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A simple correlation to predict drug solubility in supercritical carbon dioxide

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ABSTRACT

The availability of easy correlation of drug solubility in supercritical fluids without time-consuming calculations and difficult is crucially important for improvement of supercritical technology in pharmaceutical industries. This work proposes a new correlation to predict drugs solubility in CO_2. The main advantages are its simplicity and minimal input data, namely temperature and density. The proposed drug solubility correlation in CO_2 has better performance (lower AARE%) respect to eight other empirical equations. Due to data sets, the mean AARE for the proposed model was 6.88%.

1. Introduction

Nowadays, supercritical fluids (SCFs) technology has wide usages in different industrial fields such as chemical process and processing of pharmaceuticals due to non-toxic, non-flammable and high mass and heat transfer [1]. The solubility of drug in SCF is significant information for designing the operating conditions such as RESS (Rapid Expansion of Supercritical Solutions) [2], SAS (Supercritical Anti-Solvent) [3], SEDS (Solution Enhanced Dispersion by Supercritical fluids) [4], and PGSS (Solution Enhanced Dispersion by Supercritical fluids) [5]. However, it is necessary to obtain reliable experimental solubility in supercritical region to prevent disturbance to the equilibrium [6]. A correlation for estimating the solubility of drugs in $scCO_2$ would be very beneficial for the preparatory design of related processes.

Many methods were employed to provide correlations the experimental solid solubility in $scCO_2$. They are able to correlate and predict these types of experimental data can be classified as being either equation-of-state based correlations or density based correlations like semi-empirical models; however, semi-empirical models compared to equation-of-state correlations due to their relative ease of usage are often utilized and it is not needed to employ physicochemical properties such as critical properties and sublimation pressure that cannot be directly obtained experimentally and should be calculated by various methods [7].

In the present work, the accuracy of a simple explicit correlation using 31 previously published solubility data series of different drugs in $scCO_2$ were investigated. The correlation was proposed based on temperature, density and evaluated and compared with Chrastil [8], Sung and Shim [10], Adachi and Lu [11], Spark [12], Gordillo [13], Mèndez-Santiago and Teja [14] and Keshmiri [15] models by correlation of the solubility for the drugs. The results show that the proposed drug solubility correlation works much better than the others (lower AARE%).

2. Theoretical section

2.1. Empirical correlations

There are several correlations to predict the solid solubility in $scCO_2$, such as empirical correlations. These models are density based methods that the effects of temperature and pressure are both considered and also indicate that there is a linear relationship between solvent density and experimental data. The first model that commonly used to correlate the solid solubility in $scCO_2$ was developed by Chrastil [8]. This equation is given as follows:

$$\ln S = A_1 + \frac{A_2}{T} + A_3 \ln \rho \quad (1)$$

where S is the solubility ($kg\,m^{-3}$) of the species in $scCO_2$, ρ is the solvent density ($kg\,m^{-3}$), T is the temperature (K), A_1, A_2 and A_3 are characteristic constants for the binary system that depend to molar mass of the solute.

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Table 1
The reported details of solutes in supercritical CO_2.

System no.	Solute	Temperature (K)	Pressure (bar)	N	Reference
1	Anastrozole	308–348	122–355	45	[16]
2	Atorvastatin	308–348	122–355	45	[1]
3	Atropine	308–348	122–355	45	[17]
4	Benzocaine	308–348	122–355	40	[18]
5	Bisacodyl	308–348	122–355	39	[19]
6	Budesonide	308–348	122–355	21	[20]
7	Clozapine	308–348	122–355	27	[21]
8	Codeine	308–348	122–355	44	[17]
9	Exemestane	308–348	122–355	45	[16]
10	Lovastatin	308–348	122–355	45	[1]
11	Medroxyprogesterone Acetate	308–348	122–355	40	[22]
12	Naproxen	308–348	122–355	58	[18]
13	Nimodipine	313–333	100–250	21	[23]
14	Nitrendipine	333–373	117–300	42	[24]
15	Flurbiprofen	308–323	89–245	27	[25]
16	Retinol	313–353	200–350	20	[26]
17	Squalane	303–328	79–275	34	[27]
18	Theophylline	313–353	199–349	24	[28]
19	Vitamin D2 (ergocalcifero)	313–353	200–300	19	[26]
20	Vitamin E (α-Tocopherol)	313–353	199–349	24	[26]
21	Vitamin K1	313–353	200–350	24	[26]
22	Simvastatin	308–348	122–355	45	[1]
23	Fluvastatin	308–348	122–355	45	[1]
24	Rosuvastatin	308–348	122–355	45	[1]
25	Beclomethasone dipropionate	338–358	213–385	21	[20]
26	Ketoconazole	308–348	122–355	45	[29]
27	Clotrimazole	308–348	12.2–355	45	[29]
28	Cefixime trihydrate	308–328	183–335	18	[30]
29	Oxymetholone	308–328	183–335	18	[30]
30	Desoxycorticosterone acetate	308–348	122–355	45	[31]
31	Clobetasol propionate	308–348	122–355	45	[31]

Bartle et al. [9] semi-empirical model to correlate the solubility of solute in SCF is:

$$\ln\left(\frac{yP}{P_{ref}}\right) = A_1 + \frac{A_2}{T} + A_3(\rho - \rho_{ref}) \tag{2}$$

where P_{ref} (1 bar) and ρ_{ref} (700 kg m^{-3}) are reference pressure and density, respectively. A_1, A_2 and A_3 are empirical constants.

Sung and Shim [10] proposed an equation to correlate the solubility of solute in scCO_2 by adding a term to Chrastil's equation. The resulting equation expresses in the form of following empirical formula:

$$\ln\ y = A_1 + \frac{A_2}{T} + (A_3 + \frac{A_4}{T^2})\ln\ \rho \tag{3}$$

where y is the solubility in mole fraction and ρ is the CO_2 density(kg m^{-3}).

The next equation that is considered here was developed by Adachi and Lu [11]. They modified Chrastil's equation which led to the following expression:

$$\ln\ S = A_1 + (A_2 + A_3\rho + A_4\rho^2)\ln\ \rho + \frac{A_5}{T} \tag{4}$$

The fifth equation that that is considered here was recently suggested by Spark et al. [12] based on Adachi–Lu model [11] that provided an improved correlation:

$$\ln\ S = A_1 + (A_2 + A_3\rho + A_4\rho^2)\ln\ \rho + \frac{A_5}{T} + \frac{A_5}{T^2} \tag{5}$$

Gordillo et al. [13] model unlike the mentioned equations (Eqs. (1)–(5)) that do not comprise any term involving pressure, the pressure term was considered as given by following equation:

$$\ln\ y = A_1 + A_2P + A_3P^2 + A_4PT + A_5T + A_6T^2 \tag{6}$$

where P is the pressure (bar), y is the mole fraction of solute and T is the temperature (K).

Mèndez-Santiago and Teja [14] based on dilute solutions theory, the following equation were introduced:

$$T\ln(yP) = A_1 + A_2T + A_3\rho \tag{7}$$

The last of the empirical equations to correlate solute solubility, was Keshmiri et al. model [15] with input of temperature, pressure and density of pure supercritical CO_2. This equation is given as follows:

$$\ln y = A_1 + \frac{A_2}{T} + A_3P^2 + (A_4 + \frac{A_5}{T})\ln\rho \tag{8}$$

In all of the semi-empirical models, A_i coefficients are determined through data regression.

2.2. Description of simple correlation

Correlation of the experimental solubility data using previous equations was relatively resulted in poor outputs. So this research tried to present an approach to correlate solute solubility in CO_2 with high accuracy compare with other empirical method using density and temperature.

Eq. (8) presents the correlation for the estimation of solubility of drug as a function of density of CO_2 (ρ) and temperature (T) through multiple regression analyses. The unit of density (ρ) and temperature (T) are expressed in kg m^{-3}and Kelvin respectively. This new correlation has nine independent variables (A_1–A_9).

$$\ln\ y = \frac{A_1 + A_2/\rho + A_3/\rho^2 + A_4\ln\ T + A_5(\ln\ T)^2}{1 + A_6/\rho + A_7\ln T + A_8(\ln\ T)^2 + A_9(\ln\ T)^3} \tag{9}$$

In order to evaluate the proposed correlation compare with other models in calculation of solubility, the available solubility data of drugs in scCO_2 had been collected from the literatures and each model was used to them. Table 1 shows 31 binary solute scCO_2 systems also the experimental temperature and pressure ranges and data sources. The arithmetic average of the absolute values of