Different Approaches for the Modeling of the Solubility of Pharmaceutical Compounds in Supercritical Carbon Dioxide

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ABSTRACT

The empirical or theoretical approaches proposed for the modeling of the solubility in supercritical fluids present different drawbacks: the empirical models to their nature cannot be used for the extrapolation but only for the interpolation of experimental data. On the other hand, they do not need the knowledge of the pure component properties of the pharmaceutical compounds, but only of the carbon dioxide density.

Equation of state models allows the extrapolation of experimental solubility fitted data but they need the evaluation of the pure component properties of the pharmaceutical compounds: sublimation pressure or temperature and heat of fusion and some characteristic parameters typical of the used equation of state (critical temperature and pressure or characteristic temperature and pressure). This is the main drawback in the use of the EOS models since the use of group contribution methods often lead to unrealistic results.

All these solubility models can be used for correlation and not for the prediction.

Solvation theories were proposed for the correlation of partition coefficients between liquid and gas – liquid phases. An approach that combine the activity coefficient models with the solvation theories for the description of the solubility of solid compounds in supercritical carbon dioxide is presented.

INTRODUCTION

Supercritical carbon dioxide extractions have been widely used to separate and fractionate the valuable compounds in food and pharmaceutical processes [1]. In the last decade, the pharmaceutical particle formations using SCO_2, such as RESS [2–4], SAS [5–7], and PGSS [8–10] methods have received much attention as alternative precipitation methods to those with organic solvents. The knowledge of the solubility of pharmaceuticals in SCO_2 is essential for the design and the operations of the above mentioned SCO_2 methods. Experimental measurements on the solubility of these substances in SCO_2 provided essential information for the pharmaceutical end engineering process.

On the other hand, it is difficult to predict the solubility data from the solute structure because two main factors are involved: solute-solute interactions in the solid and solute-solvent interactions in SCO_2. While the solid interactions are commonly determined from endothermic or packing properties, the solute-solvent interactions are hardly determinable because different parameters affect their behavior i.e. pressure, density, temperature, polarity etc. model must be chosen. The different models proposed for the correlation of solid solutes solubility in SCO_2 [11-23] present many disadvantages. The equation of state needs large and

complicated computational methods and the knowledge of critical parameters (i.e. macroscopic critical properties). The empirical or density dependent equations cannot be used with confidence for the extrapolation. The semi empirical models like that proposed requires the enthalpy and temperature of fusion for the solid and the activity coefficient of the solute in solution. Also in this case often the models are used for correlation only. In the present paper the approach suggested allows the prediction of solubility for systems not considered in the original data base used for the definition of the model.

MODELS

Literature reports many correlations or predictions of solid solutes solubility in SCO_2 using equations of state, empirical or semi empirical equations [11–22].

In the equation of state approach [11- 13] the solubility is given by:

$$y_2 = \frac{p_2^{sub}}{P\hat{\varphi}_2^{sf}} exp\left[\frac{v_2^s}{RT}\left(P - p_2^{sub}\right)\right] \quad (1)$$

where the subscript 2 refers to the solid component; v_2^s and p_2^{sub} are the molar volume and the sublimation pressure of component 2 and $\hat{\varphi}_2^{sf}$ is the fugacity coefficient of the component 2 in the supercritical fluid and must be calculated using an equation of state. Alternatively the solubility can be expressed with reference to sub cooled liquid:

$$y_2 = \frac{f_{20}^l(T,P)}{P\hat{\varphi}_2^{sf}} exp\left[\int_{P_0}^{P} \frac{v_2^s - v_2^l}{RT} dP + \frac{\Delta h_2^f}{RT_2^f}\left(1 - \frac{T_2^f}{T}\right)\right] \quad (2)$$

where f_{20}^L is the fugacity of the component 2 in the liquid state at the temperature of the systems and the triple point pressure (since the triple point pressure P_0 is normally very low this corresponds to the vapour pressure), Δh_2^f and T_2^f are the heat of fusion and the melting point of the component 2.

The most used equation of state for the evaluation of the fugacity coefficients is the well-known Peng-Robinson cubic equation of state where the two parameters a and b are given through the simple Van der Waals mixing rules:

$$a = \sum_i^N \sum_j^N x_i x_j a_{ij} \qquad b = \sum_i^N \sum_j^N x_i x_j b_{ij} \quad (3)$$

$$a_{ij} = \sqrt{a_i a_j} \cdot (1 - k_{ij}) \qquad b_{ij} = \frac{b_i + b_j}{2} \cdot (1 - l_{ij}) \quad (4)$$

where x is the molar fraction and k_{ij} and l_{ij} are the binary interaction parameters.

Parameters a_i and b_i are given by

$$a_i(T) = 0.457235 \cdot \frac{\alpha_i(T_{ri}, \omega_i) R^2 T_{ci}^2}{P_{ci}} \quad (5)$$

with

$$\alpha_i(T_{ri}, \omega_i) = [1 + (0.37464 + 1.54226\omega_i - 0.26992\omega_i^2) \cdot (1 - \sqrt{T_{ri}})]^2 \quad , \quad (6)$$

$$b_i = 0.077796 \cdot \frac{RT_{ci}}{P_{ci}} \quad (7)$$

ω is the acentric factor, T_c and P_c are the critical constants and T_r is the reduced temperature.
In the empirical equations the solubility is directly correlated to density and temperature using a number of empirical parameters. Among the different equations proposed two equations are chosen, the Chrastil and the Mendez-Santiago and Teja [18 - 23] equations.
The Chrastil equation is:

$$\ln c = k ln\rho + \frac{a}{T} + b \quad (8)$$

where c is the concentration of the solute is supercritical fluid with the unit of kg m^{-3}, ρ is the density (kg m^{-3}) of supercritical carbon dioxide, k, a and b are three adjustable parameters.
The Mendez- Santiago and Teja equation is:

$$Tln(y_2 P) = a + b\rho + cT \quad (9)$$

where y_2 is the mole fraction of the solid in the supercritical phase, P is the pressure and a, b and c are adjustable parameters
The solubility of the solid in CO_2 in terms of standard state fugacities is.

$$y_2 = \frac{1}{\gamma_2} \frac{f_2^{0S}(P^0)}{f_2^{0L}(P^0)} \quad (10)$$

where γ is the activity coefficient of the solute in solution. The ratio of the standard state fugacities is only dependent on the properties of the solute. Prausnitz et al. [24] have expressed this ratio in terms of measurable properties with

$$\frac{f_2^{0S}(P^0)}{f_2^{0L}(P^0)} = \frac{1}{RT^2} \int_{T_2^{tp}}^{T} \Delta h_2^{tp} dT + \int_{T_{tp}}^{T} \Delta C_{Cp,2}^{Tp} dT - \frac{1}{RT} \int_{P_2^{tp}}^{P^0} \Delta v_2^{tp} dP \quad (11)$$

where the superscript *tp* refers to the triple point, but can be replaced by the melting point T^f with little error. ΔCp is the specific heat difference between drug in liquid and solid phase, Δv is the drug volume difference between the liquid and solid phase respectively. The terms that include ΔCp and Δv are much smaller than Δh^f and at moderate pressures, tend to cancel each other out, leaving a much simpler expression:

$$\frac{f_2^{0S}(P^0)}{f_2^{0L}(P^0)} = \exp\left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right)\right] \quad (12)$$

Combining eq 10 with eq 12:

$$y_2 = \frac{1}{\gamma_2^{\infty}} \exp\left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right)\right] \quad (13)$$

Since the solubility in CO_2 is low, we assume that γ is independent of concentration and equal to γ_2^{∞}.
Recently Su et al. [22] proposed to use the equation (3) with the activity coefficient expressed by the modified regular solution model coupled with the Flory-Huggins term:

$$ln\gamma_2^{\infty} = \left(\frac{v_2}{RT}\right)(\delta_1 - \delta_2)^2 + 1 - \left(\frac{v_2}{v_1}\right) + ln\left(\frac{v_2}{v_1}\right) \quad (14)$$

where v and δ are respectively the molar volume and the solubility parameter that can is defined by:

$$\delta_i = \left(\frac{\Delta U_i^{vap}}{v_i}\right)^{0.5} \quad (15)$$

where ΔU_i^{vap} is the molar internal energy of vaporization.

In the proposed approach the v and δ values for the supercritical carbon dioxide are calculated using different equations of state, the heat of fusion and the internal energy of vaporization for the solute are calculated using respectively Yalkowski [25] and Fedors [26] group contribution methods and v_2 is taken as adjustable parameter calculated by regression of experimental solubility data for each system. The authors found that v_2 can be conveniently given by:

$$lnv_2 = \equiv \alpha ln\rho + \alpha \quad (16)$$

where ρ is the density of supercritical carbon dioxide and α and β are two adjustable parameters. This approach will be referred in the following as "Chen two par." Assuming a constant value for β = -12.89 the model defined as "Chen 1 par." is obtained.

The activity coefficient can be expressed with the reduced LFER Abraham equation [27 - 35] considering only the hydrogen bond acidity, the dipolarity/polarizability descriptors and McGowan's volume:

$$ln\gamma_2^{\infty} = Ee + aA + sS + vV \quad (17)$$

The *e*, *a*, *s* and *v* coefficients are obtained by fitting experimental solubility data for different drugs in supercritical carbon dioxide.

Since the *ln y* should theoretically be linearly related to the density of CO_2 and we use the relationship between activity coefficient and the partial molar volume $\overline{v}_2$ proposed by Eckert et al. [15].

$$\overline{v}_2 = v_2^S - AZRT\rho \quad (18)$$

A is an adjustable parameter, Z is the compressibility factor, v_2^S is the solid molar volume of the drug.

$$A = c + v_1 V + s_1 S - \left(\alpha \frac{T_2^f}{T}\right) \quad (19)$$

Where *c* and ɑ are the constants.

Combining the different equations, the solubility can be calculated as:

$$\ln y = \left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right)\right] - ln\gamma_2^{\infty} + A\rho_r \quad (20)$$

RESULTS AND DISCUSSION

The different approaches described present different drawbacks. The equation of state needs large and complicated computational methods and the knowledge of critical parameters (i.e. macroscopic critical properties) and the calculation of these values for the pharmaceutical compounds is sometimes questionable to the very large differences in the values obtained using the different group contribution methods.

The empirical models due to their less theoretical background cannot be used to extrapolate data in ranges of temperature and pressure different from those of the experimental data fitted.

The semi empirical models like that proposed requires the enthalpy and temperature of fusion for the solid and the activity coefficient of the solute in solution. Enthalpies of fusion data are abundant in the literature [22], or they can be quickly measured in a differential scanning calorimeter (DSC). Both semi empirical models described require the evaluation, by fitting

experimental solubility data, of a number of parameters. In this sense it seems that they are not presenting particular advantages respect to the other approaches.
In the approach proposed in this work the parameters of the model are evaluated by fitting contemporaneously the data of different systems pharmaceutical compounds - supercritical carbon dioxide. In particular the solubility of 39 drugs for about 400 solubility data are fitted in order to obtain the solvation parameters. These solvation parameters can be used for the estimation of the solubility of solid compounds in supercritical carbon dioxide provided that melting properties and characteristics pure component parameters are known.
Table 1 reports a comparison between the different models (for sake of brevity data are reported only for a selected number of componds). It is interesting to observe that the proposed method gives AAD % deviations of the same order respect to the others despite that

Solute	**EOS**	**This work**	**Chen two par.**	**Chen 1 par.**	**Chrastil**	**Santiago Teja**
Aspirin	61.28	12.34	11.5	19.7	5.2	4.7
Budesonide	20.89	28.02	11.5	17.3	11.5	11.2
Caffeine	8.06	14.0	20.4	31.6	21.3	28.1
Chlorothalonil	23.14	33.7	22.6	23.7	19.8	19.6
Cholesterol	17.61	19.9	7.0	8.6	6.0	6.2
Cholesteryl acetate	25.83	24.27	15.4	24.9	10.1	9.3
Flurbiprofen	26.32	16.78	21.0	23.8	8.4	9.8
Medroxyprog.ace.	33.49	37.01	17.2	22.7	17.5	16.8
Vanillic acid	22.42	12.0	12.0	20.0	10.2	11.4

Table 1: Comparison (AAD %) between the different approaches

he is using “universal parameters” that means not specific for the particular system under consideration.

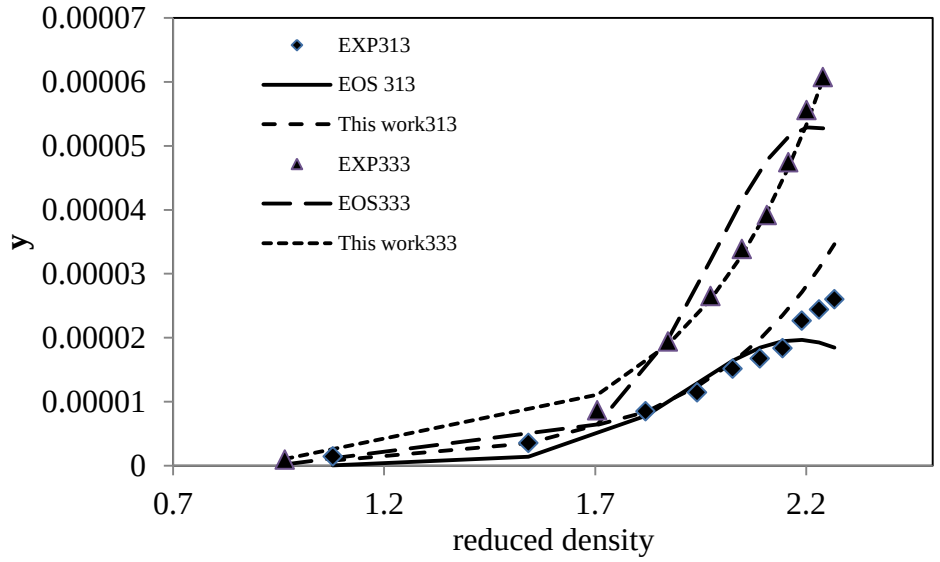

Figure1: Comparison between the EOS and the proposed approaches for the solubility of vanilic acid

In Figure 1 the results obtained with the Peng Robinson equation of state and the proposed model are compared. The proposed model is able to follow correctly the variation of the solubility with the reduced density whereas the equation of state gives an anomalous

maximum. Similar behavior is obtained for the solubility of aspirin (reported in Figure 2) where the equation of state presents relative large deviations, probably ascribed to the values

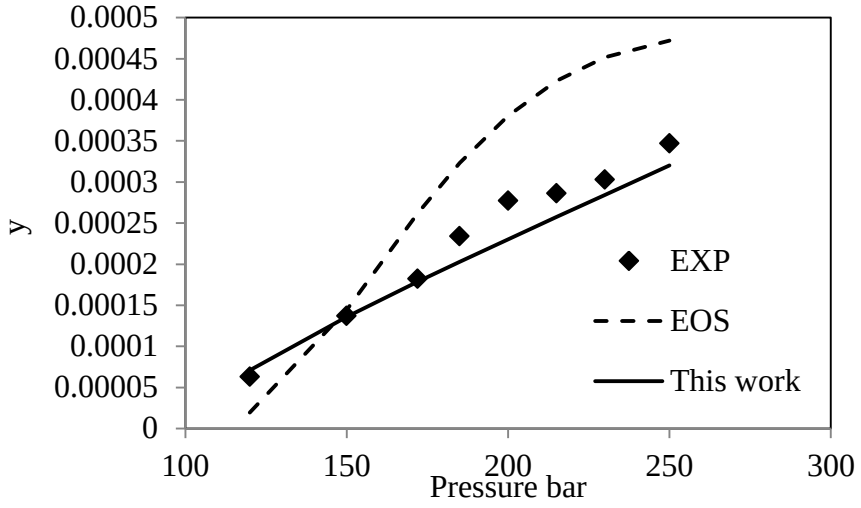

Figure 2: Solubility of aspirin at 328 K

of the critical properties of the drug.

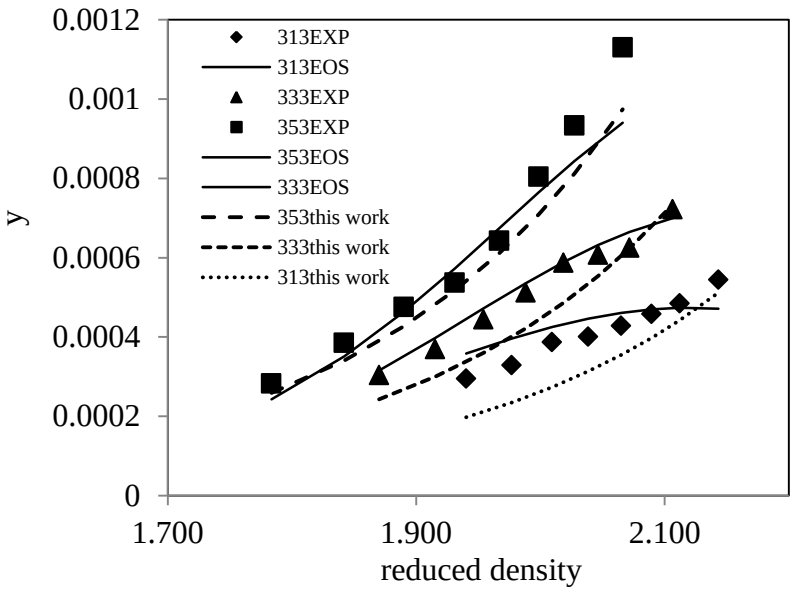

Figure 3: Caffeine solubility at three different temperatures

Figure 3 reports a comparison between the equation of state approach and that proposed for the description of the solubility of caffeine. It is interesting to notice that the new approach is able to describe correctly the effect of temperature on the solubility.

CONCLUSION

The new approach proposed for the correlation and the prediction of the solubility of pharmaceutical compounds in supercritical carbon dioxide compares satisfactory with the empirical and equation of state models. The main advantage presented by the method is the

need of pure component properties and the use of generalized constants.

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