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An improved empirical model to calculate solute solubility in supercritical carbon dioxide

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To provide more accurate solubility predictions in supercritical carbon dioxide (SC-CO_2) using an empirical model employing density as an independent variable, the density of SC-CO_2 at different temperatures and pressures has been calculated and compared with experimental densities. The average percentage deviation (APD) has been determined as an accuracy criterion and the obtained APD for the equations studied were between 1.3 ($\pm$1.4)–11.6 ($\pm$8.9)%. To show the effects of density values on solubility prediction, the solubility of 18 drug compounds in SC-CO_2 has been calculated using an empirical equation with respect to temperature, pressure and density. The APD values for correlative analysis was 8.5 ($\pm$5.8)% for the most accurate density values calculated by BACK equation of state. A minimum number of experimental data (i.e. 6 points) has been used to train the model then the solubility at other temperatures and pressures has been predicted and the APD value for the most accurate densities obtained was 14.2 ($\pm$9.4)%. This prediction error could be considered as acceptable when it is compared with RSD values for repeated measurements ($\sim$10%) and the proposed predictive method could be employed in industry to calculate the solubility of a drug using a limited number of experimental data.

1. Introduction

Supercritical fluids (SCF) are extensively used as extracting solvents, transporting media in chromatography, desorbing media in the regeneration of sorbents, reaction media in material processing and expanding fluids in the rapid expansion of supercritical solution (RESS) or gas antisolvent (GAS) processes. The knowledge of the solubility of a drug in SCF is an important consideration for the SCF process design. Collecting solubility data by experiment is time consuming and costly. *Ab initio* prediction of the solubility of drugs in SCF is not possible at the present and research on predictive procedures is continuing. As a solution, it is possible to train an empirical model employing a limited number of experimental solubility data and then predict the solubility at other temperatures and pressures of interest. A number of empirical equations have been proposed to calculate the solute solubility with respect to temperature, pressure and density as independent variables. Most of these equations have recently been reviewed and compared [1]. In addition to the empirical equations, various equations of state have also been employed in different publications [2–5] for modeling the solubility data. The complex calculations and a number of physico-chemical properties required with the equations of state are the main limitations of these equations in pharmaceutical industry where researchers are interested in a simple and easy to use methods.

Supercritical carbon dioxide (SC-CO_2) is the most popular and widely used SCF, because it is a non-toxic, non-flammable, easy to obtain and a low costly solvent. It possesses low critical temperature and pressure which makes SC-CO_2 an appropriate fluid for thermolabile compounds like pharmaceuticals and our study is restricted to this particular fluid. In this communication, the effects of density of pure SC-CO_2 calculated on the prediction capability of drugs solubility have been studied using a model employing density of SC-CO_2 as an independent variable by an empirical equation [1] and an equation of state [6]. To choose the most accurate equation of state to compute the density of SC-CO_2, the experimental density values of SC-CO_2 ($N = 192$) at temperatures of 300–450 K and pressures of 80–450 bar have been collected from a reference [7] and the densities calculated have been compared with the corresponding densities experimentally obtained. Then the solubility of 18 pharmaceutical compounds in SC-CO_2 [8–15] has been employed to compare the accuracy of an equation [1] employing density values calculated by either an empirical model or an equation of state.

2. Investigations, results and discussion

2.1. Computational methods

The simplest empirical equation to correlate density of SC-CO_2 (ϱ) to temperature (T) and pressure (P) is:

$$\ln \varrho = -27.091 + 0.609\sqrt{T} + \frac{3966.170}{T} - \frac{3.445P}{T} + 0.401\sqrt{P} \qquad (1)$$

Table 1: Average percentage deviation (APD) for different equations of state provided in PE freeware [6] to calculate density of SC-CO_2

No.	Equation of state	APD	S.D.
1	Van der Waals	11.6	8.9
2	Peng-Robinson	11.0	19.1
3	Soave-Redlich-Kwong	6.7	4.4
4	Redlich-Kwong	4.1	4.1
5	Dohrn-Prausnitz	2.7	3.1
6	Elliot-Suresh-Donohue	8.3	4.6
7	PR-VT, Mathias	2.0	2.7
8	BACK	1.3	1.4
9	Saft-ConvexBody	1.3	1.4
10	Saft-Conventional	3.7	10.0
11	SRK-VT, Peneloux-3P	3.7	3.5
12	SRK, Mathias-Copeman	7.2	4.4
13	SRK, heavy hydrocarbons	6.6	4.4
14	Anderco, linear	2.9	3.1
15	Patel-Teja	2.5	2.8
16	Trebble-Bishnoi	3.4	2.9
17	CPA-PR (a,b,om)	2.0	2.7
18	SAFT-HR/vdw	3.7	10.0

The model has been developed [1] employing experimental densities at different temperatures and pressures ($N = 192$) [7]. In addition to this empirical model, in a computer software provided as an online program (PE freeware) by Brunner's research group, a number of equations of state was presented to calculate the density of SC-CO_2 [6]. A list of the equations is shown in Table 1 and for more details of these equations, readers could be referred to the guidebook of the program [6]. These calculations provide an interpolation method to calculate the density of SC-CO_2 at temperatures and pressures of interest. The calculated density values are employed to compute drug solubility in SC-CO_2 by an empirical equation proposed in a recent work [1]. The model is:

$$\ln y_2 = K_0 + K_1 P + K_2 P^2 + K_3 PT + \frac{K_4 T}{P} + K_5 \ln \varrho \quad (2)$$

where y_2 is the solute mole fraction solubility in SC-CO_2, $K_0 - K_5$ are the model constants and ϱ is the density of pure SC-CO_2 at different pressures and temperatures [1].
The calculated densities and/or solubilities were compared with experimental (observed) values and the mean of the absolute percentage deviation (APD) was calculated as an accuracy criterion. The APD was calculated using:

$$\mathrm{APD} = \frac{100}{N} \sum \frac{|\text{calculated} - \text{observed}|}{\text{observed}} \quad (3)$$

where N is the number of data points in each set. All calculations carried out using SPSS software (version 10).

2.2. Results and discussion

The calculated density values using eq. (1) have been employed to calculate the corresponding APD value. The obtained APD and its standard deviation is $10.5 \pm 8.8\%$. This value shows that the model fits well the experimental density data. The calculated APD values for the equations of state studied in this work have been presented in Table 1. As shown, the APD of eq. (1) lies within those of equations of state where some of the equations of state produced APD values higher than that of eq. (1) and most of them produced less APD's. Careful examination of APD values in Table 1 reveals that the BACK and SAFT-ConvexBody equations of state are the most accurate equations ($\mathrm{APD} = 1.3 \pm 1.4\%$) for calculating the density of pure SC-CO_2. These two equations produced the same accuracy as expected, because the BACK equation could be obtained from the SAFT-ConvexBody equation by setting all m parameters of the equation to unity [6]. More details of these equations have been explained elsewhere [6].
The experimental solubility data of 18 different solutes of pharmaceutical interested in SC-CO_2 have been fitted to eq. (2) using density values calculated by eq. (1) and BACK equation of state. The calculated solubilities have been used to compute the APD values for different solutes. This method has been called correlative analysis.

Table 2: List of solutes studied in this work, the reference for experimental data, number of data points (N), and average percentage deviations (APDs) for correlative and predictive analyses for eq. (2)

No.	Analyte	Ref.	APD for correlative analysis			APD for predictive analysis		
			N	Empirical	Back	N	Empirical	Back
1	p-Acetoxyacetanilide	[8]	16	18.9	12.9	10	25.2	15.5
2	Caffeine	[9]	24	2.9	2.9	18	8.1	5.1
3	beta-Carotene	[10]	27	18.5	18.7	21	22.7	23.3
4	Ketoprofen	[11]	15	12.4	6.0	9	31.9	14.1
5	Nicotinic acid	[8]	17	9.6	6.3	11	13.4	9.9
6	Penicillin G	[2]	18	11.8	10.9	12	22.0	16.9
7	Piroxicam	[12]	9	7.2	2.3	3	19.6	5.1
8	Pyrocatechol	[13]	32	5.1	5.5	26	19.5	15.6
9	Resorcinol	[13]	32	2.3	3.8	26	7.4	10.9
10	Retinol	[14]	20	6.7	6.5	14	8.5	8.7
11	Sulfadimethoxine	[15]	19	19.3	13.4	13	98.3	30.5
12	Sulfamerazine	[15]	18	22.7	18.4	12	80.9	39.1
13	Sulfamethazine	[15]	20	6.1	4.3	14	28.3	7.0
14	Theobromine	[9]	23	3.6	4.4	17	4.1	8.1
15	Theophylline	[9]	24	4.7	4.4	18	5.9	5.5
16	Vitamin D_2	[14]	19	4.0	7.3	13	7.7	11.2
17	Vitamin D_3	[14]	23	19.8	20.3	17	25.9	23.1
18	Vitamin K_1	[14]	24	7.4	5.0	18	15.9	7.0
			Mean	10.2	8.5		24.0	14.2
			SD	6.8	5.8		25.2	9.4

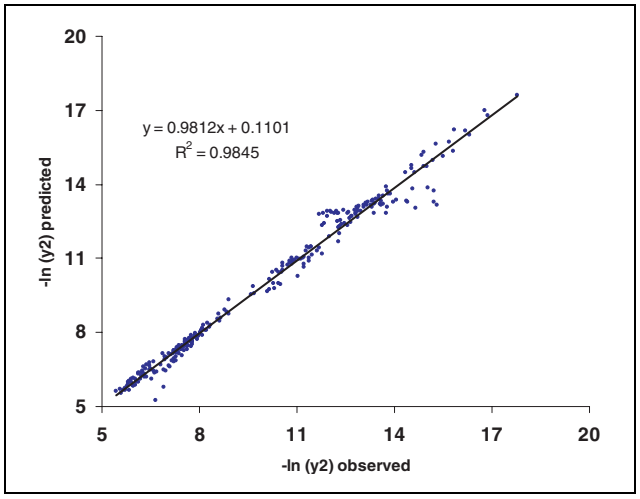

Fig. 1: Plot of predicted $-\ln(y_2)$ by eq. (2) versus observed $-\ln(y_2)$ for density values calculated by eq. (1)

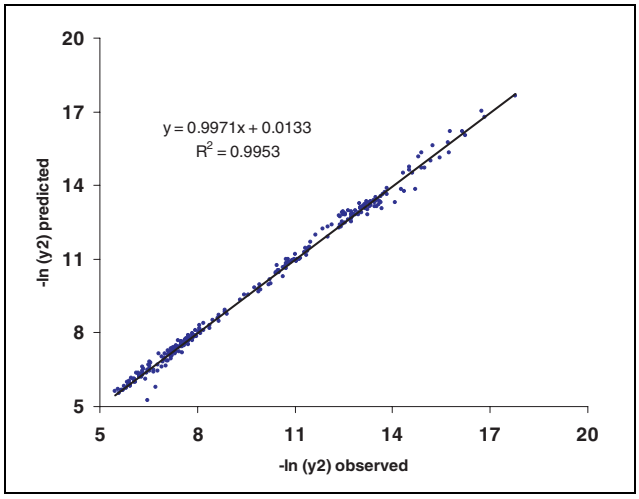

Fig. 2: Plot of predicted $-\ln(y_2)$ by eq. (2) versus observed $-\ln(y_2)$ for density values calculated by BACK equation of state

The obtained APDs of eq. (2) for two density sources are shown in Table 2. The mean APDs for correlative analysis are 10.2 ($\pm$6.8) and 8.5 ($\pm$5.8) for eq. (1) and BACK equation of state, respectively. The mean difference between APDs is evaluated using a paired t-test and the results show that the mean difference is statistically significant ($t = 2.4$, $p < 0.03$). This means that by using accurate densities, more accurate correlation is provided and it is obvious that such a model provides more accurate predictions.

To assess the effects of densities employed from eq. (1) and BACK equation of state on the prediction capability of eq. (2), six experimental solubility data points at two temperatures (the highest and the lowest) and three pressures (the highest, the middle and the lowest) have been used to train the model, then the solubility at other data points were predicted using the trained model. This method has been called predictive analysis and has been done for density values from eq. (1) and BACK equation of state. The obtained APDs are also shown in Table 2. The overall APD for the studied cases are 24.0 ($\pm$25.2) and 14.2 ($\pm$9.4) for eq. (1) and BACK equation of state, respectively. As expected the cases producing high APD for correlative analysis, have produced high APD for predictive analysis. The mean difference between two overall APDs is statistically significant ($t = 2.4$, $p < 0.03$). This prediction error (14.2%) could be considered acceptable when it is compared with the relative standard deviations of around 10% for repeated solubility measurements [16]. Although, the produced predictive APD is slightly higher than RSD values, the estimated solubilities are sufficient for process design in SCF technology using a reduced set of experimental data.

Figs. 1 and 2 show the predicted $-\ln(y_2)$ versus observed values for eq. (2) employing density values calculated by eq. (1) and BACK equation of state. In Fig. 1, $R^2 = 0.9845$, $F = 17168$, $N = 271$ and the sum of squared residuals is 39.6, whereas the corresponding values for Fig. 2 are: $R^2 = 0.9953$, $F = 56956$, $N = 271$ and the sum of squared residuals is 12.1. The high R^2 and F values and the low sum of squared residuals for the BACK equation of state indicate that density values calculated using this equation provide more accurate solubility predictions by eq. (2). This could also be justified from small APD values from Table 2.

In conclusion, the density values for pure SC-CO_2 could be calculated by the BACK equation of state. The accurate densities are able to improve the solubility prediction capability of a previously proposed model (i.e. eq. (2)) by a factor of 1.7 and this prediction method could be employed in pharmaceutical industry to speed up the technology design of a SCF process.

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