model, and R^2 is the correlation coefficient (Eq. (23), [56]). R_{adj} is an appropriate parameter for comparing models with different numbers of independent variables.

$$R^2 = 1 - \frac{SS_E}{SS_T} \quad (23)$$

where SS_E is the error sum of squares and SS_T is the total sum of squares.

The ability of a model to correlate the solubility data could be evaluated using *F*-value, as introduced in the following [56]:

$$F\text{-value} = \frac{SS_R/Q}{SS_E/(N-Q-1)} = \frac{MS_R}{MS_E} \quad (24)$$

where SS_R is the regression sum of squares, MS_R is the mean square regression, and MS_E is the mean square residual.

RESULTS AND DISCUSSION

In this work, solubility data of six pharmaceutical compounds were correlated using four methods: EoSs, empirical and semi-empirical models, regular solution model coupled with the Flory-Huggins equation, and ANN methodology. To evaluate the results, experiments were carried out according to our previous work [9].

1. EoS Model

First, solubility data of the pharmaceutical compounds were correlated by two EoSs (SRK and modified-Pazuki) with two different mixing rules (vdW2 and mrPR) using three different sets of estimated solid properties. As observed in Table 4, for each component, the values estimated by different models were quite different. Tables 5-10 present AARD, R_{adj} and *F*-values along with the values of interaction parameters of the studied EoSs and mixing rules for each component, according to which, the best EoS, mixing rule and estimation method (in terms of accuracy) were determined.

1-1. 2-Phenyl-4*H*-1,3-benzoxazin-4-one

Presented in Table 5 are correlation results for the solubility of

Table 5. The correlation results for the solubility of 2-phenyl-4*H*-1,3-benzoxazin-4-one in SC-CO_2, at 308, 318 and 328 K, with the SRK and modified-Pazuki (modPAZ) EoSs and vdW2 and mrPR mixing rules for the three different sets of estimated solid's properties

Model	Parameters	T=308 K			T=318 K			T=328 K		
		Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3
SRK-vdW2	k_{12}	0.2204	0.0723	0.0574	0.165	−0.0107	−0.0305	0.09	0.0957	0.0750
	l_{12}	0.0765	−0.2	−0.2225	−0.0755	−0.4425	−0.4790	−0.2381	−0.0782	−0.1136
	AARD (%)	7.64	8.99	9.26	17.81	19.97	20.42	22.44	24.49	24.84
	F-value	6.06	4.71	4.83	2.28	1.09	1.05	6.38	6	5.41
	R_{adj}	0.7835	0.7124	0.7083	0.4712	0.2712	0.1612	0.8104	0.7980	0.7720
SRK-mrPR	k_{12}	0.1943	0.1364	0.1287	0.1976	0.1423	0.1341	0.1828	0.1289	0.1225
	$k_{21}*10^5$	1.2232	−3.2247	−3.5272	0.9296	−1.7203	−1.9661	0.4371	0.1152	0.1579
	AARD (%)	7.56	9.41	9.73	17.52	24.57	25.37	17.75	25.66	26.38
	F-value	6.56	4.21	3.41	4.47	0.6981	0.55	13.22	5.28	5.15
	R_{adj}	0.7844	0.6972	0.6925	0.7056	0.1788	0.1187	0.8960	0.7906	0.7713
modPAZ-vdW2	k_{12}	0.0373	−0.2139	−0.2470	−0.0625	−0.3638	−0.4061	0.0537	−0.2353	−0.4725
	l_{12}	−0.1003	−0.4978	−0.5399	−0.2869	−0.8016	−0.8628	−0.005	−0.4522	−0.9532
	AARD (%)	7.69	9.07	9.35	18.98	21.18	21.63	23.96	25.87	26.45
	F-value	6.35	4.12	3.72	1.99	0.47	0.37	6.74	4.65	3.37
	R_{adj}	0.7776	0.6855	0.6611	0.3975	0.3246	0.3033	0.7925	0.7409	0.6670
modPAZ-mrPR	k_{12}	0.0857	0.0125	0.0002	0.0827	0.0114	−0.0027	0.0574	−0.0125	−0.0276
	$k_{21}*10^5$	−1.4034	−7.9265	−8.5061	−0.7734	−4.9218	−5.3987	0.0351	−0.5565	−0.6932
	AARD (%)	8.21	10.64	12.30	22.31	29.88	30.82	24.05	29.69	30.37
	F-value	6.16	3.85	3.57	2.12	0.08	0.01	5.18	3.67	2.37
	R_{adj}	0.7718	0.6755	0.6509	0.2626	0.2001	0.1121	0.7858	0.6859	0.6444

Table 6. The correlation results for the solubility of Azodicarbonamide in SC-CO_2, at 308, 318 and 328 K, with the SRK and modified-Pazuki (modPAZ) EoSs and vdW2 and mrPR mixing rules for the three different sets of estimated solid's properties

Model	Parameters	T=308 K			T=318 K			T=328 K		
		Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3
SRK-vdW2	k_{12}	0.4579	0.4995	0.4802	0.3248	0.3763	0.3548	0.4306	0.4716	0.4505
	l_{12}	0.5299	0.5865	0.5596	0.0245	0.1474	0.1124	0.3163	0.3979	0.3663
	AARD (%)	18.15	18.24	18.49	8.99	9.19	9.71	11.15	11.27	11.55
	F-value	12.07	11.95	10.05	8.81	8.35	7.28	3.45	3.28	2.92
	R_{adj}	0.8571	0.8558	0.8521	0.8132	0.8048	0.7817	0.6411	0.6282	0.5956
SRK-mrPR	k_{12}	0.3001	0.2976	0.3068	0.3179	0.3145	0.3219	0.3379	0.3326	0.3390
	$k_{21}*10^7$	6.1136	5.6512	5.3113	0.5041	2.9801	2.1612	2.6601	3.2201	2.8801
	AARD (%)	10.55	7.59	8.50	8.95	8.85	9.48	10.17	9.56	10.12
	F-value	42.73	57.36	52.80	9.06	10.17	8.37	4.96	5.86	4.81
	R_{adj}	0.9553	0.9663	0.9635	0.8176	0.8345	0.8052	0.7285	0.7633	0.7220
modPAZ-vdW2	k_{12}	0.0553	0.1068	0.0935	0.05	0.1395	0.0819	0.1489	0.2697	0.2117
	l_{12}	−0.2098	−0.1131	−0.1062	−0.26	−0.0763	−0.1618	−0.0552	0.1881	0.1042
	AARD (%)	18.81	18.99	19.81	9.87	10.07	10.61	11.64	11.73	12.03
	F-value	0.12	0.10	0.08	7.03	6.65	5.77	3.74	2.74	2.51
	R_{adj}	0.2238	0.2131	0.2054	0.7752	0.7652	0.7375	0.6627	0.5758	0.5493
modPAZ-mrPR	k_{12}	0.1411	0.1605	0.1389	0.1583	0.1726	0.1521	0.1743	0.1860	0.1654
	$k_{21}*10^7$	4.5391	5.2940	4.8022	−5.7245	−1.5973	−3.3630	0.7362	1.79	1.0696
	AARD (%)	16.04	13.46	14.95	10.38	10.29	11.0	11.48	11.16	11.78
	F-value	18.05	26.04	21.49	5.05	5.92	4.6	3.92	3.42	2.74
	R_{adj}	0.9	0.9286	0.9147	0.7091	0.7427	0.6884	0.5947	0.6394	0.5767

2-phenyl-4*H*-1,3-benzoxazin-4-one in SC-CO_2. From the complete analysis of Table 5, it is concluded that when it comes to the estimation of the critical properties and Pitzer's acentric factor, Wilson and Jasperson's first-order and definition methods (Set 1) always produce the best correlation results, respectively, for the SRK and modified-Pazuki EoSs. This result could be attributed to the differences in the used values of the solid sublimation pressure since the solid sublimation pressure significantly affects the experimental correlation using cubic EoS models. This effect should be considered when selecting and using an estimation method for the properties [21].

By comparing the values of the statistical criteria (AARD, R_{adj} and F value) along the three isotherms presented in Table 5, it is concluded that with set 1 of the estimated properties, it was better to use mrPR mixing rule along with SRK EoS and SRK-mrPR. But when sets 2 and 3 were used, SRK EoS with twin-parametric vdW mixing rule (SRK-vdW2) ended up with more accurate solutions. Finally, for obtaining good correlation results for the solubility of 2-phenyl-4*H*-1,3-benzoxazin-4-one using the SRK EoS, it was preferable to use set 1 of the estimated properties coupled with the mrPR mixing rule.

Based on the values of the statistical criteria in Table 5, when vdW2 was used as the mixing rule, the most accurate correlation results were obtained with modified-Pazuki EoS. Therefore, the modified-Pazuki EoS with vdW2 mixing rule showed the most appropriate results when set 1 was used as the estimation method.

Generally, compared to modified-Pazuki EoS, the SRK EoS correlated the solubility of 2-phenyl-4*H*-1,3-benzoxazin-4-one in SC-CO_2 more accurately with either of the mixing rules (vdW2 and mrPR).

1-2. Azodicarbonamide

As shown in Table 6, for both of the cubic EoSs with vdW2 mixing rule, the three isotherms indicated that set 1 was the most reliable property estimation method. However, when mrPR was used as the mixing rule, Joback method coupled with definition method (set 2) (for estimating the critical properties and Pitzer's acentric factor, respectively) produced the most valid estimations for both of the EoSs.

Along the three isotherms, the SRK EoS produced lower AARD values (i.e., higher R_{adj} and *F*-value) with mrPR mixing rule rather than the vdW2 mixing rule. So, for obtaining good correlation results for solubility of Azodicarbonamid using the SRK EoS, it is better to estimate the properties by set 2 along with mrPR mixing rule.

Upon using the modified-Pazuki EoS, the lowest correlation error (i.e., minimum *AARD* and maximum R_{adj} and *F*-value) with mrPR mixing rule was obtained at 308 and 328 K, while the minimum correlation error with vdW2 mixing rule was found at 318 K. At 308 K, the values of AARD were significantly different, as opposed to the situation at the two other temperatures. This can be seen in Fig. 1. According to the results, the SRK EoS correlated the solubility of Azodicarbonamid in SC-CO_2 with higher accuracy with either of the mixing rules (vdW2 and mrPR), as compared to the modified-Pazuki EoS.

1-3. Propyphenazone

As can be seen in Table 7, for both of the cubic EoSs along the three isotherms for both of the mixing rules, set 1 produced the most accurate contribution group set for property estimation. Both of the EoSs in the three sets showed better correlations with vdW2

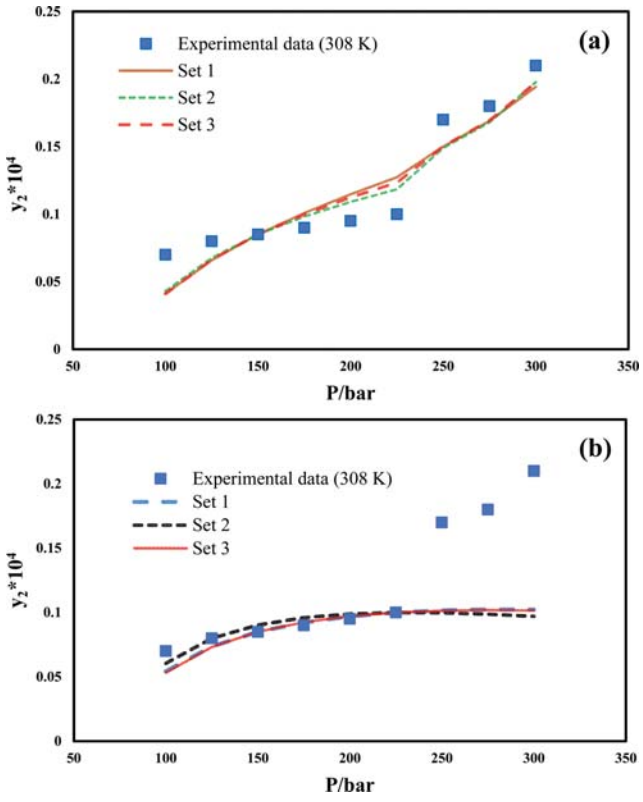

Fig. 1. Experimental solubility of Azodicarbonamide in SC-CO_2, at 308 K and correlation results in different sets of estimated properties obtained with: (a) Modified-PAZ-mrPR model and (b) modified-PAZ-vdW2 model.

mixing rule rather than mrPR mixing rule. Accordingly, better correlation results were obtained when SRK and modified-Pazuki EoSs were used with the vdW2 mixing rule and set 1 as the contribution group set. Similarly, the SRK EoS correlated the solubility of Propyphenazone in SC-CO_2 with minimum errors.

1-4. Sulindac

Table 8 represents the correlation results for experimental solubility of Sulindac in SC-CO_2. As can be observed, for the SRK EoS along the four isotherms with vdW2 mixing rule, minimal error was obtained when set 1 was used as the estimation method. However, when mrPR mixing rule was used, minimal correlation errors (minimum AARD, maximum R_{adj} and *F*-value) at 308 and 318 K were achieved with set 2, while set 1 ended up with minimal error at 328 and 338 K. In this case (SRK-mrPR), at all temperatures except 308 K, the AARD values corresponding to different sets were significantly different.

For the modified-Pazuki EoS with either of the both mixing rules, set 1 of the estimated properties led to successful correlation results. According to Table 8, for obtaining good correlation results for the solubility of Sulindac using the SRK EoS, it was better to use the vdW2 mixing rule and set 1 of the estimated properties. Also, the minimal correlation results with the modified-Pazuki EoS could be obtained using vdW2 mixing rule and set 1; the only exception in this respect was the case at 318 K wherein the mrPR mixing rule with set 1 produced the lowest correlation errors.

1-5. Thymidine

Table 9 shows correlation results for the experimental solubility of Thymidine in SC-CO_2. According to the obtained values of AARD, R_{adj} and *F*-value, none of the EoSs in the three isotherms

Table 7. The correlation results for the solubility of Propyphenazone in SC-CO_2, at 308, 318 and 328 K, with the SRK and modified-Pazuki (modPAZ) EoSs and vdW2 and mrPR mixing rules for the three different sets of estimated solid's properties

Model	Parameters	T=308 K			T=318 K			T=328 K		
		Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3
SRK-vdW2	k_{12}	0.1482	0.1177	0.1032	0.0498	0.0143	0.0239	0.0499	0.0163	−0.0002
	l_{12}	0.0393	−0.0199	−0.0442	−0.1786	−0.2557	−0.2203	−0.1437	−0.2136	−0.2429
	AARD (%)	5.88	6.17	6.46	14.02	14.52	15.34	19.53	20.19	21.04
	F-value	56.3	46.03	44.28	149.87	127.43	119.84	595.56	568.31	346.06
	R_{adj}	0.9771	0.9738	0.9723	0.9917	0.9903	0.9901	0.9988	0.9978	0.9964
SRK-mrPR	k_{12}	0.1336	0.1452	0.12	0.1186	0.1305	0.1948	0.1061	0.1166	0.0897
	$k_{21}*10^2$	5.9696	−2.9612	−4.8937	−9.4403	−17.921	−20.502	−4.4456	−8.6493	−10.782
	AARD (%)	5.89	6.69	7.29	17.22	19.2	20.3	21.07	22.14	23.52
	F-value	54.1	43.15	36.8	139.4	84.71	68.29	585.7	505.22	293.23
	R_{adj}	0.9773	0.9716	0.9668	0.9913	0.9854	0.9819	0.9979	0.9975	0.9957
modPAZ-vdW2	k_{12}	−0.0902	−0.1417	−0.1595	−0.2886	−0.3520	−0.3770	−0.2922	−0.3529	−0.3749
	l_{12}	−0.1550	−0.2573	−0.2649	−0.4817	−0.6172	−0.6348	−0.4365	−0.5611	−0.5731
	AARD (%)	6.52	6.7	6.99	15.47	15.97	16.73	19.01	19.68	20.56
	F-value	41.93	40.01	37.5	66.92	60.15	51.19	476.44	455.93	442.35
	R_{adj}	0.9708	0.9694	0.9674	0.9816	0.9795	0.9760	0.9974	0.9973	0.9972
modPAZ-mrPR	k_{12}	−0.0075	−0.0087	−0.0209	−0.0315	−0.0332	−0.0457	−0.1097	−0.1207	−0.1355
	$k_{21}*10^3$	−2.1518	−3.6874	−3.7502	−3.9056	−5.2170	−5.2841	3.5782	3.5143	3.5049
	AARD (%)	9.53	11.51	12	25.04	27.47	28.22	26.84	28.08	28.94
	F-value	24.15	17.54	16.18	24.91	17.10	15.51	50.57	40.45	40.44
	R_{adj}	0.950	0.9321	0.9266	0.9515	0.9304	0.9236	0.9757	0.9697	0.9697

Table 8. The correlation results for the solubility of Sulindac in SC-CO_2, at 308, 318, 328 and 338 K with the SRK and modified-Pazuki (modPAZ) EoSs and vdW2 and mrPR mixing rules for the three different sets of estimated solid's properties

Model	Parameters	T=308 K			T=318 K			T=328 K			T=338 K		
		Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3
SRK-vdW2	k_{12}	0.2152	0.0421	0.0077	0.2056	0.007	−0.0741	0.1379	−0.037	−0.104	0.0662	−0.0897	−0.1519
	l_{12}	0.2591	−0.0256	−0.0531	0.2876	−0.0460	−0.1821	0.2036	−0.0758	−0.1763	0.1060	−0.1269	−0.2156
	AARD (%)	6.51	9.14	10.99	5.73	9.59	12.19	9.71	15.98	19.65	8.62	18.64	24.18
	F-value	53.38	28.44	34.68	85.63	14.59	7.68	93.43	50.52	36.23	4034.97	79.04	29.62
	R_{adj}	0.9725	0.9495	0.9582	0.9827	0.9051	0.8307	0.9842	0.9710	0.96	0.9996	0.9813	0.9514
SRK-mrPR	k_{12}	0.1019	0.0559	0.0279	0.0802	0.0275	0.0026	0.0480	−0.0037	−0.0317	0.0164	−0.0348	−0.0552
	$k_{21}*10^3$	158.891	20.3761	−32.1740	7.8718	1.6004	0.7270	0.5652	−0.0766	−0.2984	0.0263	−0.0253	−0.0261
	AARD (%)	9.85	7.92	13.16	25.63	7.9	16.6	10.81	20.1	28.43	7.83	27.08	36.21
	F-value	12.61	71.17	21.20	9.37	287.93	116.66	76.43	65.87	31.18	226.78	57.46	84.92
	R_{adj}	0.8916	0.9793	0.9331	0.8580	0.9948	0.9873	0.9807	0.9776	0.9537	0.9934	0.9744	0.9826
modPAZ-vdW2	k_{12}	−0.1061	−0.6284	−0.9776	−0.1353	−0.6319	−1.0957	−0.2132	−0.8656	−1.0746	−0.2562	−0.6579	−0.9406
	l_{12}	−0.0437	−0.6692	−1.0145	−0.0283	−0.5827	−1.1144	−0.0795	−0.8869	−0.9360	−0.0666	−0.3882	−0.5587
	AARD (%)	6.29	8.96	10.99	7.58	12.55	15.17	15.84	22.87	28.64	20.13	30.97	35.83
	F-value	95.61	29.90	22.50	47.06	36.23	6.85	50.56	16.28	11.63	111.10	25.95	14.78
	R_{adj}	0.9845	0.9518	0.9368	0.9689	0.9599	0.7999	0.9741	0.9103	0.8831	0.9863	0.9448	0.9063
modPAZ-mrPR	k_{12}	−0.0773	−0.2524	−0.4027	−0.1154	−0.2940	−0.4481	−0.1616	−0.3438	−0.5257	−0.2119	−0.4067	−0.5711
	$k_{21}*10^3$	3.5940	−466.29	−828.44	1.5264	−13.142	−26.606	−0.1398	−1.6973	2.6974	−0.0108	−0.1376	−0.2424
	AARD (%)	6.61	28.14	36.38	7.47	37.32	46.72	20.58	43.12	50.43	24.22	48.13	56.71
	F-value	27.27	2.36	0.36	444.73	14.46	4.14	40.68	12.35	7.13	62.01	18.95	5.5
	R_{adj}	0.9745	0.5584	0.4301	0.9966	0.9043	0.7448	0.9611	0.8946	0.8193	0.9766	0.9256	0.7745

Table 9. The correlation results for the solubility of Thymidine in SC-CO_2, at 308, 318 and 328 K, with the SRK and modified-Pazuki (mod-PAZ) EoSs and vdW2 and mrPR mixing rules for the three different sets of estimated solid's properties

Model	Parameters	T=308 K			T=318 K			T=328 K		
		Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3
SRK-vdW2	k_{12}	−0.1953	−0.3556	−0.4273	−0.5504	−0.7597	−0.9713	−0.3573	−0.5420	−0.7328
	l_{12}	−0.7405	−1.1008	−1.1480	−1.9085	−2.5214	−3.1340	−1.1971	−1.6578	−2.1258
	AARD (%)	19.73	21.94	24.77	31.36	33.20	35.63	36.02	37.82	40.27
	F-value	0.04	0.02	0.01	0.02	0.012	0.009	0.007	0.006	0.004
	R_{adj}	0.3121	0.3058	0.3041	0.1203	0.1198	0.1102	0.1213	0.1198	0.1104
SRK-mrPR	k_{12}	0.0375	−0.0242	−0.0906	0.0122	−0.0507	−0.1159	0.0113	−0.0509	−0.1186
	$k_{21}*10^9$	−1.6309	−2.3762	−2.9901	−2.5151	−5.8073	−3.6365	−0.8465	−1.0979	−1.2858
	AARD (%)	26.15	29.22	33.06	24.24	46.89	27.87	34.65	35.45	37.02
	F-value	0.008	0.007	0.005	0.02	0.005	0.01	0.003	0.0028	0.002
	R_{adj}	0.1313	0.1301	0.1295	0.1307	0.1181	0.1298	0.1405	0.1398	0.1385
modPAZ-vdW2	k_{12}	−1.1887	−2.3113	−4.8350	−1.8735	−3.5982	−7.0804	−1.6259	−3.1447	−5.8013
	l_{12}	−1.8365	−2.8879	−5.0735	−3.3521	−5.6406	−9.4990	−2.6607	−4.5034	6.9052
	AARD (%)	20.59	23.57	25.80	29.16	30.83	33.11	37.42	39.3	41.74
	F-value	0.017	0.015	0.014	0.008	0.008	0.007	0.006	0.005	0.005
	R_{adj}	0.2405	0.2388	0.2352	0.1998	0.1960	0.1945	0.1901	0.1890	0.1888
modPAZ-mrPR	k_{12}	−0.3258	−1.1297	−1.9921	−0.3571	−0.8298	−2.3829	−0.4074	−0.9453	−2.5299
	$k_{21}*10^9$	−6.4189	5.4882	0.9970	−6.7405	−13.841	1.1913	0.1956	0.4726	1.7382
	AARD (%)	31.74	59.17	75.14	25.76	27.31	71.04	70.85	76.41	71.15
	F-value	1.21	0.003	0.001	2.23	2.21	0.001	0.001	0.001	0.001
	R_{adj}	0.2914	0.1986	0.1012	0.3011	0.3002	0.1034	0.1009	0.1004	0.1006

with either of the three sets could acceptably correlate the experimental solubility data.

1-6. Capecitabine

Correlation results for the experimental solubility of Capecitabine in SC-CO_2 are seen in Table 10. For both EoSs and all isotherms with both of the mixing rules, set 2 served as the best method for correlating Capecitabine's solubility in SC-CO_2. The results reported in Table 10 indicated that when SRK EoS was used, regardless of the used set of properties and isotherms, vdW2 mixing rule produced the best correlation results than mrPR mixing rule. The same was the case for modified-Pazuki EoS. According to the above findings, the best correlation results for the solubility of Capecitabine using SRK and modified-Pazuki EoSs could be found with the vdW2 mixing rule and set 2.

In the case of modified-Pazuki EoS, the values of AARD, R_{adj} and *F*-value obtained using vdW2 mixing rule were significantly

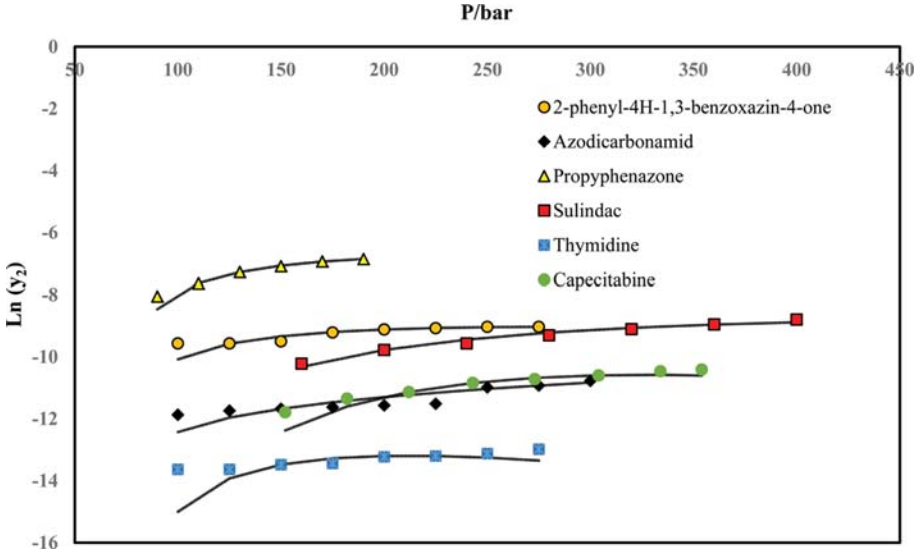

Fig. 2. Experimental and correlation results for the six compounds, correlated with SRK EoS with the vdW2 mixing rule and Set 1 of estimated properties, at 308 K.

Table 10. The correlation results for the solubility of Capecitabine in SC-CO_2, at 308, 318, 328, 338 and 348 K with the SRK and modified-Pazuki (modPAZ) EoSs and vdW2 and mrPR mixing rules for the three different sets of estimated solid's properties

Model	Parameters	T=308 K			T=318 K			T=328 K			T=338 K			T=348 K		
		Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3	Set 1	Set 2	Set 3
SRK-vdW2	k_{12}	−0.1516	−0.0302	−0.1329	−0.2235	−0.0970	−0.2054	−0.2946	−0.1565	−0.2785	−0.3051	−0.2270	−0.2904	−0.3606	−0.2079	−0.3496
	l_{12}	−0.3240	−0.0975	−0.2700	−0.4724	−0.2275	−0.4163	−0.6242	−0.3438	−0.5693	−0.5994	−0.4844	−0.5484	−0.7063	−0.3947	−0.6618
	AARD (%)	12.49	10.87	13.34	18.18	15.95	19.27	22.05	18.91	23.56	30.49	26.87	31.78	35.83	33.65	36.91
	F-value	17.07	34.33	14.31	10.40	23.61	10.16	11.23	48.26	8.06	36.66	49.66	35.63	32.55	55.83	29.24
	R_{adj}	0.9062	0.9513	0.8898	0.8536	0.9447	0.8501	0.8976	0.9734	0.8906	0.9530	0.9676	0.9408	0.9488	0.9688	0.9433
SRK-mrPR	k_{12}	−0.0361	0.0059	−0.0347	−0.0520	−0.0090	−0.0510	−0.0686	−0.0228	−0.0679	−0.0835	−0.0383	−0.0833	−0.1018	−0.0532	−0.1020
	$k_{21}*10^5$	−28.226	−9.1596	−21.168	−9.4304	−3.5080	−7.36	−5.9425	−2.1030	−3.7040	−2.1591	−0.8845	−1.7584	−1.7845	−0.5751	−1.4920
	AARD (%)	22.65	14.15	22.11	32.86	22.99	32.39	40.87	31.36	40.79	47.12	38.03	47.04	52.61	44.28	52.69
	F-value	7.70	21.49	8.30	9.61	21.14	9.25	9.48	34.23	14.33	21.16	44.20	21.59	21.20	45.32	21.69
	R_{adj}	0.8105	0.9242	0.8222	0.8432	0.9320	0.8318	0.8356	0.9512	0.8899	0.9231	0.9618	0.9245	0.9232	0.9593	0.9248
modPAZ-vdW2	k_{12}	−1.9676	−1.0611	−2.0699	−2.2031	−1.2453	−2.3213	−2.2615	−1.4288	−2.390	−2.5268	−1.6539	−2.6661	−2.5407	−1.6447	−2.69
	l_{12}	−2.1021	−1.1164	−2.1255	−2.4264	−1.3717	−2.4646	−2.4153	−1.6241	−2.4652	−2.7808	−1.9405	−2.8332	−2.690	−1.8202	−2.7553
	AARD (%)	12.33	10.70	13.13	19.24	16.98	20.35	26.41	21.83	27.65	33.56	30.82	34.87	39.54	36.18	40.38
	F-value	17.29	38.41	15.06	9.38	12.32	8.23	40.98	47.89	41.51	27.34	29.34	26.41	40.90	44.16	40.19
	R_{adj}	0.9073	0.9563	0.8948	0.84	0.8740	0.8209	0.9547	0.9647	0.9594	0.9434	0.9519	0.9369	0.9618	0.9622	0.9581
modPAZ-mrPR	k_{12}	−0.9902	−0.4429	−1.0572	−1.0730	−0.5623	−1.0802	−1.1045	−0.5956	−1.1185	−1.0889	−0.6304	−1.0333	−1.1216	−0.6644	−1.1976
	$k_{21}*10^7$	2.5069	−1.6042	2.4447	0.9108	0.4895	0.5689	0.3829	0.1879	0.2203	0.0919	0.0716	0.0518	0.0353	0.0285	0.0350
	AARD (%)	38.56	25.93	26.42	50.59	37.66	44.18	52.13	43.90	49.85	51.42	48.26	74.95	60.30	56.03	61.38
	F-value	1.67	3.007	3.15	1.01	3.72	1.19	0.95	9.36	4.87	7.02	13.11	1.32	7.38	12.86	6.33
	R_{adj}	0.4577	0.6564	0.6171	0.2240	0.6611	0.2266	0.2220	0.8395	0.7246	0.7953	0.8808	0.2902	0.8035	0.8787	0.7771

Table 11. The comprehensive comparison among different models (empirical and semi-empirical, regular solution and ANN models)

Component	Chrastile			MST			Spark et al.			Bian et al.			Regular solution			ANN		
	AARD (%)	*F* value	R_{adj}	AARD (%)	*F* value	R_{adj}	AARD (%)	*F* value	R_{adj}	AARD (%)	*F* value	R_{adj}	AARD (%)	*F* value	R_{adj}	AARD (%)	*F* value	R_{adj}
2-Phenyl-4*H*-1,3-benzoxazin-4-one	13.69	15.26	0.7513	16.41	13.06	0.7886	9.79	30.86	0.8523	11.39	27.62	0.8439	10.56	14.28	0.8026	2.41	142.55	0.9751
Azodicarbonamide	11.13	7.50	0.5848	14.44	2.05	0.3340	9.96	11.58	0.6687	10.49	11.04	0.6675	15.30	1.64	0.2678	4.68	245.07	0.9834
Propyphenazone	11.64	456.04	0.9924	8.73	426.31	0.9904	8.32	546.62	0.9926	6.10	564.12	0.9942	22.45	11.64	0.8078	13.71	212.16	0.9868
Sulindac	9.0	342.99	0.9808	8.64	919.31	0.9951	8.77	418.35	0.9842	10.93	953.72	0.9930	31.99	12.42	0.7479	8.40	9553.7	0.9995
Thymidine	11.34	36.47	0.8881	18.74	3.66	0.5435	7.70	101.91	0.9568	7.82	102.31	0.9562	8.19	54	0.9451	3.52	590.91	0.9947
Capecitabine	8.68	1291.12	0.9925	9.37	506.21	0.9874	8.37	1441.97	0.9933	8.72	2430.2	0.9957	31.76	12.29	0.6818	4.75	1500.31	0.9960
Mean	10.57	358.23	0.8650	12.27	311.77	0.7732	8.83	425.22	0.9078	9.39	681.50	0.9084	21.77	17.71	0.7088	5.93	2040.78	0.9893

different from those of mrPR mixing rule, indicating the superiority of the vdW2 mixing rule.

Analyzing Table 10, it is observed that, SRK EoS could correlate the solubility of Capecitabine in SC-CO_2 at higher accuracy (lower error) with either of the mixing rules, sets of properties, and temperatures, except for the temperature of 308 K and the vdW2 mixing rule.

In general, taking the above correlation results into account, for all of the pharmaceutical compounds studied herein, it can be concluded that (i) the effect of the contribution-group methods (property estimation method) is rather insignificant and predictive power of EoSs increased using vdW2 and mrPR mixing rules, as indicated by hardly insignificant differences between AARD values related to the three sets in most cases. So, vdW2 and mrPR mixing rules are appropriate for EoS calculations. (ii) Joback method with Lee and Kesler relationship (set 3) are not appropriate for estimating properties of the pharmaceutical compounds used in this work. (iii) In most cases, SRK EoS works better than the modified-Pazuki (see for example Fig. 2). As can be observed in Fig. 2, good correlation results were achieved for the six compounds using

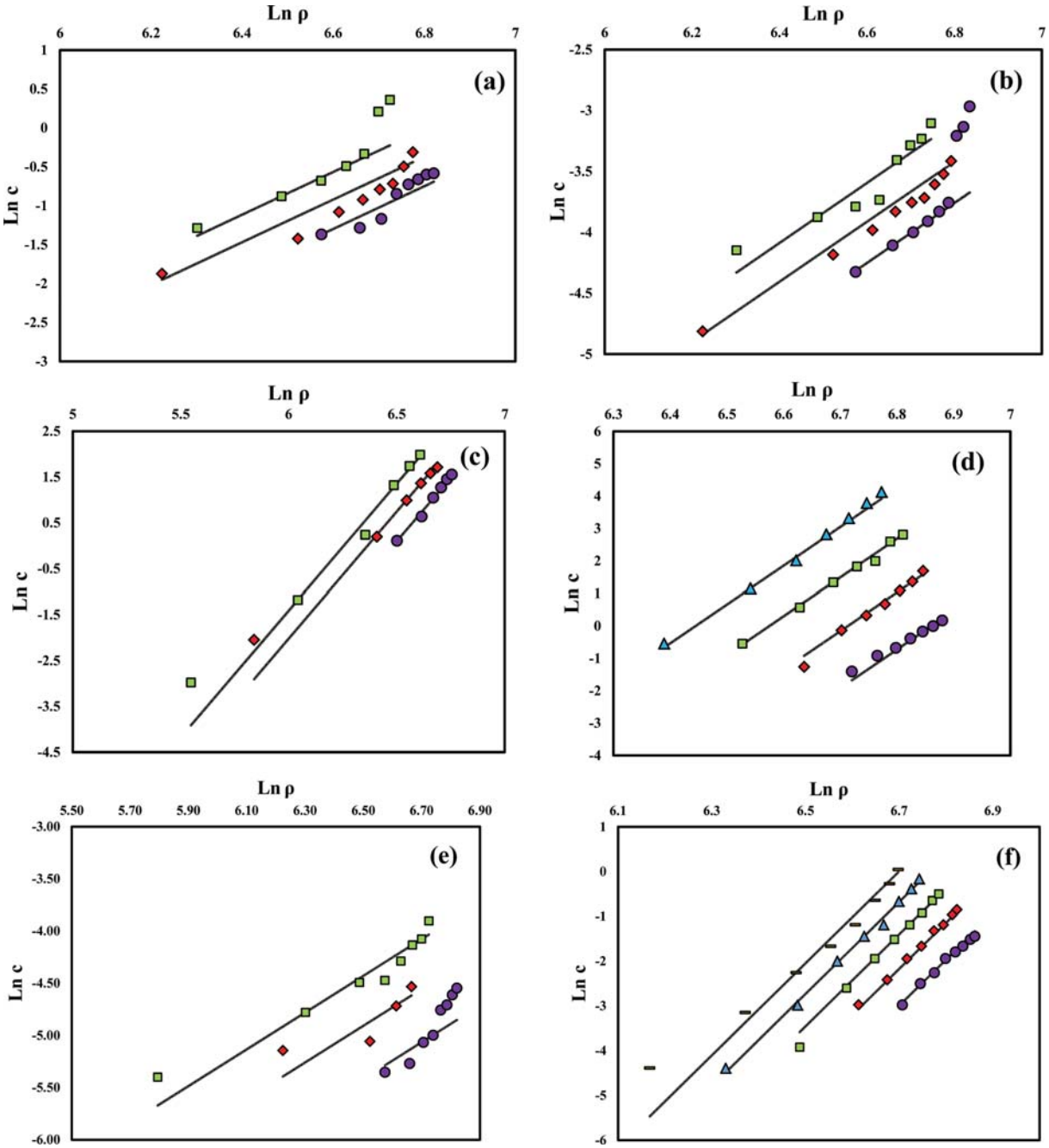

Fig. 3. Experimental and correlation results for solubility of (a) 2-phenyl-4*H*-1,3-benzoxazin-4-one (b) Azodicarbonamide (c) Propyphenazone (d) Sulindac (e) Thymidine (f) Capecitabine in SC-CO_2 using Chrastil model (● 308 K ◆ 318 K ■ 328 K ▲ 338-348 K).

the SRK EoS with vdW2 mixing rules and set 1 at 308 K.

2. Empirical and Semi-empirical, Regular Solutions with Flory-Huggins Equation and ANN Models

All of the considered models (empirical and semi-empirical, regular solution and ANN models) were comprehensively compared based on particular statistical criteria: AARD, R_{adj} and *F*-value (Table 11). Based on the table, Sparks et al. and Bian et al. models provided more precise fits, as compared to other models. Note that with four constants, the Sparks et al. model correlated the experimental solubility data of all compounds more accurately than Bian et al. model with five parameters, with the only exception in this respect being Propyphenazone. Further examining Table 11, the MST model provided a better fit to the solubility of Sulindac in SC-CO_2 (AARD (%)=8.64), as compared to those of the Sparks et al. and Bian et al. models (AARD (%)=8.77 and 10.93, respectively), indicating the dependence of the choice of empirical or semi-empirical model producing the best fit to the solubility data on the different operating conditions. This result has been further supported by Tabernero et al. [2]. Sparks et al. combined Adachi and Lu [57] and Del Valle and Aguilera [29] models to address the problem with the temperature and hence decrease the value of AARD value in the correlation [2]. Figs. 3-6 show the correlation results for all of the compounds using the four different empirical and semi-empirical models. Also, calculated values of the constant parameters for each model by the least square method are reported in Tables A-D in Appendix.

Comparing the values of AARD, R_{adj} and *F*-value between the regular solution model and empirical or semi-empirical models, the correlation accuracy of the regular solution model for all of the compounds is inferior to those of empirical or semi-empirical models (Sparks et al. and Bian et al. models). This was because the

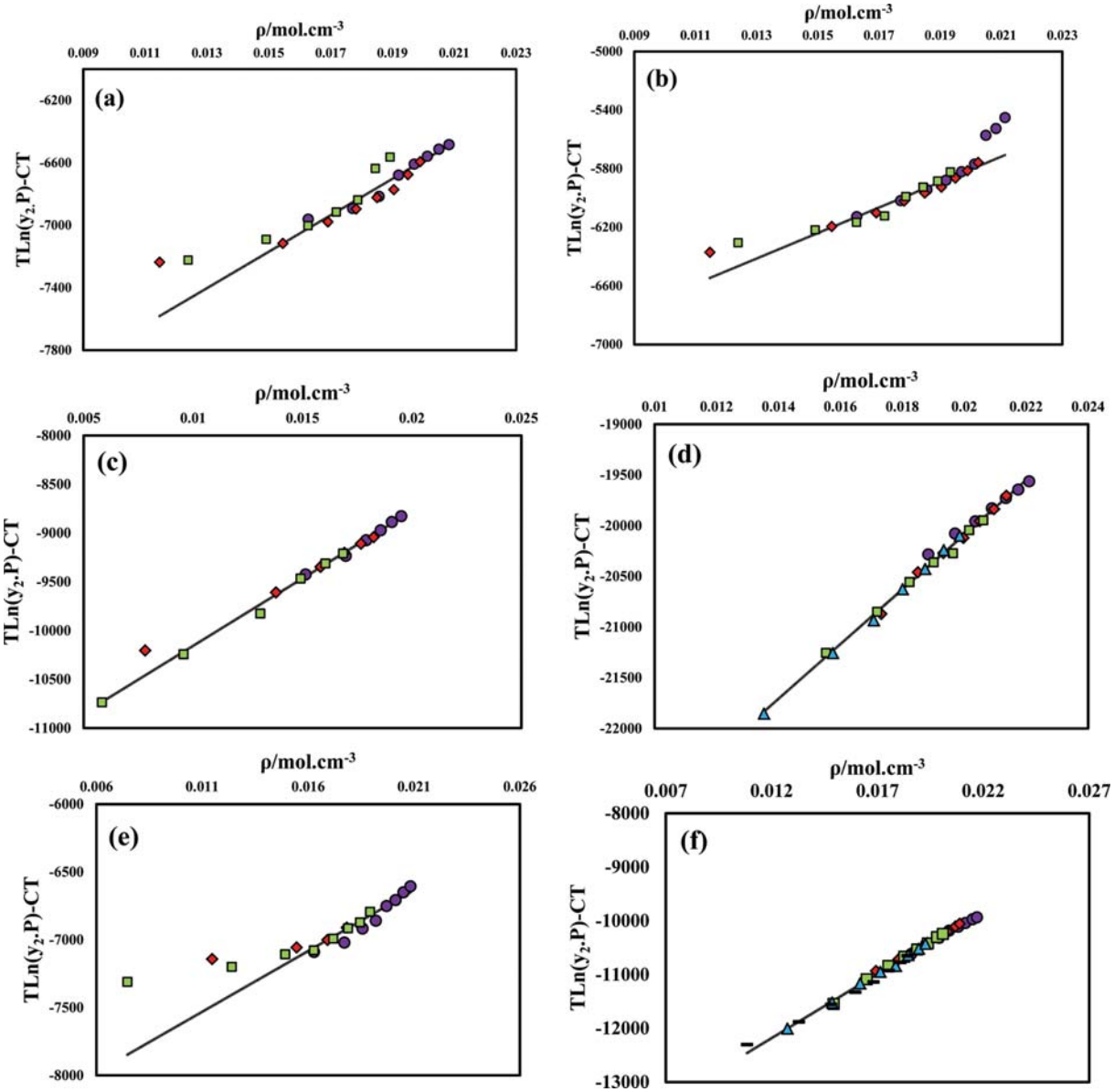

Fig. 4. Experimental and correlation results for solubility of (a) 2-phenyl-4*H*-1,3-benzoxazin-4-one (b) Azodicarbonamide (c) Propyphenazone (d) Sulindac (e) Thymidine (f) Capecitabine in SC-CO_2 using MST model (● 308 K ◆ 318 K ■ 328 K ▲ 338-348 K).

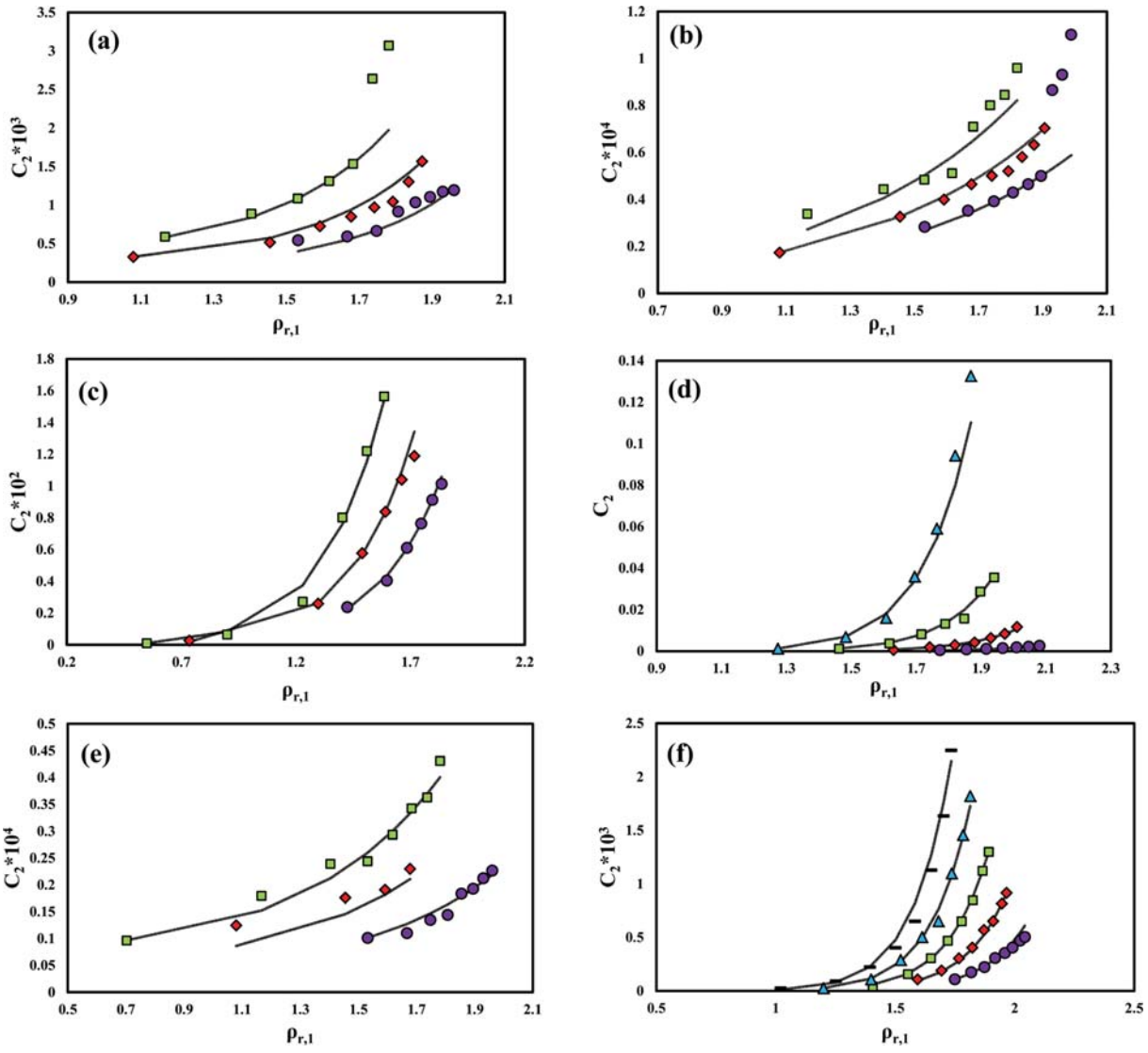

Fig. 5. Experimental and correlation results for solubility of (a) 2-phenyl-4*H*-1,3-benzoxazin-4-one (b) Azodicarbonamide (c) Propyphenazone (d) Sulindac (e) Thymidine (f) Capecitabine in SC-CO_2 using Sparks et al. model (● 308 K ◆ 318 K ■ 328 K ▲ 338-348 K).

regular solution model has two adjustable parameters, while Sparks et al. and Bian et al. models have four and five adjustable parameters, respectively. In the meantime, the regular solution model provided better correlation results for the solubility of 2-phenyl-4*H*-1,3-benzoxazin-4-one and Thymidine, as compared to the Chrastil and MST models. In Fig. 7, the correlation results obtained using the regular solution model are reported. Also, calculated values of the adjustable parameters for regular solution model by the least square method are given in Table E in Appendix.

Fig. 8 shows the correlation coefficient (R^2) of the testing data versus the number of neurons in the hidden layer. This graph clearly indicates that for the particular case studied in this research, the minimum error could be achieved with 6 neurons in the hidden layer.

In the following, the ANN and empirical and semi-empirical models were compared in terms of correlation of solubility of six pharmaceutical compounds. As shown in Table 11, generally speaking, the ANN method was more accurate than either of empirical or semi-empirical models. Mean AARD (%), R_{adj} and *F*-value were obtained as 5.93, 0.9893, and 2040.78, respectively, for the ANN method. However, the best empirical and semi-empirical models had mean AARD, R_{adj} and *F*-value equal to 8.83, 0.9078, and 425.22, respectively, for Sparks et al. model, and 9.39, 0.9084, and 681.50, respectively, for Bian et al. model. For the correlation of the solubility of Propyphenazone, the fit obtained with the Bian et al. model was better than the ANN method.

The following reasons support the superiority of neural network over empirical and semi-empirical correlations. As stated before, neural networks are generally weighed, thereby producing more accurate results for nonlinear problems. Moreover, final results of the ANN method are independent of the particular operating conditions [40]. Also, the correlation results in Table 11 revealed that the ANN method is more accurate than the regular solution model.

The cross plots where the experimental data (target) were compared to the calculated results using the neural network at differ-

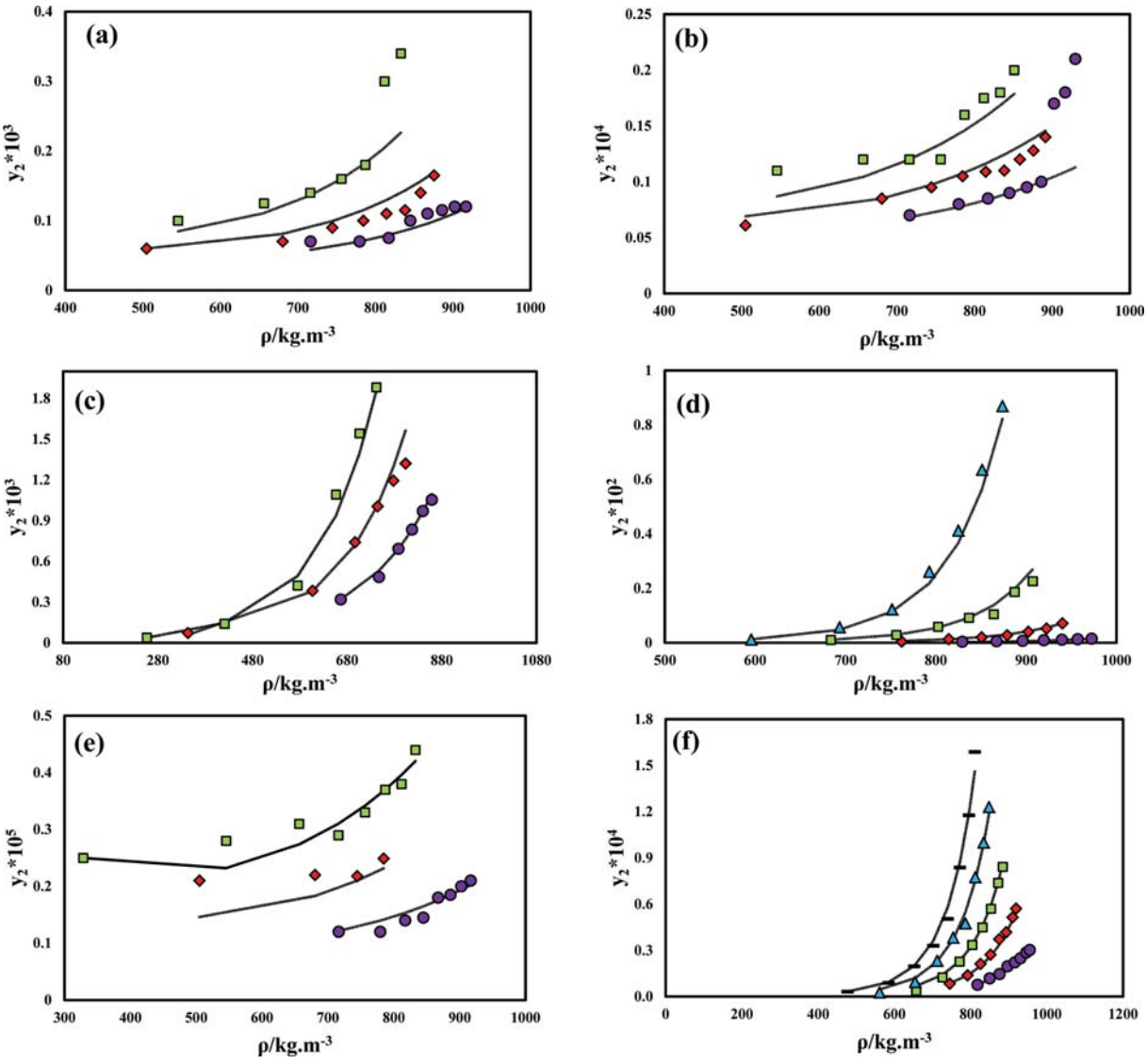

Fig. 6. Experimental and correlation results for solubility of (a) 2-phenyl-4*H*-1,3-benzoxazin-4-one (b) Azodicarbonamide (c) Propyphenazone (d) Sulindac (e) Thymidine (f) Capecitabine in SC-CO_2 using Bian et al. model (● 308 K ◆ 318 K ■ 328 K ▲ 338-348 K).

ent steps (training, validation and testing steps) are presented in Fig. 9, indicating that the predicted model fitted well fitted to the experimental data. The corresponding correlation coefficients to the training, validation, testing, and the entire datasets were found to be 0.92286, 0.85039, 0.9650,6 and 0.91999, respectively, which are satisfactory.

3. Comprehensive Comparison of All Models

In general, considering all of the results presented in sections 3.1 and 3.2 and Tables 5-11, the ANN represents the best method, in terms of accuracy, for correlating experimental solubility of pharmaceutical compounds in SC-CO_2. It should be emphasized that this method does not provide any predictivity due to lack of theoretical background.

CONCLUSIONS

Experimental solubility of solid drug in SCFs is a key factor in the design of pharmaceutical processing. However, given that such solubility data is lacking for most pharmaceutical products in SCFs, it should be estimated through correlations based on different models developed based the experimental data.

In this study, four different approaches were applied: cubic EoS, empirical and semi-empirical models, regular solution with the Flory-Huggins equation, and ANN. According to the results, SRK and modified-Pazuki EoSs with vdW2 and mrPR mixing rules were chosen for correlating the solubility of solid drugs. Given the importance of the values of physicochemical properties of solids, three different sets of solid properties were used. Correlation results for each compound were investigated and the combination of EoS, mixing rule and set of estimated properties associated with the highest accuracy was determined. In general, the effect of the choice of the contribution-group method (physical property estimation method) was ruled out upon using vdW2 and mrPR mixing rules; as such, vdW2 and mrPR mixing rules were chosen for EoS cal-

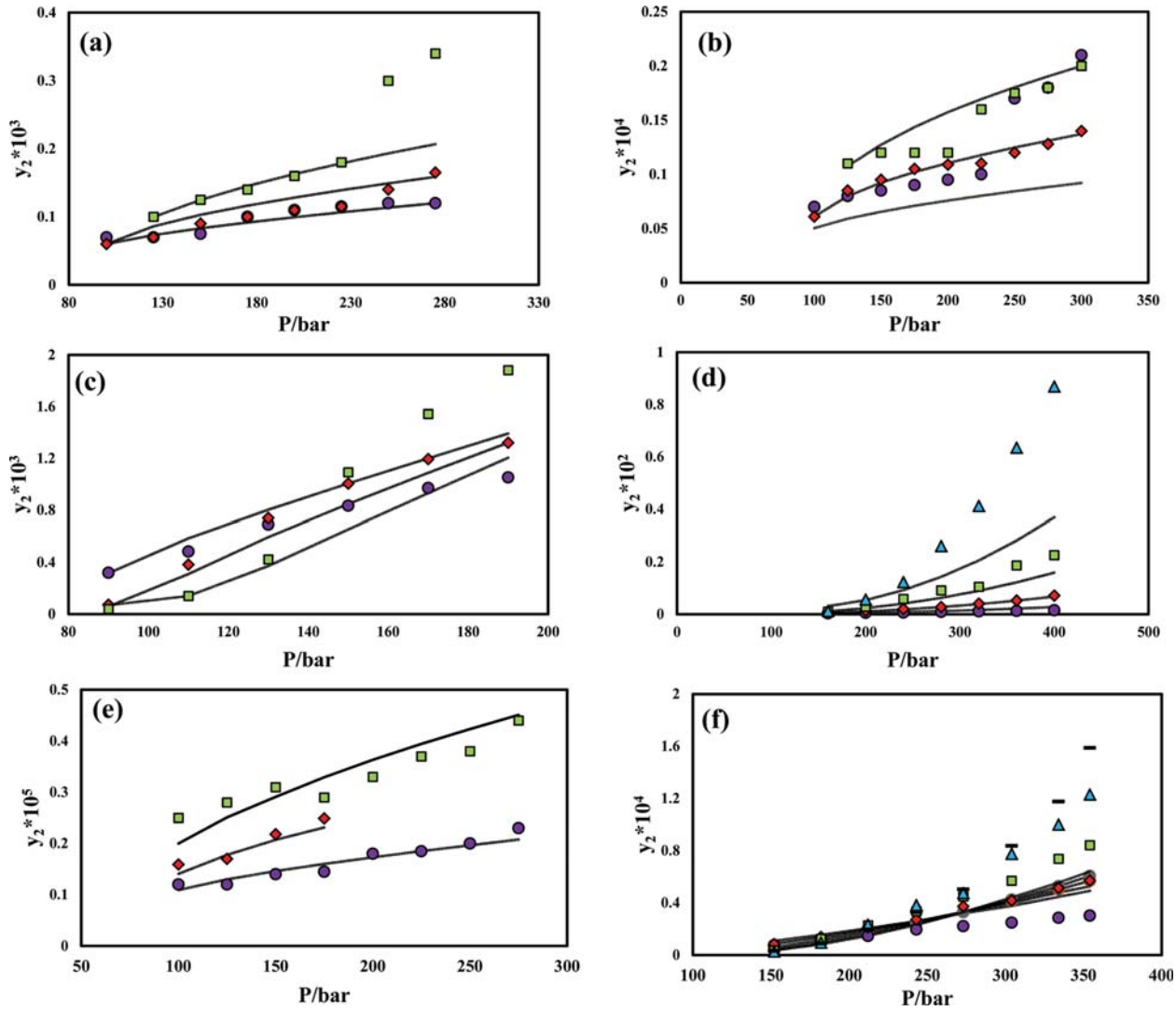

Fig. 7. Experimental and correlation results for solubility of (a) 2-phenyl-4*H*-1,3-benzoxazin-4-one (b) Azodicarbonamide (c) Propyphenazone (d) Sulindac (e) Thymidine (f) Capecitabine in SC-CO_2 using the regular solution model (● 308 K ◆ 318 K ■ 328 K ▲ 338-348 K).

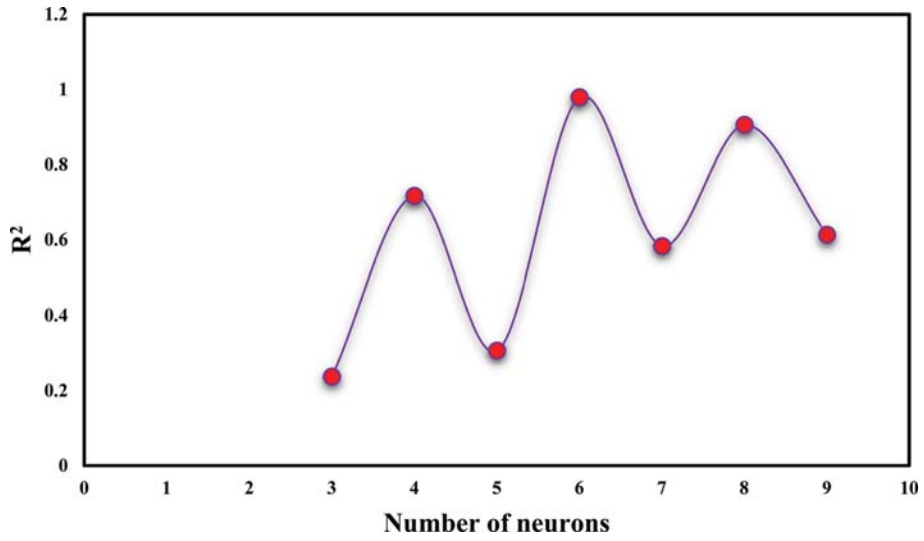

Fig. 8. R^2 of testing data vs. number of neurons in hidden layer.

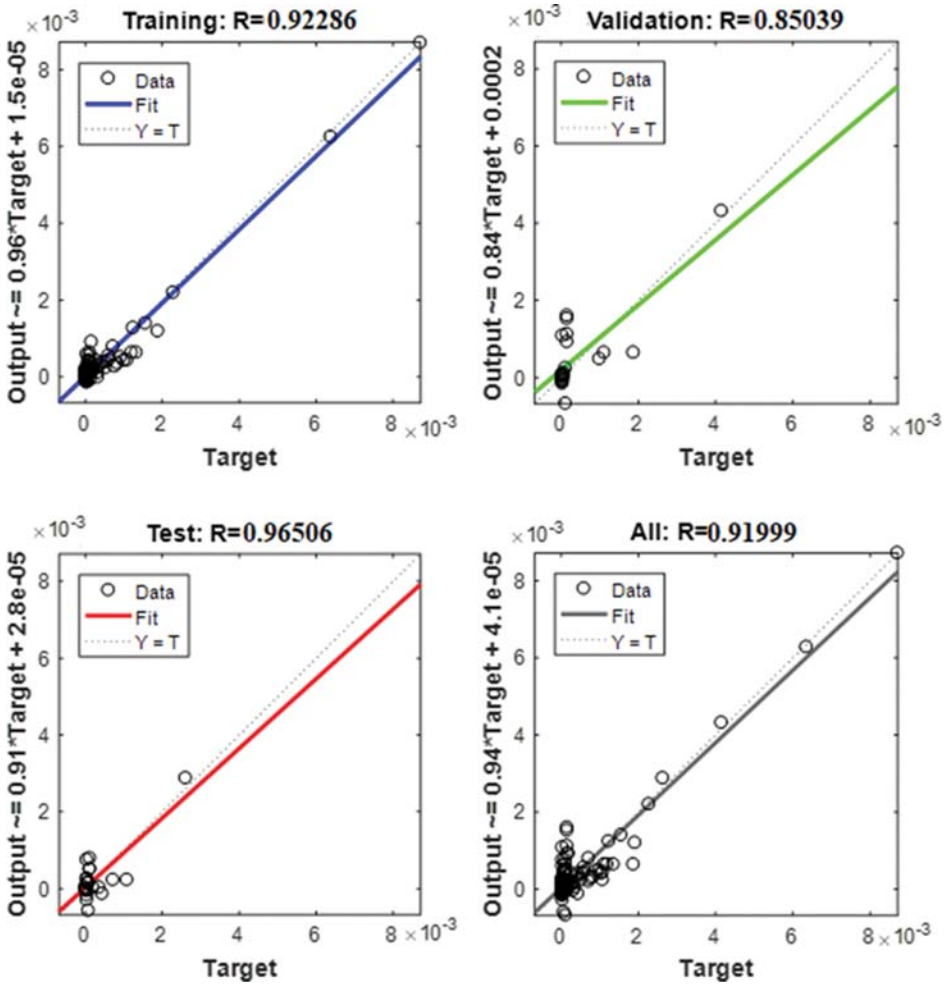

Fig. 9. The scatter diagrams that compare the experimental data (target) against the calculated neural network data in each step.

culations. Set 3 failed to produce appropriate estimation of physical properties of the pharmaceutical compounds used in this work. In the present study, SRK EoS outperformed the modified-Pazuki EoS.

Four popular empirical and semi-empirical models (Chrastil, Mendez-Santiago-Teja, Spark et al. and Bian et al. models) were applied to correlate the solubility of the solid drugs. Accordingly, Sparks et al. and Bian et al. models provided the lowest mean AARD values. But when it came to the solubility of Sulindac, MST model provided a better fit (AARD (%)=8.64), as compared to Sparks et al. and Bian et al. models (AARD (%)=8.77 and 10.93, respectively).

The results obtained with the regular solution model with Flory-Huggins equation were not as good as the best empirical or semi-empirical models (Sparks et al. and Bian et al. models), while the results obtained from the regular solution model were more accurate than those Chrastil and MST models as far as the solubilities of 2-phenyl-4*H*-1,3-benzoxazin-4-one and Thymidine were concerned.

Finally, comparing ANN to other models studied herein (EoS, empirical and semi-empirical models and the regular solution model), the ANN method outperformed the other models as it provided a better fit in these systems.

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NOMENCLATURE

Symbol

AARD : average absolute relative deviation
c : solubility of solute [g/L]
c_s : concentration of solute (g/L) in the collection vial
f_2^s : fugacity of pure solute in solid phase
f_2^l : fugacity of pure solute in supercritical phase

F(x) : transfer function
M_s : solute molecular weight [g/mol]
M_{CO2} : CO_2 molecular weight [g/mol]
MS_R : mean square regression
MS_E : mean square residual
N : number of data points
P : pressure
Q : number of independent variables
R^2 : correlation coefficient
R_{adj} : adjusted correlation coefficient
S : equilibrium solubility
SS_E : error sum of squares
SS_T : total sum of squares
T : temperature [K]
U : internal energy [cal/mole]
v_2^s : solid molar volume [cm^3/mol]
y_2 : molar fraction solubility of the solute
Z : number of curve-fitting parameters

Greek Symbols

Φ : fugacity coefficient
ρ : density [$kg \cdot m^{-3}$]
ρ_c : critical density
ρ_r : reduced density
ρ_{ref} : reference density
γ_2^∞ : activity coefficient
δ : solubility parameter $(cal/cm^3)^{0.5}$
ω : acentric factor

Superscripts

Exp : experimental value
Calc : calculated value
Sub : sublimation
SCF : supercritical phase
Vap : vaporization

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APPENDIX

Table A. The correlation results for the solubility of six pharmaceutical compounds in SC-CO_2 using Chrastil's model

Component	k	a	b	AARD (%)	*F*-value	R_{adj}
2-Phenyl-4*H*-1,3-benzoxazin-4-one	2.7458	−3699.0617	−7.4106	15.75	15.26	0.7513
Azodicarbonamide	2.4619	−3319.8880	−9.7219	12.58	7.50	0.5848
Propyphenazone	5.5250	−6342.8578	−15.2229	13.97	556.04	0.9924
Sulindac	11.9446	−17245.1819	−25.9574	10.08	342.99	0.9808
Thymidine	1.7600	−4989.3962	−0.6575	13.34	36.47	0.8881
Capecitabine	10.2790	−8044.3101	−45.7510	9.38	1291.12	0.9925

Table B. The correlation results for the solubility of six pharmaceutical compounds in SC-CO_2 using MST model

Component	A	B	C	AARD (%)	*F*-value	R_{adj}
2-Phenyl-4*H*-1,3-benzoxazin-4-one	−8921.7856	116828.9637	17.6389	18.87	13.06	0.7886
Azodicarbonamide	−7543.0956	86911.8548	12.6333	16.32	2.05	0.3340
Propyphenazone	−11541.2739	138397.9829	27.0492	10.47	426.31	0.9934
Sulindac	−25480.6347	269516.4496	60.7129	9.68	919.31	0.9951
Thymidine	−8514.4174	89459.0232	13.9915	22.05	3.66	0.5435
Capecitabine	−15049.9414	238893.6199	27.7194	10.13	506.21	0.9874

Table C. The correlation results for the solubility of six pharmaceutical compounds in SC-CO_2 using Sparks et al. model

Component	e_0	e_1	α	β	AARD (%)	*F*-value	R_{adj}
2-Phenyl-4*H*-1,3-benzoxazin-4-one	−1.6385	2.2566	7.6645	−16.4607	11.85	27.86	0.8423
Azodicarbonamide	0.9439	0.7522	−1.1370	−10.4096	11.77	10.58	0.6587
Propyphenazone	3.6286	1.0365	13.5567	−21.7376	10.70	446.62	0.9906
Sulindac	9.9063	0.7936	42.4073	−57.4805	10.23	418.35	0.9842
Thymidine	−0.1238	1.2049	3.2467	−15.6760	9.63	101.91	0.9560
Capecitabine	7.9996	1.0151	12.1770	−27.1071	9.30	1441.97	0.9933

Table D. The correlation results for the solubility of six pharmaceutical compounds in SC-CO_2 using Bian et al. model

Component	e_0	e_1	e_2	e_3	e_4	AARD (%)	*F*-value	R_{adj}
2-Phenyl-4*H*-1,3-benzoxazin-4-one	−2.7831	0.0034	−29.2176	−5.9673	6.4355	14.56	30.62	0.8539
Azodicarbonamide	−1.7409	0.0023	59.23	−4.0555	−1.9864	12.99	11.04	0.6675
Propyphenazone	2.0952	0.0042	37.22	−8.8256	−21.0332	8.44	264.12	0.9842
Sulindac	−0.5395	0.0088	−3139.8845	−17.1523	0.5572	13.31	953.72	0.9930
Thymidine	−2.1446	0.0012	−3833.9254	−1.2641	10.1865	10.42	102.31	0.9562
Capecitabine	−1.3493	0.00584	490.2901	−10.4370	−8.6298	9.97	2430.20	0.9960

Table E. The correlation results for the solubility of six pharmaceutical compounds in SC-CO_2 using the Regular solution model

Component	α	β	AARD (%)	*F*-value	R_{adj}
2-Phenyl-4*H*-1,3-benzoxazin-4-one	−0.4378	−5.7374	10.56	14.28	0.8026
Azodicarbonamide	−0.3288	−7.3143	15.30	1.64	0.2678
Propyphenazone	−0.3590	−6.0968	22.45	11.64	0.8078
Sulindac	−1.6219	4.1298	31.99	12.42	0.7479
Thymidine	−0.4379	−5.6674	8.19	54	0.9451
Capecitabine	−0.3709	−5.6751	31.76	12.29	0.6818