SOLUBILITY OF DIFLUNISAL IN SUPERCRITICAL CARBON DIOXIDE: EXPERIMENTAL DETERMINATION AND CORRELATION

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ABSTRACT

The solubility of diflunisal, a non-steroidal anti-inflammatory drug (NSAID), in supercritical carbon dioxide ($scCO_2$) was measured in the temperature range between 308.2 and 328.2 K and in the pressure range between 9 and 25 MPa, using a static analytical method. In addition, the experimental data was satisfactorily correlated by the employment of a cubic equation-of-state-based model (the Peng-Robinson cubic equation of state - PR-EOS - together with the conventional van der Waals mixing and combining rules).

INTRODUCTION

Diflunisal (5-(2,4-difluorophenyl)-2-hydroxy-benzoic acid) (Figure 1) is a salicylate derivative possessing antipyretic, analgesic and anti-inflammatory activities [1]. It belongs to the family of the non-steroidal anti-inflammatory drugs (NSAIDs) and it is commonly used to relieve mild to moderate pains and inflammations caused by arthritis or other inflammatory conditions. Although NSAIDs are amongst the most frequently used drugs in the world, their oral administration is often limited because of their potential to cause adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa [2]. These problems are mainly caused because of the poor water solubility of these type of drugs. For this reason, considerably efforts have been made for the development of newer and better formulations for oral delivery systems of NSAIDs. Some of the present investigated strategies include also supercritical-based processes namely in the field of particle generation using supercritical carbon dioxide ($scCO_2$) technologies [3-4], such as Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent (SAS) and Particles from Gas Saturated Solutions (PGSS).

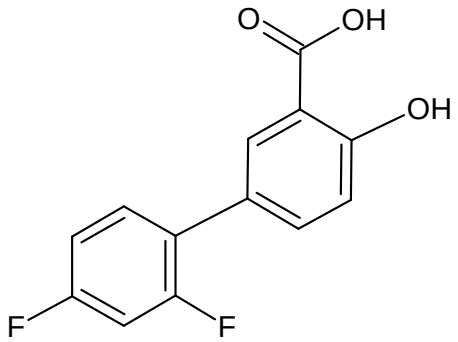

Figure 1. Chemical structure of diflunisal (5-(2,4-difluorophenyl)-2-hydroxy-benzoic acid).

The accurate knowledge of the equilibrium solubility of pharmaceutical products in the employed supercritical fluid (SCF), at different conditions of temperature and pressure, is indispensable for the design of any SCF-based process. Following our previous works [5-6] in which we have reported the experimental solubility of several different drugs in $scCO_2$, in the present work we present the experimental solubility of diflunisal in $scCO_2$, at different temperature and pressure conditions, using a static analytical method. We also present the correlation of the obtained experimental data by using the well-known Peng-Robinson cubic equation of state with the conventional van der Waals mixing and combining rules.

MATERIALS AND METHODS

Materials

Carbon Dioxide (CAS 124-38-9, purity > 99.998%) was purchased from Praxair, ethanol (CAS-64-17-5, purity > 99.5%) was obtained from Panreac Quimica SA and diflunisal (CAS 22494-42-4, 100% pure) was obtained from Sigma-Aldrich.

Experimental procedure

The solubility of diflunisal in $scCO_2$ was measured using a static analytic high-pressure apparatus, described in detail elsewhere [5-6]. The equilibrium solubility of the solid in $scCO_2$ is attained in a stainless steel equilibrium visual cell, with an internal volume of approximately 30 cm^3, immersed in a thermostatic water bath. The cell is initially loaded with the solid drug and a magnetic stirrer. Carbon dioxide is then pumped into the cell, using a high-pressure pump, until the desired operational pressure is attained. Pressure is measured with a high-pressure transducer, calibrated between 0 and 5000 psi. After stirring the mixture at a fixed temperature and pressure (for one hour), a small sample is taken through a six-port high-pressure sampling valve. This sample is quickly depressurized, with the gas being expanded into a calibrated balloon at room temperature. The amount of solubilized solid, which precipitates in the expansion lines and in a small glass trap, is later collected by washing (with ethanol) the lines and the glass trap. Later, this amount is posterior quantified using a UV-vis spectrophotometric method. The amount of CO_2 in each sample is calculated using the Virial equation-of-state and considering the observed pressure increase in the calibrated balloon, due to the performed expansion.

RESULTS

The obtained experimental mole fraction solubilities of diflunisal in $scCO_2$, at 308.2, 318.2, and 328.2K, and at pressures between 9 and 25 MPa, ranged between 0.54×10^{-6} and 8.07×10^{-6}. Each data point is the average of, at least, three replicate measurements with percentage relative standard deviations (RSD) values between 15.1% (T= 328.2 K, P= 9.1 MPa, $y_2= 0.54\times10^{-6}$) and 2% (T= 328.2 K, P= 19.3 MPa, $y_2= 4.59\times10^{-6}$).

The solubility of a solid solute (y_2) in equilibrium with a fluid at high pressure can be calculated using the following expression:

$$y_2 = \frac{P_2^{sub}}{P}\frac{1}{\varphi_2^{SCF}}\exp\left[\frac{v_2\left(P-P_2^{sub}\right)}{RT}\right] \quad (1)$$

In Equation (1), P_2^{sub}, is the sublimation pressure of the solid, v_2, is the molar volume of the solid and, φ_2^{SCF}, is the fugacity coefficient of the solid in the fluid phase. The fugacity coefficient is usually estimated by an equation-of-state. In this work, we used the well-known

Peng-Robinson cubic equations of state (PR-EOS) [7] and, to evaluate mixture parameters, the classical van der Waals (vdW) mixing rules with the conventional combining rules with two adjustable parameters. The binary interaction parameters, k_{12} and l_{12}, were obtained by fitting the experimental data through the minimization of the objective function average absolute relative deviation (*AARD*), defined as:

$$AARD(\%) = \frac{100}{N}\sum_{n}\frac{\left|y^{cal} - y^{\exp}\right|}{y^{\exp}} \qquad (2)$$

In this equation, N, is the number of experimental data points, y^{cal}, is the calculated solubility and y^{exp} is the experimental solubility.

To correlate the solubility of a solid in a SCF, and using Equation (1) and the PR-EOS, it is necessary to know the critical properties and acentric factors of the solid and SCF, as well as the sublimation pressure and molar volume of the solid. For carbon dioxide, the experimental values of these properties can be easily found in literature. On the contrary, for most organic solids these properties are unknown and must be estimated by correlations and/or by group contribution methods. In Table 1, we present the values of these calculated/estimated properties for diflunisal and the corresponding employed methods to calculate them.

Figure 2 shows the experimental data and the correlated curves obtained for the three investigated isotherms, using the PR EOS and the vdW mixing rules with two adjustable parameters (Fitted parameters: T= 308.2, k_{12}= 0.140, l_{12}= -0.081, *AARD*= 17.3%; T= 318.2, k_{12}= 0.194, l_{12}= 0.070, *AARD*= 20.6%; T= 328.2, k_{12}= 0.190, l_{12}= -0.071, *AARD*= 23.3%).

Table 1. Estimated critical and thermophysical properties of diflunisal.

				$10^4 \times P_2^{sub}$/Pa		
T_c/K	P_c/MPa	ω	$10^6 \times v_2$/m^3 mol^{-1}	308.2 K	318.2 K	328.2 K
869.8[a]	3.211[a]	0.897[a]	125.5[b]	0.33[c]	1.42[c]	5.63[c]

[a] Estimated by Constantinou-Gani (first order) method [8].
[b] Estimated by Fedors method [9].
[c] Experimental values [10].

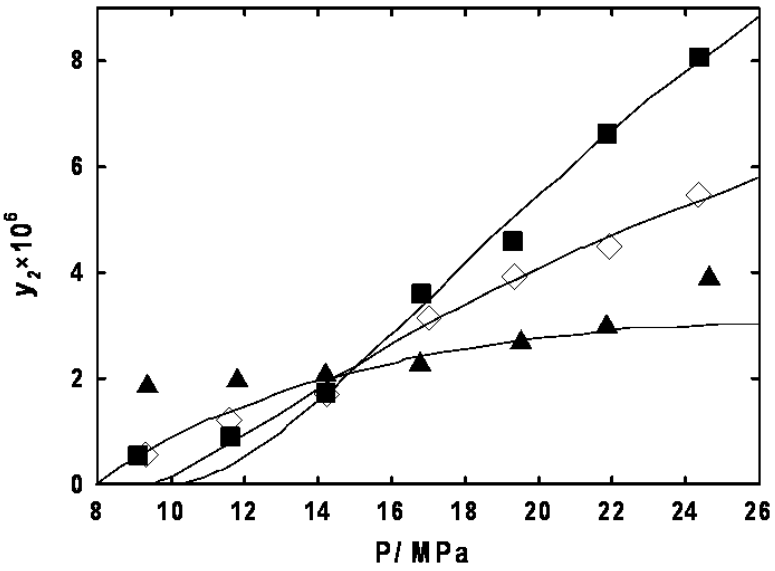

Figure 2. Mole fraction solubility of diflunisal in $scCO_2$. Experimental: 308.2 K (▲), 318.2 K (◊) and 328.2 K (■).(—) calculated with the PR EOS and the vdW mixing rules with two adjustable parameters.

CONCLUSIONS

The solubility of diflunisal in $scCO_2$ was experimentally determined at 308.2, 318.2 and 328.2, and at pressures between 9 and 25 MPa, using a static analytical method. A cubic equation-of-state model (Peng Robinson EOS), together with the classical van der Waals mixing rules, was used to correlate the obtained experimental data. Satisfactory correlation results were obtained.

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