EXPERIMENTAL STUDY OF HIGH PRESSURE FLUID PHASE EQUILIBRIA OF TERNARY SYSTEMS INVOLVING SULFATHIAZOLE, LIGHT ORGANIC SOLVENT AND CARBON DIOXIDE

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ABSTRACT

Supercritical carbon dioxide (CO_2) is used for a large number of solid treatment processes such as impregnation, extraction or precipitation. In this last application, supercritical CO_2, can be used both as a solvent (RESS processes) or an anti-solvent (SAS processes). One of the most important applications using these technologies is the generation of pharmaceutical particles. Indeed, in addition to obtaining a clean product which is a key point for pharmaceutical molecules, the use of carbon dioxide allows a particle characteristics control really attractive. Such a control requires the knowledge of the different phases in presence for given conditions.

In the present work, we are interesting in sulfathiazole, a pharmaceutical active ingredient. Because of its low solubility in CO_2, supercritical recrystallization is generally carried out through an SAS process. For a better control of this process, high pressure fluid phase equilibria of ternary systems involving sulfathiazole, light organic solvent and CO_2 were measured through a synthetic method. Two different solvents were considered: acetone and methanol. The bubble points of the considered systems were determined for temperatures ranging from 308 to 333 K. These results will be used to develop a predictive thermodynamic model well adapted to the studied systems.

INTRODUCTION

Because of their interesting physico-chemical properties intermediary between gases and liquids, supercritical fluids are merged as a “clean” alternative to several conventional processes. Industrial applications cover several fields such as extraction, impregnation, chemical reaction, crystallization,…

A good control of high pressure processes requires the knowledge of the fundamental properties of the involved systems. Among others, it is important to have information about the high pressure fluid phase behaviour (the number, the nature and the composition of the present phases).

Fluid phase equilibria of binary systems involving supercritical fluids are quite abundant in bibliography. However, there is still a lack of data concerning multi-component systems phase behaviour. For instance, such information are of great importance while carrying out crystallization through supercritical anti-solvent (SAS) processes.

In these processes, the solid solutes to be recrystallized have low solubilities in supercritical CO_2. Therefore, they are first dissolved in a solvent, having a good affinity with the supercritical fluid. Solution is then brought into contact with CO_2. Simultaneous transfer of the supercritical fluid towards the liquid solution and transfer of the solvent towards the supercritical phase occur, which results in the supersaturation of the solute and then its precipitation. Among other parameters, the phase behaviour plays a key role in the properties of the resulting powder [1, 2]. Previous studies [2, 3] show that the miscibility conditions influence significantly the dispersion mode when the organic solution is injected in dense CO_2 through a capillary, and therefore the particle properties. Under complete miscibility conditions, particles would apparently be generated by a gas phase nucleation and growth within the expanding plume, while, under partial miscibility conditions, the nucleation occurs within individual liquid droplets.

In this study, we have focused on studying the phase behaviour of ternary systems involving CO_2, light organic solvents and sulfathiazole. This pharmaceutical molecule has been frequently used in SAS processes [3–8]. More precisely, we are interested in determining the influence of the presence of sulfathiazole on the miscibility conditions of CO_2 and acetone or CO_2 and methanol.

MATERIALS AND METHODS

REAGENTS

The solid solute used within this work is sulfathiazole (4-amino-*N*-(1,3-thiazol-2-yl) benzenesulfonamide) (STH) which skeletal formula is presented in Figure 1. It is supplied from Fluka (Germany) and has a molar assay higher than 98%.

The studied organic solvents are acetone (purity>99.5%) and methanol (purity>99,9%) and are both supplied from Sigma Aldrich. CO_2 (purity 99.7%) is provided by “Air liquide”.

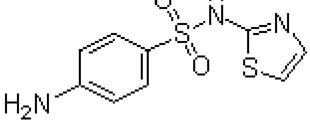

Figure 1 : Skeletal formula of sulfathiazole ($C_9H_9N_3O_2S_2$)

HIGH-PRESSURE EXPERIMENTAL SET-UP

The phase equilibrium data of the CO_2+sulfathiazole+organic solvent ternary system were determined through the so-called synthetic method [9]. Phase transitions resulting from pressure variations are determined through direct visualisations without sampling. The high pressure experimental set-up is illustrated in Figure 2. It is mainly composed of a high pressure variable-volume view cell (Top industries S. A., France). Its volume can be adjusted from 4 to 12 cm^3 by moving an internal piston. The cell is equipped with a magnetic stirrer, a double jacket connected to a thermostated bath and a sapphire window. Visualisations are insured by a video camera connected to a monitor.

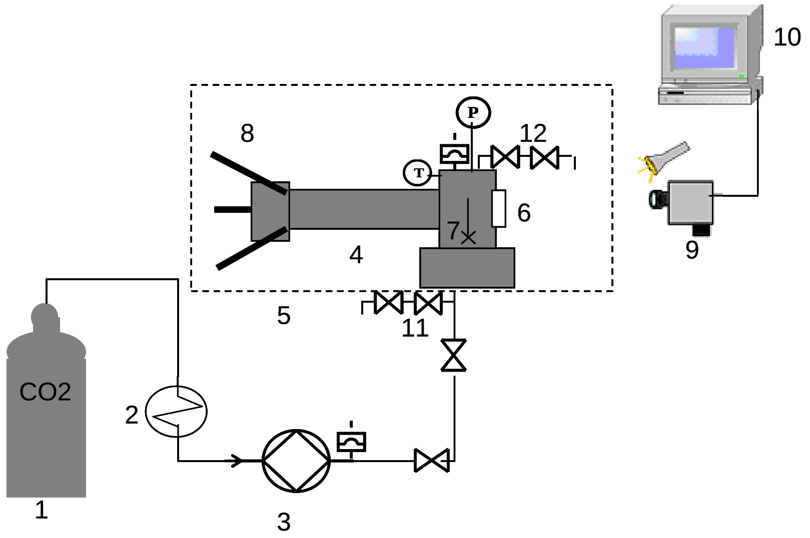

Figure 2 : Scheme of the high pressure experimental set-up

1 CO_2 bottle; 2 Cool bath; 3 Liquid pump; 4 High pressure cell; 5 Thermostated bath; 6 Sapphire window; 7 Magnetic stirrer; 8 Internal piston; 9 Video camera; 10 Monitor; 11/12 Sampling lines

EXPERIMENTAL PROCEDURE

In a typical experiment, the high pressure cell is first loaded with a known mass of a sulfathiazole/organic solvent solution preheated at 308 K. The composition of this solution is fixed slightly under the saturation yield at 308 K and atmospheric pressure.

The desired quantity of CO_2 determined by double weighing is then added to the cell. As soon as the CO_2 is introduced, solid precipitation manifests itself as an opaque film on the window. The system is then set to the desired temperature (± 0.2 K) and is magnetically stirred to insure a good homogenisation. When the thermal equilibrium is reached, the pressure of the known composition triphasic solid/liquid/vapour (SLV) mixture is increased gradually by moving the internal piston to reach a biphasic solid/fluid (SF) mixture. In order to assess the SLV-SF transition pressure, the system is decompressed slowly until the appearance of a second phase. For delimiting precisely the pressure, the compression-decompression cycles are reproduced many times, and the so determined pressure has an accuracy higher than ± 0.05 MPa. At the end of the experiment, the cell is heated in order to determine the bubble pressure at a higher temperature for the same composition conditions.

RESULTS

Solubility in organic solvents

As it has already been specified, the organic solvent/sulfathiazole solution is first introduced in the high pressure cell with a composition slightly lower than the solubility conditions at 308 K and atmospheric pressure.

The solubility of sulfathiazole in both methanol and acetone was therefore measured using a transparent cell with a double jacket connected to a thermostated bath to regulate the temperature. The obtained solubilities are given in Table 1 in mass and molar fractions.

Table 1 : Solubility of sulfathiazole in methanol and acetone at 308 K

	Mass solubility fraction ($\times10^{-2}$)	Molar solubility fraction ($\times10^{-3}$)
Acetone	1.93±0.05	4.47±0.13
Methanol	1.74±0.04	2.21±0.05

Phase equilibrium behaviour

CO_2/ Acetone binary system

Before studying the ternary system behaviour, the phase equilibria of CO_2/acetone binary system was studied at 308 K. The bubble pressures were measured for molar CO_2 fractions (x_{CO2}) varying between 0.26 and 0.80 as illustrated in Table 2.

Table 2 : Bubble pressures of the CO_2/Acetone binary system at 308 K

x_{CO2}	P (MPa)
0.268	1.89
0.322	2.14
0.478	3.35
0.562	4.06
0.744	5.22
0.787	5.73

Bubble pressures were compared to those obtained by Chang *et al.* [10], as illustrated in Figure 3. Experimental and bibliographical curves are very close, which represents a validation of our experimental set-up.

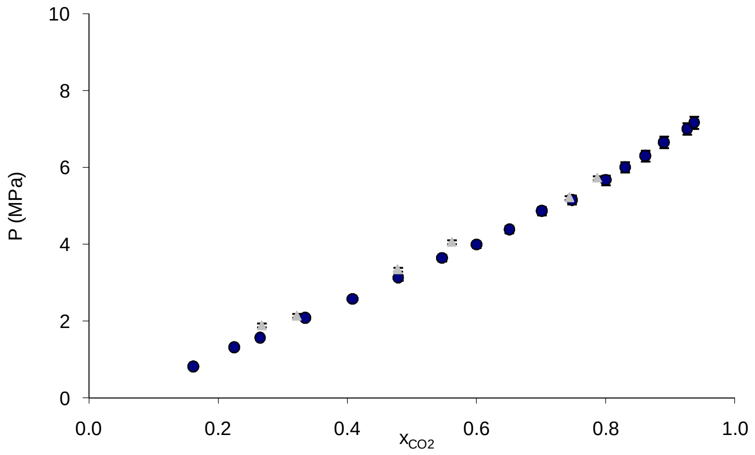

Figure 3 : Fluid phase equilibria of the binary system CO_2 / acetone at 308 K: experimental results (▲); bibliographical results (●) [10]

CO_2 / acetone / STH ternary system

The SLV-SF transition pressures of the ternary system CO_2 / acetone / STH were determined at 308 and 318 K for several molar CO_2 fractions varying between 0.48 and 0.96. The measured pressures are reported in Table 3 with a precision of ± 0.05 MPa. All the reported compositions (Z_{CO2}, $Z_{acetone}$ and Z_{STH}) correspond to the global ones. Nevertheless, the quantities of STH are so small that their influence on the CO_2 and acetone composition can be neglected.

Table 3 : SLV-SF transition pressures of CO_2 /acetone /STH ternary system at 308 and 318 K

Z_{CO2}	$Z_{acetone}$	Z_{STH}	P (MPa) T= 308 K	P (MPa) T= 318 K
0.4793	0.5187	0.0020	3.76	4.31
0.5246	0.4741	0.0013	4.08	4.73
0.6450	0.3537	0.0014	5.42	6.99
0.7176	0.2813	0.0011	5.95	7
0.7911	0.2083	0.0006	6.63	7.8
0.8964	0.1032	0.0004	7.39	8.55
0.9595	0.0404	0.0002	7.61	9.37

In order to evaluate the influence of the STH on the miscibility conditions of acetone and CO_2, we have superimposed the experimental curves of the ternary system with the P-x diagram of the CO_2/acetone binary system at 308 K (c.f. Figure 4). It can be noticed that the presence of small quantity of STH in the cell, leads to a quite significant increase in the transition pressures.

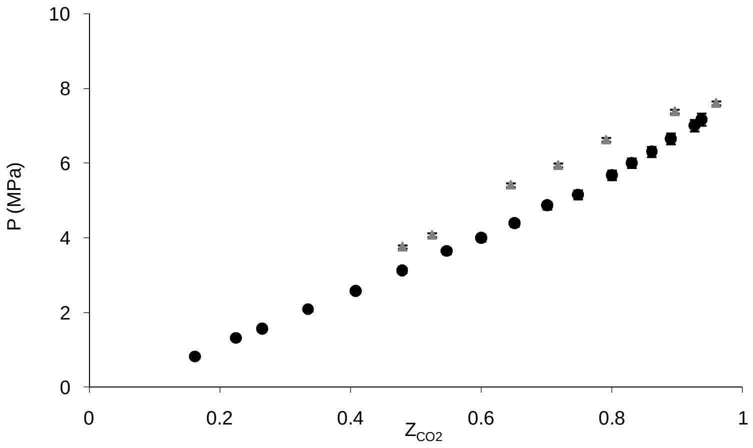

Figure 4 : Experimental SLV-SF transition pressures of the ternary system CO_2 / acetone / STH at 308 (▲) and bibliographical binary bubble pressures at 308 K [10] (●).

As expected, increasing the temperature leads to an increase in the transition pressures (c.f. Figure 5).

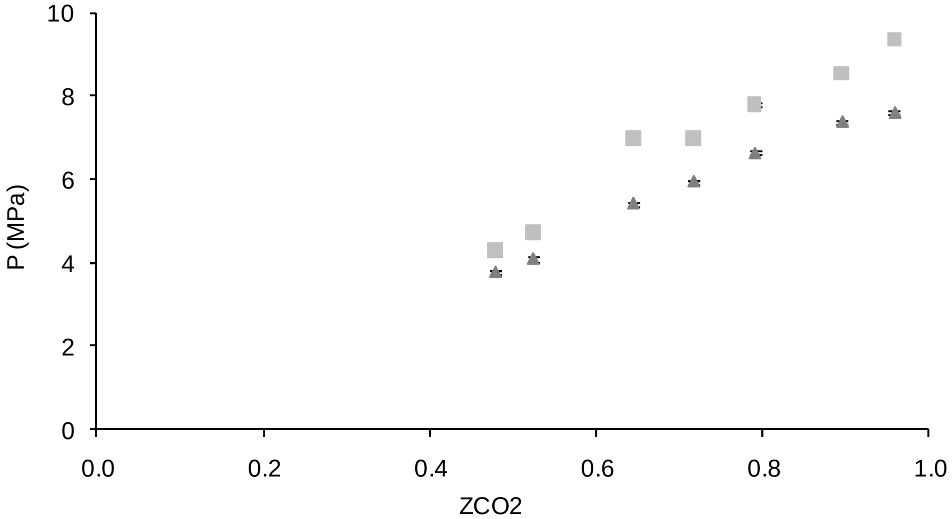

Figure 5 : Experimental SLV-SF transition pressures of the ternary system CO_2 /Acetone / STH at 308 (▲) and 318 K (■)

CO_2 / Methanol / STH ternary system

The SLV-SF transition pressures of the ternary system CO_2 / methanol / STH were also determined at different temperatures (308, 318 and 333 K) and for several CO_2 molar fractions varying between 0.26 and 0.60 (c.f. Table 4).

Table 4 : SLV-SF transition pressures of CO_2 / methanol / STH ternary system at 308, 318 and 338 K.

Z_{CO2}	$Z_{Methanol}$	Z_{STH}	P (MPa) (T=308 K)	P (MPa) (T=318 K)	P (MPa) (T=333 K)
0.2980	0.7007	0.0013	5.95	6.91	8.51
0.4060	0.5930	0.0010	6.39	7.51	9.30
0.4443	0.5548	0.0009	7.23	-	10.41
0.5599	0.4393	0.0007	7.25	-	10.60
0.5909	0.4083	0.0007	7.15	8.50	10.64

In Figure 6 and Figure 8, the experimental curves of the ternary system are superimposed with the P-x diagram of the CO_2/methanol binary system at respectively 308 and 333K. Since no bibliographical binary curves were found at 318 K, in Figure 7, the experimental curves for the ternary systems at 318 K were compared to results of literature obtained at 320 K for a binary system [11].

The presence of STH in the cell has the same influence as that observed for the CO_2/methanol system. The triphasic to biphasic transition pressures are slightly higher than that of the binary bubble pressures. This effect seems to be more significant for the lowest studied temperature (308 K).

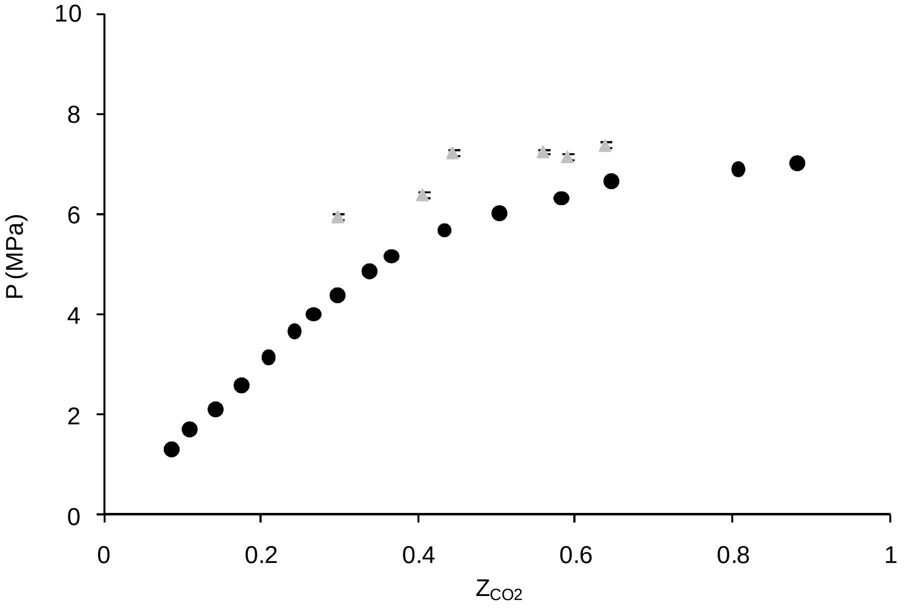

Figure 6: Experimental SLV-SF transition pressures of the CO_2 / methanol / STH ternary system (▲) and bibliographical bubble pressures of the CO_2/methanol binary system [10]. (●) at 308 K

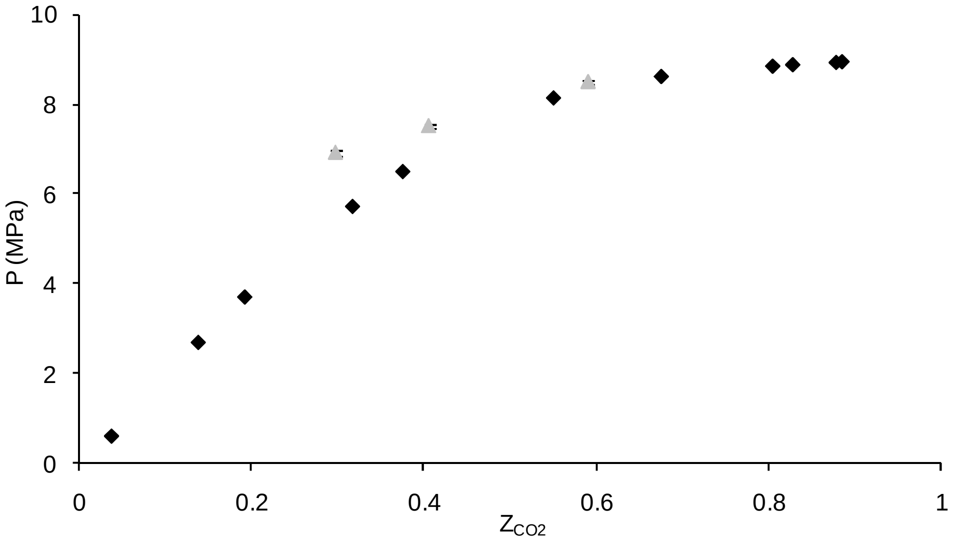

Figure 7 : Experimental SLV-SF transition pressures of the CO_2 / methanol / STH ternary system at 318 K (▲) and bibliographical bubble pressures of the CO_2/methanol binary system at 320 K [11] (●)

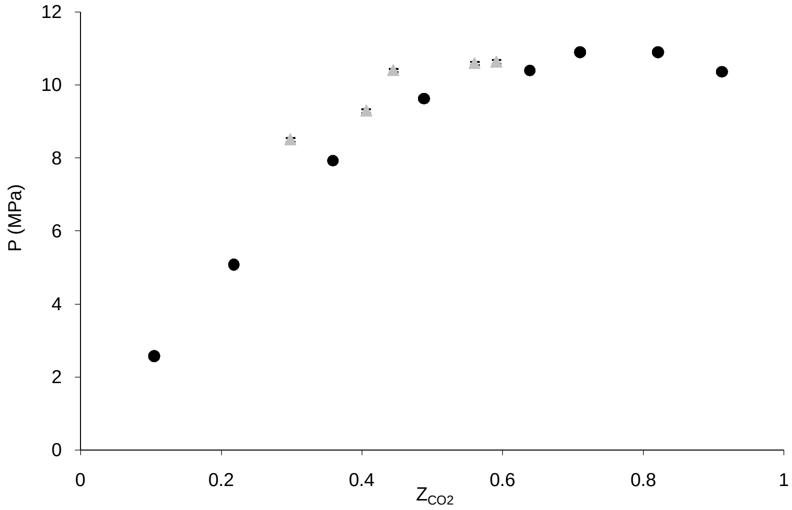

Figure 8 : Experimental SLV-SF transition pressures of the CO_2 / methanol / STH ternary system (▲) and bibliographical bubble pressures of the CO_2/methanol binary system [12] (●) at 333 K.

CONCLUSION

Two ternary systems CO_2 / acetone / STH and CO_2 / methanol / STH were studied by experimental determination of the SLV-SF transition pressure at different temperatures through a visual synthetic method.

As expected, an increase in the temperature leads to an increase in the transition pressures for both studied systems.

The isothermal evolutions of the SLV-SF transition pressure as a function of CO_2 composition present similar aspects as that of the bubble pressures of the corresponding CO_2/solvent binary system. Nevertheless, while superimposing the two curves at the same temperature, it can be noticed that the SLV-SF transition pressures are higher than the binary bubble pressures for both studied systems at 308 K. This means that the presence of sulfathiazole influences the miscibility of CO_2 and the organic solvents. Therefore, while carrying out the SAS process, in order to be in complete miscibility conditions for the system system CO_2/ organic solvent, work pressure should be higher than the SLV-SF transition one in the presence of the solute.

To be able to predict the phase transition pressure in presence of a solute at different compositions and different temperatures, a predictive thermodynamic model well adapted to the studied system should be developed. For that purpose, experiments in presence of sulfathiazole will be extended to a larger field of temperatures and compositions. Furthermore, other organic solvents are also being studied.

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