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Solubility of a Pharmaceutical Solid in Supercritical Mixtures : Measurements and Modelling

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The solubility in supercritical fluids of a solid of pharmaceutical interest has been investigated by means of an original apparatus. Solubility values of this solid in supercritical pure CO_2 in the pressure range 8-30 MPa are reported along the isotherms 308.15 and 318.15 K. The data are then correlated using the Chrastil model, an empirical density-based model. The effect of a cosolvent, ethanol, has been examined under supercritical solutions as well.

INTRODUCTION

Particle generation from supercritical solutions is a very attractive technique for the pharmaceutical industry. It leads to excellent product purity, in fine and monodisperse powders. Moreover, this type of process gives the further advantage of being feasible in mild operating conditions. Among the available process are Rapid Expansion of a Supercritical Solution (RESS) and Supercritical Anti-Solvent (SAS) [1]. However to develop these techniques, knowledge of the solid solubility in the corresponding involved medium is the primary basic information required.

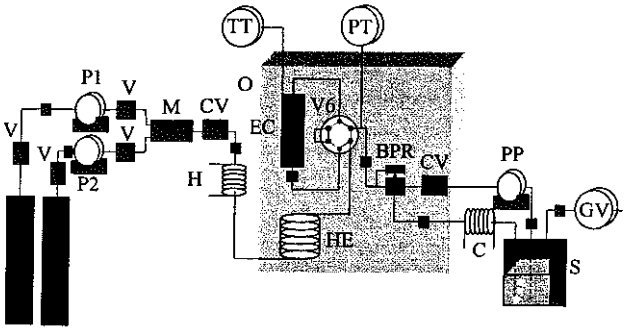
To carry out accurate measurements of the solubilities in pure and mixed solvents, an original apparatus has been developed. It is based on an open circuit method : the composition of the phase is obtained by analyses and the solvent flows continuously through the solid compound.

The objective of this work was to measure the influence of temperature and pressure on the solubility level of this solid in pure CO_2, which is the most common supercritical fluid used. The solubility was studied in mixtures of CO_2 and cosolvent(s) as well, which are often used in supercritical applications to increase the solubility.

EXPERIMENTAL SECTION

Experimentally determined equilibrium solubility data were obtained by using a continuous flow apparatus, well described previously [2]. The flow diagram of the apparatus is shown in Figure 1. The two liquids, carbon dioxide (Air Liquide S.A., 99.995 %) and ethanol (DDA Industrie, 99.5 %), are compressed by means of two high pressure syringe pumps, P1 and P2, at constant flow rates depending on the desired composition. The mixing of the two liquids is achieved through a mixer, M. The homogeneous high-pressure liquid then passes through a heater, H, used to rapidly heat the solvent to temperatures above its critical temperature. The supercritical fluid then enters an oven, O, where the solubility cell, EC, is thermo-regulated within 0.05 K. The heat exchanger, HE, placed in the oven, enables the solvent to reach the desired extraction temperature. Downstream the HE, a 6 way–2 position high pressure valve is inserted in the line to either direct the fluid to the cell or to bypass it. EC contains three cylindrical compartments placed one above the other, inside which the solid powder is packed. They are fitted at their bottom with stainless steel sintered disks to prevent stripping of the solid and to achieve a good dispersion of the supercritical

solvent. Temperature in the cell is measured directly in its body through a 4-wire 100 Ω platinum probe and the pressure in the out-stream line of the cell. The pressure of the supercritical phase is monitored upstream and released downstream through the BPR, which maintains the pressure constant to within 0.5 % during the experiment. At the outlet of the BPR, the pressure is reduced to atmospheric pressure. Thus, a recovering solvent stream is used to get the solute in liquid state for collection, to avoid potential clogging. Finally a separator S is used to vent off the gas and collect the solvent phase. The total volume of gaseous CO_2 (extraction solvent) is measured by means of a gas volumeter GV and the concentration of solid in the recovering liquid phase by gas or liquid chromatography. These two data and the total volume of the solute recovering liquid solvent being determined, the solubility, y_2, of the solid in supercritical fluid can be calculated.



V : 2 way valves; P1, P2 : high pressure pumps; M : mixer; CV : checking valve; H : heater;
O : thermostated oven; HE : heat exchanger; V6 : 6 way-2 position valve; EC : equilibrium cell;
TT : temperature transducer; PT : pressure transducer; BPR : back pressure regulator;
C : cooler; S : separator; PP : peristaltic pump; GV : gas volumeter;

Figure 1 : flow diagram apparatus

To confirm that the phase flowing outside the cell is saturated, measurements have been performed at various flow rates. When variation of the flow rate has no sensitive effect on the measured solubilities in a given range, the equilibrium is confirmed in this range. This range is only valid for the studied compound, and therefore, must be confirmed for each solute.

The validity of the technique was determined by measuring naphthalene solubility in supercritical CO_2 at two temperatures, 308.15 and 318.15 K. Measurements were then compared with corresponding data available in the literature [3].

In the case of our pharmaceutical solid, a CO_2 flowing time of 30 minutes at 1 $ml.mn^{-1}$ was enough to obtain a reproducibility and uncertainty of the solubility data within 5%. The recovering solvent used was ethanol. The cosolvent was ethanol as well, so the HPLC analysis are the same with or without cosolvent (solid dissolved in ethanol). To verify that no solid residue had been left in the recovering solvent line, analyses on the ethanol used for cleaning this line were performed.

DATA CORRELATION

Modeling the solubility of solids using density as the independent variable does not require the physical properties of the solid, which are not available for complex solids. There exist several empirical density-based correlations. In this work, solubilities are correlated by one of these methods.

This method uses the model proposed by Chrastil [4]. This model may be regarded as a macroscopic description of the surroundings of the molecules in the fluid phase. It is based on the hypothesis that one molecule of a solute A associates with k molecules of a solvent B to form one molecule of a solvato-complex AB_k in equilibrium with the system. The definition of the equilibrium constant through thermodynamic considerations leads to the following expression for the solubility:

$$\ln(C_2) = k \ln(\rho_1) + \frac{a}{T} + b \qquad (1)$$

where C_2 is the concentration of the solute in the supercritical phase and ρ_1 the density of the fluid phase. k is the association number, a is dependent on the heat of solvation and heat of vaporization of the solute and b is dependent on the molecular weights of the species. k, a and b are adjusted on solubility experimental data.

The Eq. (1) suggests linear relationship between ln (C_2) and ln (ρ_1), with a slope equal to k. Solid solubility is very low and the increase of density due to the presence of the solid is negligible. In consequence, the density of the saturated supercritical phase is taken equal to the density of pure carbon dioxide, which is calculated by using the Peng-Robinson equation of state [5] (PR EoS).

T =308.15 K			T =318.15 K		
P (MPa)	ρ_1 (kg.m^{-3})[a]	10^7 y_2	P (MPa)	ρ_1 (kg.m^{-3})[a]	10^7 y_2
9.86	644	0.68	9.33	375	0.14
10.35	667	0.74	9.92	447	0.27
12.56	738	1.39	10.79	528	0.78
15.35	796	2.35	12.01	601	1.17
19.85	860	4.23	14.86	698	3.50
22.28	887	4.96	15.08	704	3.59
25.41	916	5.64	19.59	790	6.83
27.46	933	5.71	20.20	799	7.38
29.73	950	6.44	25.30	861	10.79
			25.55	863	11.18
			30.19	905	15.67

[a] calculated with the PR EoS [5]

Table 1 : Solubility data in supercritical CO_2 at 308.15 and 318.15 K

RESULTS

The solubility, y_2, of the solid was measured at 308.15 and 318.15 K. The data are listed in Table 1 and represented vs. pressure in Figure 2. The effect of pressure on the solute solubility follows the expected trends, the solubility increasing with pressure for the two temperatures studied. Solubility is found as an increasing function of temperature over the investigated pressure range.

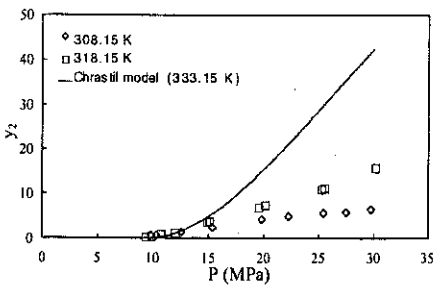


Figure 2: solubility of the solid in pure supercritical CO_2 vs. pressure

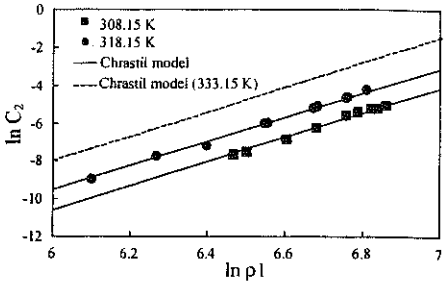


Figure 3: concentration of solid in pure supercritical CO_2 vs. density

The parameters of the Chrastil correlation are presented in Table 2. The two isotherms are well fitted by this correlation, the average absolute deviation (AAD) being about 7 %. The obtained k values show a small temperature dependence. If the data of the two isotherms are gathered before parameter adjustment, the AAD remains practically the same (see bottom line of Table 2). Hence, k can be considered as temperature independent. The plot of ln (C_2) vs. ln (ρ_1) displays parallel lines, with a slope k equal to 6.55 (Figure 3). Thus the correlation can be written:

$$\ln(C_2) = f(T,P) = k \ln\left[\rho_1^{EoS}(T,P)\right] + \frac{a}{T} + b \qquad (2)$$

This provides a relation between C_2, P and T with constant values of k, a and b for this solute, very useful for prediction purposes. As an example of prediction, solubility data estimated at 333.15 K are represented in Figures 2 and 3.

T (K)	Pts	$\ln C_2 = k \ln\rho + a/T + b$			
		k	$a/10^3$	b/10	AAD (%)[a]
308.15	9	7.11	-6.92	-31.26	6.25
318.15	11	6.44	-7.97	-23.06	7.12
All	20	6.55	-10.89	-14.62	7.68

[a] $AAD = (1/n)\sum_{i=1}^{n}\left|(C_{2,cal} - C_{2,exp})/C_{2,exp}\right|_i * 100$

Table 2: results for the Chrastil correlation

The choice of a cosolvent depends on its availability in high purity, its toxicity and its physical and chemical characteristics. A first screening of potential candidates led us to choose ethanol. Solid solubilities at 20 MPa and 318.15 K for different ethanol mole fractions, y_3, are presented in Table 3.

T=318.15 K – P=20 MPa	
y_3	$10^7 y_2$
0	7.38
4.0	34.61
7.6	144.24
7.7	143.06
10.2	285.95
16.2	737.43
17.1	802.72

Table 3: solubility data in supercritical CO_2 with ethanol as a cosolvent

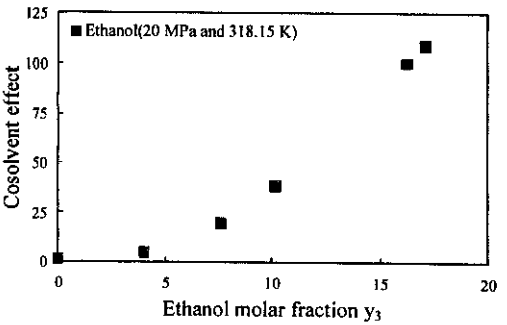


Figure 4: cosolvent effect as a function of cosolvent concentration

To better illustrate the enhancement due to its introduction, the cosolvent effect is defined as the ratio of the solubility obtained with cosolvent to that obtained without cosolvent at the same temperature and pressure. The effect of the cosolvent at 318.15 K and 20 MPa is shown as a function of ethanol molar fraction in Figure 4. From this Figure, it is clear that the solubility is increased using ethanol. This solubility enhancement is the result of additional interactions between the solute and the cosolvent. The solute solubility is a nonlinear function of ethanol fraction. For instance, the solubility is multiplied by a factor 10 with a solvent composed of about 6 % of ethanol, and by a factor 50 for about 11 % of ethanol in the solvent.

CONCLUSION

A continuous flow apparatus was used to determine the solubility behavior of a pharmaceutical solid in pure supercritical carbon dioxide at 308 and 318 K between 8 and 30 MPa. A low solubility behavior is observed over the investigated range of temperatures and pressures. The solubility is an increasing function of both pressure and temperature.

The solubility data presented here are well correlated using the Chrastil model, with a maximum AAD of 8 %. This model allows the determination of the association number (about 6.5), which characterizes the formed solvato-complexes, and the solubility prediction at other temperatures.

The effect of ethanol as a cosolvent was investigated. The cosolvent effect at 20 MPa and 318.15 K shows a nonlinear dependence on the cosolvent concentration. 6% of ethanol is enough to enhance the "solid" solubility by a factor 10. This factor increases rapidly with ethanol molar fraction (x 50 for 11% ethanol).

NOMENCLATURE

a, b : coefficients for Eq. (1)
AAD : average absolute deviation
C : concentration ($kg.m^{-3}$)
k : association number (Chrastil model)
P : pressure (MPa)
T : temperature (K)
y : mole fraction

Greek symbols
ρ : density ($kg.m^{-3}$)

Subscripts
1 : light solvent component (carbon dioxide)
2 : heavy solute component (solid)
3 : cosolvent

Superscripts
EoS : calculated by means of an equation of state

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