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Solubility of pharmaceutical compounds in supercritical carbon dioxide

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ABSTRACT

The solubility of pharmaceutical solid compounds in supercritical carbon dioxide is of great importance in a wide range of applications that include: development of drug delivery systems, powder processing, and precipitation/crystallization processes.

This manuscript aims to estimate the solubility behavior of pharmaceutical compounds in supercritical fluids using an activity coefficient model based on linear solvation energy relationships. The parameters of this model were further generalized as a function of the properties of the pharmaceutical compounds. The selected compounds include antioxidants, antibiotics, steroids and anti-inflammatory and their solubility data were collected from literature.

This model is able to estimate the solubility of the pharmaceutical compounds in supercritical carbon dioxide within acceptable accuracy for more than 60% of the proposed systems.

1. Introduction

Supercritical fluids technologies in chemical processes have attracted much attention in recent years finding wide application also in pharmaceutical field. In particular, supercritical CO_2 (SCO_2) has been generally applied in extractions, purifications, separations [1,2] and crystal growth [3,4].

Carbon dioxide has been frequently used as supercritical fluid because of nontoxic and inflammable characteristics and the mild critical properties. Supercritical carbon dioxide extractions have been widely used to separate and fractionate the valuable compounds in food and pharmaceutical processes [5]. In the last decade, the pharmaceutical particle formations using SCO_2, such as RESS [6–11], SAS [12–16], and PGSS [17–21] 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.

Literature reports many correlations or predictions of solid solutes solubility in SCO_2 using equations of state [22–24], or semi empirical equations [25–31].

The equation of state needs large and complicated computational methods and the knowledge of critical parameters (i.e. macroscopic critical properties).

The semi empirical models like ours require 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 [32], or they can be quickly measured with a differential scanning calorimeter (DSC). Since the solubility of solids in liquids is usually insensitive to the quality of the solution model, an ideal solution model often performs adequately. For solids of low solubility solute–solvent interactions are significant, and an appropriate activity coefficient model must be chosen. In this paper, supercritical carbon dioxide is treated as an expanded liquid.

2. Method

The proposed model was based on 39 pharmaceutical molecules and 329 data points were collected from literature (Table 1). Among these solids, we included antioxidants, anti-inflammatories, steroidal substances, cardiogenic substances. The Newton's method was used to determine the parameters of each equation [33] and it was employed to perform the nonlinear regression analysis between experimental and theoretical data.

The activity coefficient drug parameters were taken from ADME database [61].

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Table 1
Data sources for solubility data.

Compound	References
9,10-Anthraquinone	[34]
Aspirin	[35]
Budesonide	[36]
Caffeine	[37]
Chlorthalonil	[38]
Cholesterol	[39]
Cholesteryl acetate	[39]
Cyproterone acetate	[40]
Codeine	[41]
p-Coumaric acid	[42]
Diazepam	[41]
Exemestane	[43]
Ferulic acid	[44]
Flurbiprofen	[45]
Ketoprofen	[46]
Lovastatin	[47]
Medrossiprogesterone acetate	[40]
Methyl gallate	[48]
Methylparaben	[49]
Methimazole	[50]
Naproxen	[51]
Nifedipine	[52]
Nimesulide	[46]
Nimodipine	[53]
Nitrendipine	[52]
Penicillin G	[54]
Progesterone	[55]
Propranolol	[50]
Protocatechualdehyde	[48]
Protocatechuic acid	[48]
Salicylic acid	[56]
Simvastatin	[47]
Stigmasterol	[57]
Sulfamerazine	[58]
Tebuconazole	[38]
Theobromine	[59]
Theophylline	[59]
Uracil	[36]
Vanillic acid	[60]

This method is a modified version of the Abraham's linear free energy relationship (LFER) correlation proposed by Bush and Eckert [25] incorporating S, the dipolarity/polarizability of the CO_2 at a given density.

This allowed us to model data at temperature closed to 313 K and pressure ranging from 100 to 500 bar, with $R^2 = 0.617$ in the logarithm of calculated solubility versus experimental one. The model shows that solubility in supercritical CO_2 is favored by the presence of S and hydrogen bond molecular acidity. Solute size and hydrogen-bond basicity are less important.

It is important to realize that the experimental data (especially when the drug is poorly soluble in CO_2) have a standard error of about 20%. Moreover in literature are reported many data at the same operative condition that showed different solubility values.

The Abraham's LFER approach needs five physicochemical properties or descriptors. In order to predict the properties of a series of solutes in a given solvent system (SP) the descriptors are combined to give the following LFER.

$$ln\,SP = c + eE + sS + aA + bB + vV \quad (1)$$

where E is the excess molar refraction, i.e., the molar refraction of the solute minus the molar refraction of an alkane of equivalent volume; S is a combined dipolarity/polarizability descriptor showing how polar or polarizable the species is; A is the total solute hydrogen bond acidity for the molecule; B is the total solute hydrogen bond basicity for the molecule; V is the McGowan characteristic volume [62].

The e, s, a, b and v coefficients can be regarded as constants for a given system and these contain the complimentary effects of the phase on the interactions. The e coefficient indicates the ability of the phase to interact with solutes via π and n electron pairs. The s coefficient gives the tendency of the phase to interact with dipolar/polarizable solutes and indicates how well the electrons in the solute will be polarized. The a and b coefficients are the hydrogen-bond basicity and the acidity of the phase respectively. The v coefficient is a combination of positive exoergic dispersion forces and a negative endoergic cavity term [63]. The numerical values of these coefficients are obtained by fitting experimental partition data.

In this work we considered only the S, A, E and V values as molecular descriptors and they are reported in Table 2.

In this formalism, the condition for equilibrium is that the fugacity of each component f_i must be equal in both phases. The subscript numbers 1 and 2 will be referred to CO_2 and pharmaceutical compound, while the superscripts S and L stand for solid and liquid, respectively. The solubility y_2 of the solute in CO_2 in terms of standard state fugacities, f_2^0, is,

$$y_2 = \frac{1}{\gamma_2}\frac{f_2^{0S}(p^0,T)}{f_2^{0L}(p^0,T)} \quad (2)$$

where γ_2 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. [64] have expressed this ratio in terms of measurable properties with:

$$\frac{f_2^{0S}(p^0,T)}{f_2^{0L}(p^0,T)} = \frac{1}{RT^2}\int_{T_2^{tp}}^{T}(\Delta H_2^{tp} + \Delta C_{p,2}^{Tp})dT - \frac{1}{RT}\int_{T_2^{tp}}^{P^0}\Delta v_2^{tp}\,dP \quad (3)$$

where the superscript tp refers to the triple point, but can be replaced by the solute melting point T_2^f with little error. $\Delta C_{p,2}$ is the difference in heat capacity of the liquid and solid solute phases; Δv is the pharmaceutical compound volume difference between the liquid and solid phase respectively and ΔH_2^f the solute enthalpy of fusion. The terms that include $\Delta C_{p,2}$ and Δv_2 are much smaller than ΔH_2^f and at moderate pressures, tend to cancel each other out, leaving a much simpler expression:

$$\frac{f_2^{0S}(p^0,T)}{f_2^{0L}(p^0,T)} = \exp\left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right)\right] \quad (4)$$

Combining Eq. (3) with Eq. (4):

$$y_2 = \frac{1}{\gamma_2^\infty}\exp\left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right)\right] \quad (5)$$

Since the solubility in CO_2 is low, we assume that γ_2 is independent of concentration and equal to γ_2^∞.

From the above equation we can assume that:

$$\ln\ y_2^\infty = \ln y_2 - \left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right)\right] \quad (6)$$

The activity coefficient can be expressed as a reduced LFER Abraham equation considering only the hydrogen bond acidity, the dipolarity/polarizability descriptors and the McGowan's volume:

$$\ln\ y_2^\infty = Ee + aA + sS + vV \quad (7)$$

The e, a, s and v coefficients obtained from fitting the values of Eq. (6), are reported in Table 3.

The $\ln y_2$ should theoretically be linearly related to the density of CO_2 ρ_1, and we use the relationship between activity coefficient and the partial molar volume $\bar{v}_2$ proposed by Eckert et al. [65].

$$\bar{v}_2 = v_2^s - AZRT_{\rho 1} \quad (8)$$