Articles

Assessment of Solubility of Ketoprofen and Vanillic Acid in Supercritical CO_2 under Dynamic Conditions

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The use of supercritical fluids, and in particular supercritical carbon dioxide (SC-CO_2), can be foreseen in a wide range of techniques and processes within pharmaceutical sciences. When dealing with both drugs and formulation adjuvants, the determination of the relevant solubilities in SC-CO_2 represents a mandatory prerequisite, underlying the development of industrial scale operations. The aim of this work concerned the experimental determination of the solubility in SC-CO_2 of vanillic acid and ketoprofen by means of an easy-to-use plant designed and assembled to operate in dynamic conditions. Its reliability was preliminarily checked by comparing solubility data obtained for salicylic acid and naphthalene with literature ones. Solubility measurements for ketoprofen and vanillic acid were carried out at 313 and 328 K in the 9−25 MPa pressure range. Crossover pressures of 16 MPa and 15 MPa were found for ketoprofen and vanillic acid, respectively. The solubility data were worked out according to a thermodynamic approach, which relies on the Peng−Robinson equation of state.

Introduction

Pharmaceutical applications of supercritical fluids (namely, supercritical carbon dioxide, SC-CO_2) are presently limited to separation and fractionation processes. Some recent reports have been concerned also with the preparation of microparticles of different materials, for example, polymers (Bodmeier et al., 1995; Thies and Müller, 1998) and proteins (Winters et al., 1996). The use of supercritical fluids can easily be foreseen in a much wider range of techniques and processes within pharmaceutical sciences, involving for instance also the preparation of peculiar crystal forms (York and Hanna, 1994; Reverchon and Donsi, 1993; Reverchon et al., 1995). When dealing with both drugs and formulation adjuvants, the determination of relevant solubilities in SC-CO_2 represents a mandatory prerequisite, underlying the development of industrial scale operations. Several studies so far have been devoted to measuring this physicochemical parameter for chemical compounds representative of families of homologues (Gurdial and Foster, 1993; Kurnik et al., 1981) and to defining thermodynamic approaches which allow a better description, and/or prediction, of the solubility in a reasonably wide range of temperatures and pressures.

The present work concerns the experimental determination of solubility in SC-CO_2 of ketoprofen and vanillic acid by means of an easy-to-use plant designed and assembled to operate in dynamic conditions (Van Leer and Paulaitis, 1980). As a further improvement, a silica cartridge, placed along the outlet, allowed for an easy and accurate quantitative recovery of the solute.

The reliability of the assembled apparatus was preliminarily validated by comparing our and literature (Gurdial and Foster, 1991; Paulaitis and McHugh, 1980) data for naphthalene and salicylic acid, whose solubilities in SC-CO_2 in the pressure/temperature range explored differ by almost 2 orders of magnitude. The plant was then used to determine the solubilities of ketoprofen and vanillic acid, which are of interest for pharmaceutical and food preparations, respectively, at various temperatures and pressures. The solubility data were worked out according to a thermodynamic approach, which relies on the Peng−Robinson equation of state (PR-EOS). The use of such an EOS implies previous acquaintance with properties of the pure compounds that form the binary, like critical pressure and temperature, boiling point, and vaporization enthalpy, some of which were not known for ketoprofen and vanillic acid and had to be estimated as the result of "group contributions".

Experimental Section

Materials. CO_2 (S.I.A.D. SpA, Cinisello Balsamo, Italy), commercialized in cylinders equipped with a stripping device, was conveyed to the plant, where it was compressed and heated to supercritical conditions. The compounds to be solubilized were salicylic acid (Sigma Chemical Co.), ketoprofen (Carlo Erba, Milan, Italy), naphthalene (BDH

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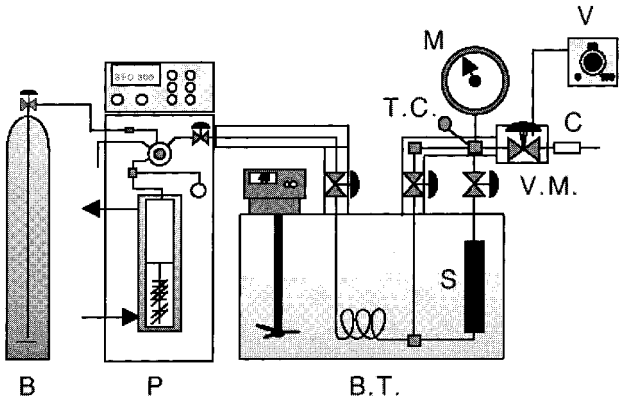


Figure 1. Schematic drawing of the apparatus assembled for solubility measurements with the dynamic method: B, CO_2 cylinder; P, SCF chromatography pump; S, saturation cell; B.T., thermostated bath; V.M., micrometric expansion valve; V, potentiometric thermoregulator; M, manometer; C, "Sep-pak Classic" cartridges.

Laboratory Supplies, Poole, U.K.), and vanillic acid (Sigma Chemical Co.). The solvents to prepare solutions for spectrophotometric determinations (double-beam JASCO UVIDEC 610 spectrophotometer) were methanol (BDH Laboratory Supplies, Poole, U.K.) and *n*-hexane (BDH Laboratory Supplies, Poole, U.K.). All materials were of 99.9% purity grade.

Apparatus. Figure 1 is a schematic drawing of the apparatus assembled to perform solubility measurements with a dynamic method. The main components were a CO_2 cylinder (B) equipped with a stripping device; a supercritical chromatography pump (P) (SFC 300, Carlo Erba) acting with a 150 mL syringe to allow SC-CO_2 fluxes in the 0.1−0.5 mL·min^{-1} range up to 45 MPa (maximum pressure); a 125 mL stainless steel saturation cell (S) and a 20 mL stainless steel coiled tube to preheat the solvent from entering the saturation cell, both immersed in a 60 L thermostated bath (B.T.), allowing a ±0.1 °C temperature drift; a refrigerating bath (CH-F3, Haake, Berlin, D) filled with ethylene glycol and equipped with an "Antidrift" system to control the temperature of the supercritical pump to within ±0.02 °C; an expansion valve (V.M.) (1666G4Y, Hoke, Cresskill, NJ) whose temperature could be manually tuned through a potentiometric thermoregulator (V); three shut-off valves; a ±0.05 MPa accuracy manometer (M) (Salmoiraghi SC 3200, Milan, Italy); and "Sep-pak Classic" cartridges (C) mod. "short" and "long" filled with silica (Waters, Milan, Italy), used as traps along the outlet line.

Methods and Procedures. The procedure followed to determine the solubility implied a previous thorough cleansing of the plant. The saturation cell was loaded with 15−20 mg of finely ground material mixed with glass fillers so as to form a noncompressible homogeneous bed. The plant pressure was finally raised by keeping the outlet valve closed in order to verify that no losses occurred. Thermostated baths and thermoregulators were switched on and stabilized before starting each determination. The pump operating at the constant-pressure mode imposed the pressure, while the micrometric valve allowed a manual tune of the flow rate. The temperature of the system was automatically regulated by the bath, while that of the expansion valve was controlled by the potentiometric feedback response. In a typical determination, the pressure of the saturation cell was raised to the desired value, its outlet valve being closed. The cell was then bypassed to attain the same pressure in the rest of the plant at the desired SC-CO_2 flux rate conditions. Once a Sep-pak cartridge had been settled just after the micrometric valve, the bypass line was closed while the SC-CO_2 was allowed to flow through the saturation cell at a given flux rate within the 0.12−0.8 g·min^{-1} range. The run finished when 20−30 g of solvent had passed through it. The cartridge beyond the micrometric valve trapped most of the solute conveyed in the SC-CO_2 stream, and its mass could be easily determined by comparing the cartridge weight before and after each run. Solute traces however were always found within the micrometric valve and along the cell-valve connection tubing. To overcome the risk of missing portions of the solute, valves, cartridge, and connection tubing were dismounted after each run and carefully washed with a solvent suitable for the solute considered, namely methanol for salicylic acid, ketoprofen, and vanillic acid, and *n*-hexane for naphthalene. The solution was then collected in a 200 mL glass volumetric flask to spectrophotometrically determine its concentration (the absorbance wavelengths considered were 255.0, 259.2, 275.6, and 304.0 nm for ketoprofen, vanillic acid, naphthalene, and salicylic acid, respectively).

Table 1. Percent of Solutes Recovered from Standard Solutions after Interaction with an Adsorbent (Silica Gel) Cartridge (Max. CV = 3%)

standard solutions (mg·L^{-1})	salicylic acid	ketoprofen	naphthalene	vanillic acid
4.01			99.9	
20.05			99.9	
4.04		99.9		
20.20		99.9		
25.61	99.5			
19.97				99.6
5.12	99.2			
3.99				98.3

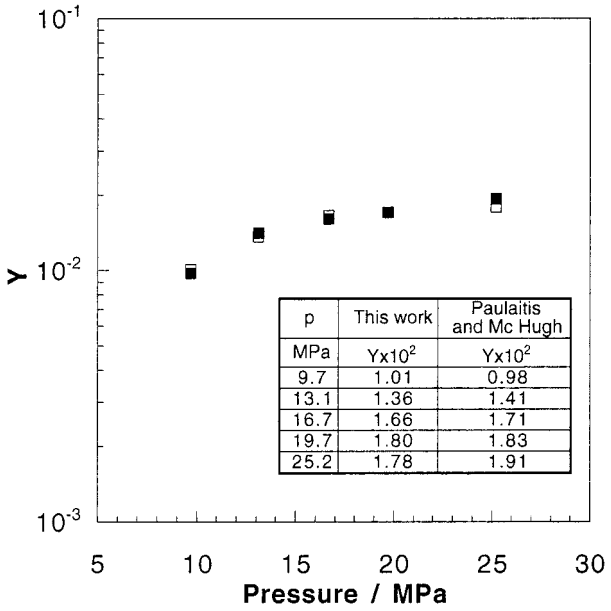
To account for possible interactions between the cartridge adsorbent (silica) and the solutes, which could affect the recovery of the latter, standard solutions of each solute were prepared in a wide concentration range. These were allowed to flow through the cartridge and spectrophotometrically checked after this passage. The percentages of solutes recovered by the Sep-pak cartridge are reported in Table 1. In all cases an almost quantitative recovery of solutes was obtained.

Results and Discussion

Verification of the Apparatus. To check the reliability of the apparatus, determinations of the solubility of naphthalene and salicylic acid were carried out at 313 and 328 K in the 9−25 MPa pressure range, since the solubilities of these compounds in the SCF solvent in these experimental conditions are well-known (Reverchon and Donsi, 1993; Paulaitis and McHugh, 1980; Gurdial and Foster, 1993; Tsekhanskaya et al., 1954; Ke et al., 1996; Kurnik et al., 1981; Mitra and Chen, 1988; Krukonis and Kurnik, 1985).

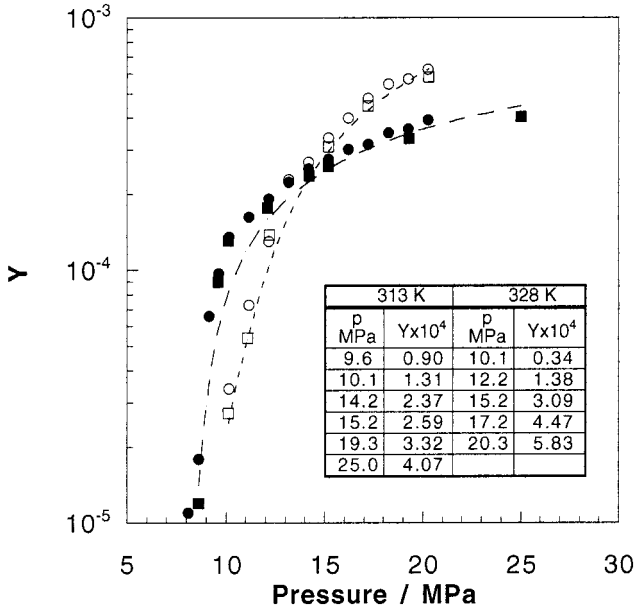
In a series of preliminary tests, solubility measurements were carried out at different flow rates ranging from 0.1 to 0.7 mL·min^{-1}. Variation of flow rate was found to have no effect on solubility, thus indicating that equilibrium solubility was measured.

The experimental solubility data, expressed as the solute mole fraction in the supercritical phase Y plotted on a semilogarithmic plane versus the experimental pressure p (Figures 2 and 3), show a trend close to that observed for other solids in previous studies. In the vicinity of the solvent critical pressure, the solubility increases with pressure and then becomes fairly constant. This effect can be ascribed to the SC solvent density that follows the same increasing trend.



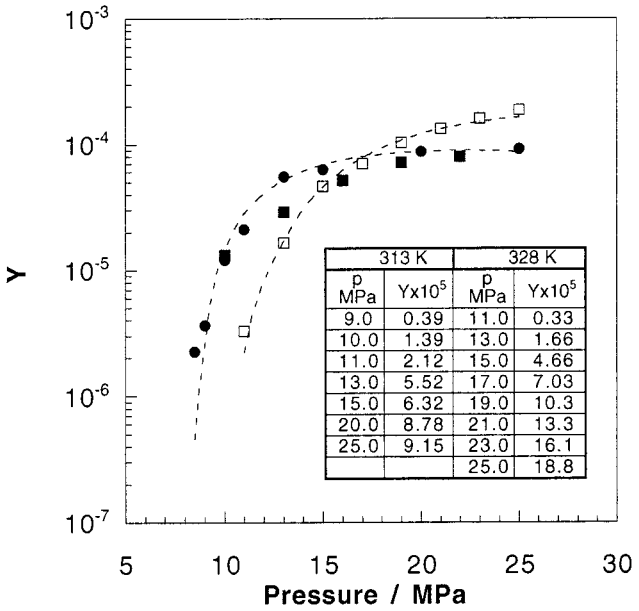
p	This work	Paulaitis and Mc Hugh
MPa	Yx10^2	Yx10^2
9.7	1.01	0.98
13.1	1.36	1.41
16.7	1.66	1.71
19.7	1.80	1.83
25.2	1.78	1.91

Figure 2. Solubility isotherms of naphthalene in SC-CO_2 at 308 K: (□) this work; (■) data from Paulaitis and Mc Hugh (1980).



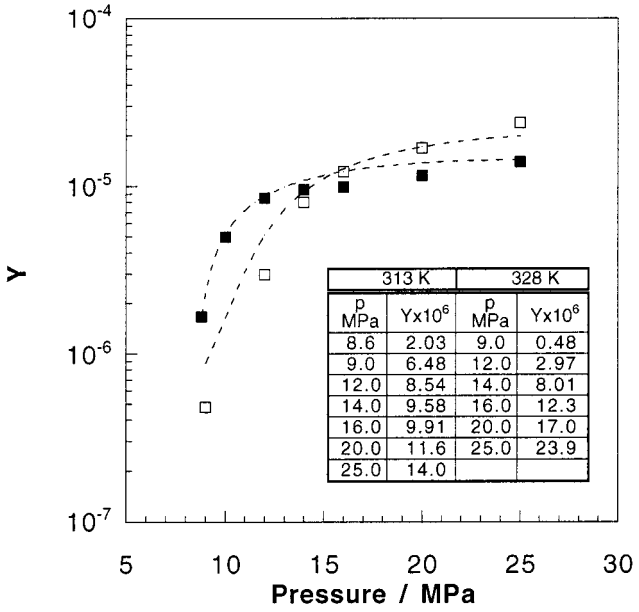
313 K		328 K	
p MPa	Yx10^4	p MPa	Yx10^4
9.6	0.90	10.1	0.34
10.1	1.31	12.2	1.38
14.2	2.37	15.2	3.09
15.2	2.59	17.2	4.47
19.3	3.32	20.3	5.83
25.0	4.07		

Figure 3. Solubility isotherms of salicylic acid in SC-CO_2: (■) this work at 313 K; (□) this work at 328 K; (●) data from Gurdial and Foster (1993) at 313 K; (○) data from Gurdial and Foster (1993) at 328 K; (- - -) PR-EOS.



313 K		328 K	
p MPa	Yx10^5	p MPa	Yx10^5
9.0	0.39	11.0	0.33
10.0	1.39	13.0	1.66
11.0	2.12	15.0	4.66
13.0	5.52	17.0	7.03
15.0	6.32	19.0	10.3
20.0	8.78	21.0	13.3
25.0	9.15	23.0	16.1
		25.0	18.8

Figure 4. Solubility isotherms of ketoprofen in SC-CO_2: (●) this work at 313 K; (□) this work at 328 K; (■) data from Macnaughton et al. (1996) at 313 K; (- - -) PR-EOS.



313 K		328 K	
p MPa	Yx10^6	p MPa	Yx10^6
8.6	2.03	9.0	0.48
9.0	6.48	12.0	2.97
12.0	8.54	14.0	8.01
14.0	9.58	16.0	12.3
16.0	9.91	20.0	17.0
20.0	11.6	25.0	23.9
25.0	14.0		

Figure 5. Solubility isotherms of vanillic acid in SC-CO_2 (Y expressed as molar fraction): (■) this work at 313 K; (□) this work at 328 K; (- - -) PR-EOS.

When different solubility isotherms are reported in the same plot, the so-called "crossover" region can be recognized around 14.5 MPa for salicylic acid, above which the solubility decreases with increasing temperatures.

Figures 2 and 3 show comparisons with the results of Paulaitis (Paulaitis and McHugh, 1980) and Gurdial (Gurdial and Foster, 1993), respectively. The mean deviation between our results and literature data can be considered satisfactory because the mean absolute deviation is <3% for naphthalene and 6% for salicylic acid. Moreover, in the case of naphthalene solubility measurements (inserted table of Figure 2), no systematic trends were observed. On the other hand, in the case of salicylic acid, a clear trend toward a systematically low solubility could be observed for our data. However, the observed differences can be explained as a consequence of a different calibration of temperature and pressure control systems.

Solubility Measurement. Figures 4 and 5 report the experimental solubilities in SC-CO_2 of ketoprofen and vanillic acid at 313 and 328 K in the 9−25 MPa pressure range. The crossover pressures are respectively 16 MPa for ketoprofen and 15 MPa for vanillic acid. The results relevant to ketoprofen at 313 K were in good agreement also with those reported by Macnaughton et al. (1996).

Modeling. The solubility of a nonvolatile solid solute (1) in a supercritical solvent (2) is determined from standard thermodynamic relationships by equating fugacities in the condensed-phase (S) and in the supercritical fluid-phase (FSC) for each component

$$f_1^{S} = f_1^{SCF} \quad (1)$$

Table 2. Fitting Parameters of Experimental Data

	salicylic acid	ketoprofen	vanillic acid	method (Reid et al., 1988)
T_c/K	864.79	1090.7	905.2	Ambrose
p_c/MPa	5.024	2.55	3.45	Ambrose
V^s/cm^3·mol^{-1}	95.70	195.6	109.2	Fedors
ω	0.7850	0.9141	0.9156	Lee−Kesler
p^{sat}(313 K)/Pa	0.286	5.34×10^{-4}	2.40×10^{-2}	Clausius−Clapeyron
k_{ij}(313 K)	0.233	0.232	0.344	
p^{sat}(328 K)/Pa	0.944	2.58×10^{-3}	9.02×10^{-2}	Clausius−Clapeyron
k_{ij}(328 K)	0.198	0.251	0.340	

The fugacity of component 1 in the supercritical phase is expressed by

$$f_1^{S} = Y_1 \varphi_1^{SCF} p \tag{2}$$

where Y_1 is the solute mole fraction in the SCF, φ_1^{SCF} is the fugacity coefficient of the solute, and p is the system pressure.

The fugacity coefficient φ_1^{SCF} can be calculated by the known thermodynamic relationships

$$RT \ln \varphi_i = -\int_{\infty}^{V}\left[\left(\frac{\partial p}{\partial n_i}\right)_{T,V,n_{j\neq i}} - \frac{RT}{V}\right] dV - RT \ln Z \tag{3}$$

The fugacity of a pure solid was calculated by integrating eq 3 within the sublimation pressure of the solute (p_1^{sat}) and the system pressure (p), with the assumption that the solubility of the supercritical fluid in the solid phase is negligible and the molar volume of the solid is constant within the pressure range considered

$$f_1^{S} = p_1^{sat} \cdot \varphi_1^{sat} \exp \int_{p_1^{sat}}^{p} \frac{V_1^{S} \cdot (p - p_1^{sat})}{RT} \tag{4}$$

where V_1^S is the molar volume of the pure solid at the temperature T, R is the gas constant and φ_1^{sat} is the fugacity coefficient of component 1 at the sublimation pressure.

Since at the sublimation pressure the whole gas phase corresponds to the pure vapor, viz. $\varphi_1^{sat} = 1$, the solubility expressed as the solute mole fraction in the supercritical phase Y_1 was obtained by combining eqs 1, 2, and 4

$$Y_1 = \frac{p_1^{sat} \exp\left[\frac{V_1^{S}(p - p_1^{sat})}{RT}\right]}{\varphi_1^{SCF} p} \tag{5}$$

The fugacity coefficient of component 1 in the supercritical phase (φ_1^{SCF}) was calculated by applying the Peng−Robinson (1976) equation of state to the relationship expressed in eq 3

$$p = \frac{RT}{(V - b)} - \frac{a}{V(V + b) + b(V - b)} \tag{6}$$

where the a and b parameters are evaluated from those of the pure components with the following mixing rules

$$a = \sum_i \sum_j Y_i Y_j (a_i a_j)^{1/2} (1 - k_{ij}) \tag{7}$$

$$(i = 1, 2, ..., n) \text{ and } (j \neq i = 1, 2, ..., n)$$

$$b = \sum_i Y_i b_i \; (i = 1, 2, ..., n) \tag{8}$$

where k_{ij} is an "adjustable" interaction parameter which is singled out through an iterative procedure aimed at the best fit of the experimental data.

Fitting of Solubility Data. The solubility data of salicylic acid, ketoprofen, and vanillic acid could be satisfactorily fitted (Figures 1−3). The PR-EOS allows for handling the experimental data concerning the solubility of the three compounds (Figures 3−5). To perform this fitting of data, it is necessary to calculate the molecular constants (T_c, p_c, ωT_b) for each component, as well as the values of pressure of sublimation at the same temperature values relevant to solubility determinations. The molecular parameters were calculated by means of a group contribution method (Reid et al., 1988) while sublimation pressure values (p^{sat}) were obtained using a modified Clausius−Clapeyron equation (Reid et al., 1988)

$$\ln p_{vpr} = h\left(1 - \frac{1}{T_r}\right) \tag{9}$$

where

$$h = T_{br} \frac{\ln(p_c/1.01325)}{1 - T_{br}} \tag{10}$$

T_r is the reduced temperature, T_{br} is the reduced normal boiling temperature, and p_c is the critical pressure.

The fitting of experimental data was found to be sensitive to the value of p^{sat}. Different p^{sat} values were obtained by use of various equations (Reid et al., 1988), as well as of eq 9, which is indeed more suitable for a liquid−vapor equilibrium under conditions far away from the critical point. In a separate trial, p^{sat} was used as an adjustable parameter: the value leading to the best fit of the solubility data was quite close to that drawn from eq 9, for both salicylic acid and ketoprofen.

In Table 2 the values of all the parameters used for fitting experimental data are reported. In the case of salicylic acid, the best fit at 313 K was obtained by assuming for the iteration parameter k_{ij} a value of 0.233, very close to that reported by Reverchon et al. (Reverchon et al., 1993) ($k_{ij} = 0.211$). At 328 K a value for $k_{ij} = 0.198$ was found. For vanillic acid, the iteration parameter was, surprisingly, independent of temperature.

Conclusions

The solubilities of two compounds of interest in the pharmaceutical and food fields were measured in supercritical CO_2 under dynamic conditions in the pressure range between 9 and 25 MPa and at the temperatures 313 and 328 K. The apparatus used is designed to improve the accuracy of the measurement with respect to the ones already described. An iterative model based on the PR-EOS adjusted to account for solute and solvent characteristics is proposed to fit the experimental data. The fitting of

experimental data was found to be largely sensitive to the value of the sublimation pressure of the solute.

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