STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLVIII, 1, 2003

THE SOLUBILITY OF DRUGS IN SUPERCRITICAL CO_2 AND THE EFFECT OF ENTRAINERS

SIMION DRAGAN[1], MIHAELA DRAGAN[2]

[1] *Faculty of Chemistry and Chemical Engineering "Babes-Bolyai" University Cluj-Napoca*
[2] *Faculty of Economics, "Babes-Bolyai" University Cluj-Napoca*

ABSTRACT. In this work the solubility of two drugs in supercritical carbon dioxide are being measured. There were investigated the solubility of terfenadine and griseofulvin in s.c. carbon dioxide at pressures in the range of 140 – 180 bar and two temperatures 313,2 K and 343,2 K.

To evaluate the solubility of the two drugs we are using an equation of Chrastil type and obtained the values for the association number k, and for the two constants a, b which take into account the enthalpy of solvation and vapourization of the solute and the molecular weight of the species. This chemicals have relatively low solubilities with values ranging from $3{,}092 \times 10^{-7}$ to $1{,}8550 \times 10^{-6}$ mole fraction. The solubilities exhibit a clear dependence on the solvent density and this has been used to provide a simple and precise correlation of the data.

The effect of ethanol added to CO_2 as an entrainer was investigated, varying its concentration in CO_2 from 1wt % to 5wt.%.

1. INTRODUCTION

In recent years there has been an increasing level of interest in utilizing supercritical fluid (SF) technology for processing pharmaceutical and nutraceutical materials. The unique feature of the supercritical state is that the solvating power strongly depends on the fluid density and can be adjusted, without changing chemical composition, by controlling the pressure and temperature. This property opens up a wide range of possibilities for selective extraction, purification and precipitation processes [1]. Extraction processes with supercritical fluids are established even in industrial scale and become again more interesting for industry.

Supercritical fluid extraction of active molecules from medicinal plants, extraction from dilute media for metabolite recovery, enzymatic reactions, precipitation, micronization and impregnation are some of the areas of application under investigation and development [2]. Purification of pharmaceuticals and detoxification of hazardous wastes are a few of the many applications in wich conventional organic solvents are being replaced by environmentally begin supercritical fluids such as carbon dioxide [3].

The experimental determination of drugs solubility in supercritical fluid system is important owing to the increasing applications of the dense gases.

Carbon dioxide is by far the most important proccesing medium because of its relatively low critical temperature and pressure (31,3^{o}C and 72,9 bar), low toxicity and low cost. In the compressed state, supercritical CO_2 can be described as a hydrophobic solvent with a polarity comparable to that of hexane or pentane.

In this work, the solubilities of two Anti-Inflammatory Drugs- Terfenadine and Griseofulvin – have been measured in supercritical carbon dioxide.

The experimental data were correlated by a semiempirical method proposed by Chrastil [4] which is based on the hypothesis that one molecule of solute associates with k molecules of supercritical fluid forming a complex in a state of chemical equilibrium.

It is well known that the addition of a cosolvent to a supercritical fluid often leads to an enhancement in the solubility of a solute [5]. In this work, we have used ethanol as a cosolvent, varying its concentration in CO_2 from 1 wt% to 5 wt%.

2. EXPERIMENTAL

The supercritical fluid – carbon dioxide – was available with purity of 99,99% from AGA Gas GmbH Hamburg.

Terfenadine and Griseofulvin were purchased from Merck Co. with purity greater than 99,9%.

The structures of the two drugs are shown in Figure 1.

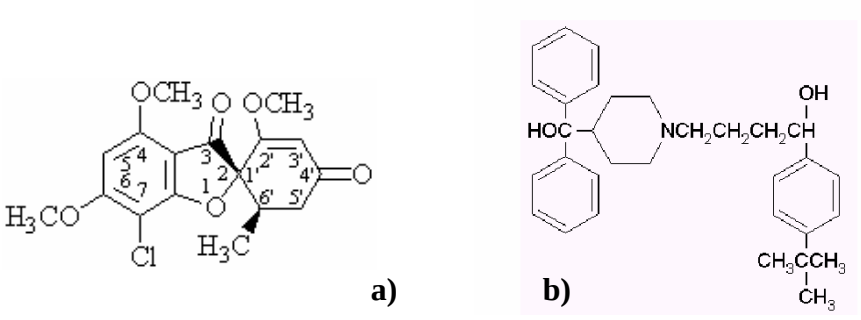

Figure1. Structure of the studied drugs: a). Grieofulvin; b). Terfenadine

Some of the available physical and chemical property data for the compounds used in this study are listed in Table 1.

Table 1.

Molar Mass M, Melting Point T_m, and Solubility S in water for the Drugs

Compound	M [g. mol^{-1}]	T_m [K]	S [mg/ml H_2O]
Terfenadine	471,29	419,2 – 421,2	0,010 at 30 C
Griseofulvin	352,8	495,2	40,1 at 25 C

The solubility of terfenadine and griseofulvin in supercritical carbon dioxide is not available in the literature. It was determined experimentally using the experimental equipment presented in Figure 2.

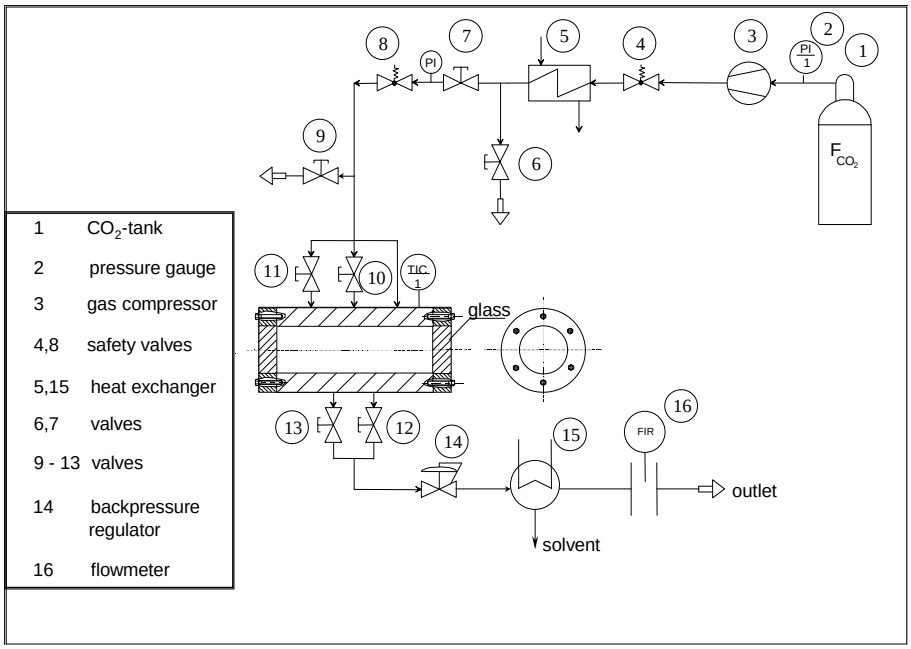

Figure 2. Flow sheet of the apparata

The main part of the experimental equippment is the autoclave with a volum of 249,5 ml. The diameter of each inlet and outlet is 1 mm. For a better mixing in the liquid phase, the autoclave can be rocked with constant velocity. The temperature is maintained by means of a heating jacket and temperature controller with an accuracy of ± 1^o C. The temperature was measured with a Pt 100 thermocouple calibrated by two points measurements. In order to determine the solubility of the two drugs in supercritical CO_2, a specific amount of the substance was filled in a metal cage, weighed and placed on the bottom of the autoclave. The autoclave was closed and heated up to a fixed temperature (40 and 70^o C).

The CO_2 gas, comes from the tank (1), is compressed in the gas pump (3) (membrane compressor, Whitey Model LC-10) and heated up to the desired temperature in the heat exchanger (5). Then CO_2, preheated to the same temperature was pumped into the autoclave up to the desired pressure (140; 160; and 180 bar) was reached. The system was stored under stirring for 24 h. The temperature could be kept constant with an accuracy of ± 1^oC and the pressure varied within 5 bar.

After the equilibrium was reached, CO_2 was vented out with a constant flow rate (~ 20 NL/hour) and then the autoclave was cooled to room temperature.

The metal cage with the rest of the substance was weighed and the amount of the dissolved substance calculated.

The amount of CO_2 in the autoclave was calculated from the known volume and corresponding CO_2 density. The values of CO_2 density were taken from NIST data base [NIST].

3. RESULTS AND DISCUSSIONS

The solubilities of the two drugs along with the temperature, pressure and density of CO_2 that corresponds to each measurement are listed in Table 2.

Table 2.

Experimental solubility for the Drugs in Supercritical CO_2

T [K]	P [bar]	D_{CO2} [g/l]	10^6 x Solubility as molar fraction	
			Terfenadine	Griseofulvin
313,2	140	763,27	0,9985	3,6006
	160	794,9	1,2939	6,2735
	180	819,51	1,5344	6,9466
343,2	140	456,62	0,33376	0,445876
	160	547,75	1,0435	1,7656
	180	612,24	1,9914	6,5678

For the description of the solubility behavior of substances in compressed gases different equations were developed including the density of the fluid [6], [7] In this work, the solubilities were correlated using the density-based equation proposed by Chrastil [4]:

$$\ln c = k \ln d + \frac{a}{T} + b \quad (1)$$

where c is the concentration of the solute in the supercritical fluid (g/L), d is the density of the fluid (g/L), k is the number of fluid molecules associating with one molecule of solute to form a solvatocomplex. The constants a, b take into account the enthalpy of solvation and vapourization of the solute and the molecular weight of the species.

The parameters k, and a,b have to be fitted to experimental data and are presented in Figures 3 and 4, and summerized in Table 3.

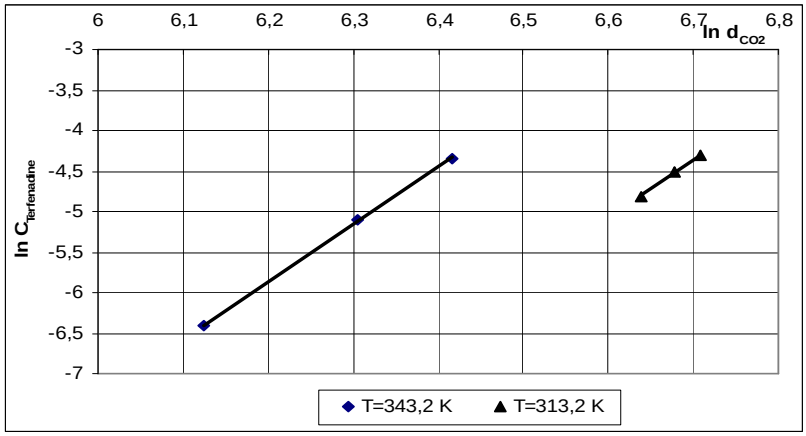

Figure 3. Solubility of terfenadine in CO_2. Determination of the solubility constants k and a, b.

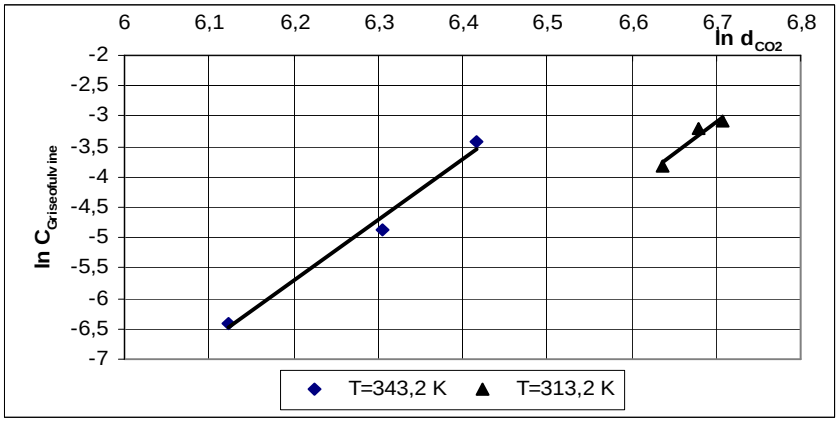

Figure 4. Solubility of Griseofulvin in CO_2. Determination of the solubility constants k and a,b

Table 3.

Solubility constants in Carbon Dioxide

Compound	k	a	b
Terfenadine	7,108	-5894,0091	-32,8513
Griseofulvin	10,152	-20480,518	-8,112

As a result, the solubility of terfenadine and griseofulvin in CO_2 can be expressed as follows:

$$\ln c = 7{,}108 \ln d - \frac{5894{,}0091}{T} - 32{,}8513 \quad (2)$$

$$\ln c = 10{,}152 \ln d - \frac{20480{,}518}{T} - 8{,}112 \quad (3)$$

The solubilities for the two systems as a function of pressure and CO_2 density comparative with the predicted solubilities with the Chrastil-equation [4] are presented in Figures 5 – 8 and summerized in Table 4.

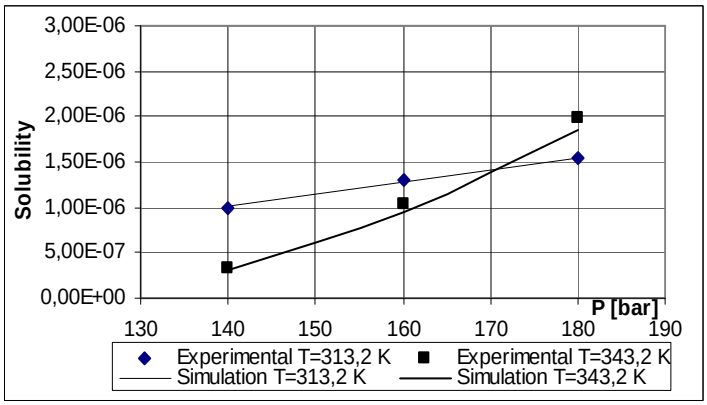

Figure 5. Mole fraction solubility of terfenadine as a function of pressure P in supercritical carbon dioxide

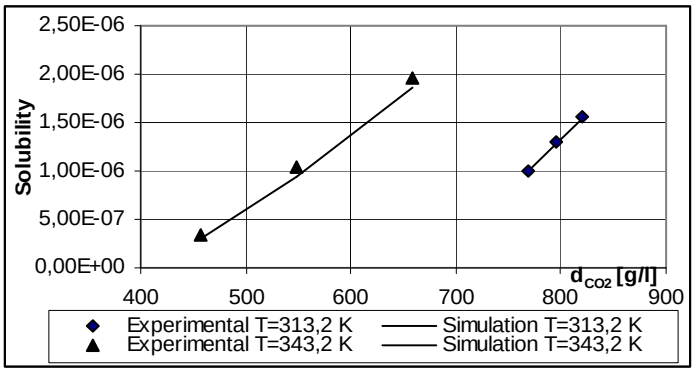

Figure 6. Mole fraction solubility of terfenadine as a function of the carbon dioxide density

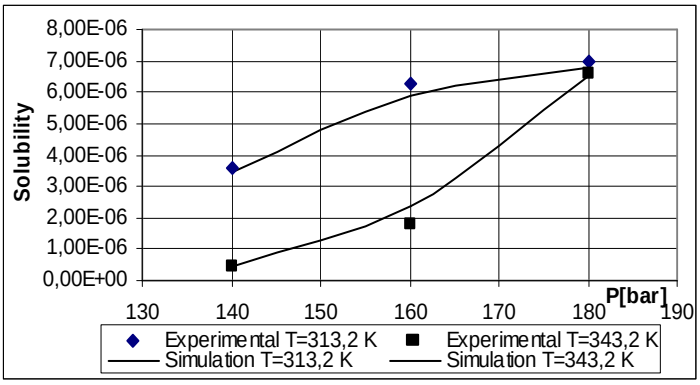

Figure 7. Mole fraction solubility of griseofulvin as a function of pressure P in supercritical carbon dioxide

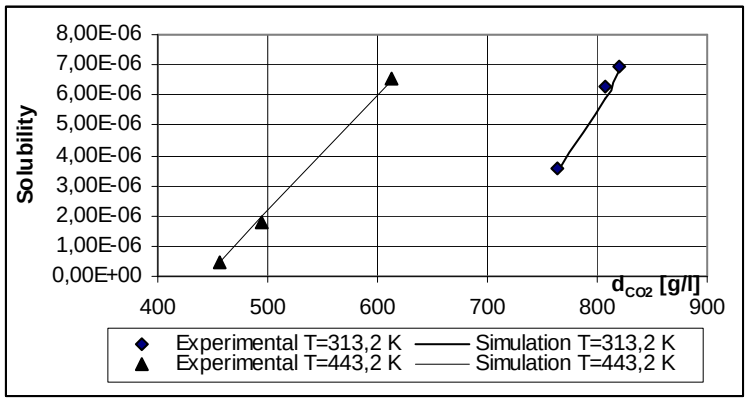

Figure 8. Mole fraction solubility of griseofulvin as a function of the carbon dioxide density

The results from Figures 5 and 7 show an increase of the terfenadine and griseofulvin solubility with the experimental pressure while the temperature was kept constant.

For terfenadine has been obtained a higher solubility at 313,2 K at a pressure of 170 bar. Over this value of pressure, the solubility is higher at 343,2 K.

In the case of griseofulvin we have noticed that in the whole range there have been obtained a higher solubility at the temperature of 313,2 K.

Figures 6 and 8 have show an increase of the terfenadine and griseofulvin solubility, with the solvent density.

The predicted solubilities values presented in Table 4 are in a good agreement with the experimental data for the two drugs.

Table 4.
Prediction of terfenadine and griseofulvin solubilities at three density values of CO_2 according to the Chrastil equation

Compound	T [K]	P [bar]	10^6x Mole fraction solubility		AAD [%]
			experimental	calculated	
Terfenadine	313,2	140	0,9985	1,004	0,55
		160	1,2939	1,2840	0,76
		180	1,5344	1,545	0,69
	343,2	140	0,3376	1,3092	7,35
		160	1,0435	0,94	7,21
		180	1,9914	1,8550	6,85
Griseofulvin	313,2	140	3,6006	3,454	4,07
		160	6,2735	5,88	6,27
		180	6,9466	6,786	2,31
	343,2	140	0,44586	0,4594	3,03
		160	1,7656	1,977	11,9
		180	6,5678	6,4962	1,09

The absolute average percentage deviation of calculated from experimental values (AAD) are for terfenadine in the range: 0,55% - 7,35% and for griseofulvin these are ranging from 1,09% to 11,9%.

In order to enhance the dissolution of the two drugs with pharmaceutical applications – terfenadine and griseofulvin – it had been used as entrainer, ethanol. The experiments were performed with ethanol concentration in CO_2 varying from 0 to 5 wt. %. The influence of the entrainer concentrations on the terfenadine and griseofulvin solubilities are presented in Figure 9.

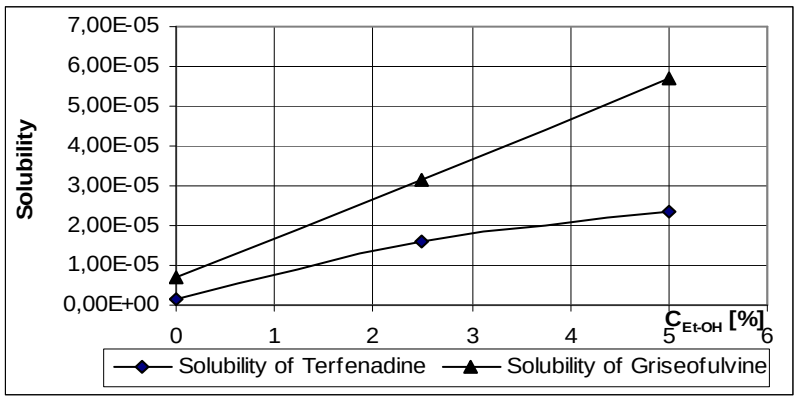

Figure 9. Influence of Et-OH concentration on the terfenadine and griseofulvin Mole Fraction Solubilities at T=313,2 K and P=180 bar

The results from Figure 9 show that the solubility of both active compounds increases significantly in presence of the entrainer.

An empirical relation which described the influence of the ethanol concentration has the following form [8]:

$$y = y_0 + n(y_0 w_e)^m \quad (4)$$

where y is the solubility of the two drugs in CO_2 with entrainer (mol/mol), y_o is the solubility of the two drugs in pure CO_2 (mol/mol) and w_e is the concentration of ethanol in CO_2 (g/g).

From our experimental data, we deduced the following relations which described the influence of ethanol added to CO_2 as an entrainer on the terfenadine and griseofulvin:

$$y = y_0 + 0{,}0745 \cdot (y_0 w_e)^{0,5} \quad (5)$$

$$y = y_0 + 137{,}04 \cdot (y_0 w_e) \quad (6)$$

The experimental solubility of the two drugs in the presence of the entrainer and the predicted solubility with the equations (5) and (6) are presented in Table 5.

Table 5.

Experimental and predicted solubility of terfenadine and griseofulvine in supercritical CO_2 with Ethanol at T=313,2K and P=180 bar.

Et-OH [%] / Compound		0	2,5	5,0
Terfenadine	$y_{\exp}$	1,5344 x 10^{-6}	1,5873 x 10^{-5}	2,3343 x 10^{-5}
	$y_{calc.}$	1,5344 x 10^{-6}	1,6311 x 10^{-5}	2,2705 x 10^{-5}
	A.A.D. [%]	0	2,76	2,73
Griseofulvin	$y_{\exp}$	6,9466 x 10^{-6}	3,1310 x 10^{-5}	5,7143 x 10^{-5}
	$y_{calc.}$	6,9466 x 10^{-6}	3,1350 x 10^{-5}	5,7048 x 10^{-5}
	A.A.D. [%]	0	0,14	0,17

4. CONCLUSIONS

The solubilities of two drugs have been measured in supercritical CO_2 at pressures between 140 – 180 bar and at temperatures of 313,2 K and 343,2 K. The experimental error is estimated for terfenadine to be in the range of 0,55% - 7,35% and for griseofulvin these are ranging from 1,09% to 11,9%.

The parameters required by the predictive method for the evaluating the solubilities of solid in supercritical carbon dioxide are the molecular weight, structure and the melting temperature.

It was shown that the addition of a small amount of ethanol as entrainer to the supercritical carbon dioxide can increase selectively the solubilities of the two drugs.

Acknowledgment*:* We greatly appreciate the support for our experimental work to the Institute of Thermodynamic and Chemical Engineering of the Technical University of Berlin and for the disccussions with Prof.Dr-Ing.W. Arlt.

LITERATURE

1. S. Bristow, B. Shekunov, P. *York, Ind. Eng. Chem. Res*., 2001, **40**, 1732 – 1739.
2. S. Macnaughton, I. Kikik, N. Foster, P.Alessi, *J.Chem. Eng. Data,* 1996, **41**, 1083 – 1086.
3. J.M. Santiago, A.S. Teja, *Fluid Phase Equilibria*, 1999, **158-160**, 501-510.
4. J. Chrastil, *J. Phys. Chem*., 1982, **86**, 3016 – 3021.
5. C.D. Saquing, F.P. Lucien, N.R. Foster, *Ind. Eng. Chem. Res*., 1998, **37**, 4190 – 4197.
6. R. Marr, T. Gamse, *Chemical Engineering and Processing*, 2000, **39**, 19 – 28.
7. S. Mitra, N.K.Wilson, *J. Chrom. Sci*., 1991, **29**, 305 – 319.
8. H. Sovova, *Journal of Supercritical Fluids*, 2001, **21**, 195 – 203.