

EXPERIMENTS AND MODELING OF CANNABINOID SOLUBILITY IN SUPERCRITICAL CARBON DIOXIDE

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Abstract

The equilibrium solubility of Δ^9 -tetrahydrocannabinol in supercritical CO₂ was investigated in the pressure range from 110 to 260 bar and temperature range 315 to 335 K by a simple and reliable dynamic method. The molar solubility range measured was from 0.08 to 3.4×10^{-4} . The cross-over region was observed at 135 bar. Furthermore, the Bartle semi-empirical model was used to correlate the data. Correlation of the results showed good self-consistency of the data obtained.

Keywords: *solubility – cannabinoids – supercritical carbon dioxide – semi-empirical model*

INTRODUCTION

Cannabis is one of the oldest medicinal plants known. At present, there is significant interest in cannabis and its medicinal uses. Cannabis contains more than 400 different known compounds, including 66 cannabinoids [1]. The major compound from cannabis, Δ^9 -THC (Δ^9 -tetrahydrocannabinol), has been registered for medical use in several countries. The poor availability of the various cannabinoids as pure compounds is an obstacle for the development of cannabinoid based drugs and for pharmacological and toxicological studies.

Cannabinoids can be extracted from the plant by organic solvents. Hydrocarbons and alcohols are often used. However, these solvents are flammable and many of them are toxic. Supercritical extraction with carbon dioxide is an alternative promising technique. Although this process requires high pressures, there is no risk of fire or toxicity, solvent removal is simple and efficient, and extract quality can be well-controlled.

In this paper, the solubility of Δ^9 -THC in supercritical CO_2 is experimentally determined and correlated with the Bartle semi-empirical model.

A common way of measuring the solubility of viscous liquid components in supercritical CO_2 is to use a non-analytical method with the Cailletet apparatus [2-4]. However, tests showed that the solubility of the Δ^9 -THC is too low to be measured in this apparatus. The minimum solubility that can be determined with the Cailletet apparatus is in the order of 3×10^{-4} . Therefore, a dynamic apparatus with an analytical method was used, as described in the next paragraph.

EXPERIMENTAL

Chemicals

CO_2 was purchased from Hoek Loos (quality 2.7). Methanol and tetrahydrofuran of HPLC reagent grade were purchased from J.T. Bakker. Δ^9 -THC with purity higher than 96.5% was kindly donated by Echo Pharmaceuticals B.V, Weesp, the Netherlands. The molecular structure of Δ^9 -THC is shown in Figure 1. Each material was used without further purification.

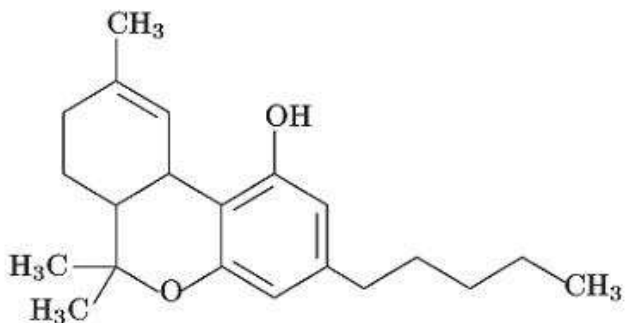


Figure 1: molecular structure of Δ^9 -THC

Apparatus and method

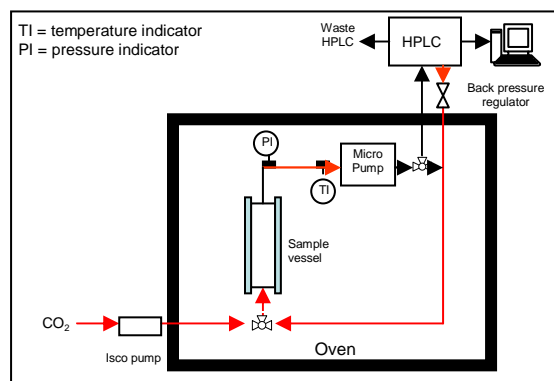


Figure 2: schematic drawing of the experimental set-up

The apparatus is designed to perform experiments up to 350 bar and in the temperature range of 293 – 423 K. The internal volume in which the sample and CO₂ circulate is about 8 mL. As shown in Figure 2, the cell is composed of a sample vessel made of stainless steel, a micro pump (Micropump INC, model 380), a pressure sensor (EFE – type VLE 700) with an accuracy of ± 0.5 bar, a thermocouple PT-100 with an accuracy of ± 0.1 K. All the components are placed in an oven (Mettler – type VLE 700) where the temperature is controlled and kept constant. The loop is connected to an HPLC to measure the concentration of the solubilised component in CO₂. All the pipes are traced to minimize heat losses. A back pressure regulator is placed at the end of the HPLC to maintain the pressure in the system. An Isco pump (model 260 D) is used to fill the system with CO₂.

The Δ^9 -THC, dissolved in methanol, is put in the sample cylinder and the solvent is evaporated with a separate vacuum pump (RNF Lab) long enough to ensure that the entire methanol is evaporated. Once the vacuum pump is disconnected, the system is closed and set at the desired temperature. After the temperature of the system reaches the desired value, the system is filled with CO₂ until the desired pressure is reached. When the conditions are stable, the CO₂ is circulated over the sample vessel. A sample is taken to be analysed with the HPLC after 2 hours and then every 30 minutes. When the concentration difference measured is less than 0.09×10^{-4} at two different times, with a pressure and temperature difference less than 5 bar and 1 K respectively, it is assumed that equilibrium is reached, and the concentration measured is recorded as the solubility.

The HPLC profiles were acquired on a Chromapack HPLC system consisting of an Isos pump, an injection valve and a UV-VIS detector (model 340 – Varian). The system is controlled by Galaxie Chromatography software. The profiles were recorded at 228 nm. The analytical column was a Vydac (Hesperia, CA) C₁₈, type 218MS54 (4.6 x 250 mm², 5 μ m). The mobile phase consisted of a mixture of methanol, distilled water and tetrahydrofuran in the proportions v/v/v = 10/4/1.

RESULTS AND DISCUSSION

The supercritical carbon dioxide solubilities of $\Delta 9$ -THC were determined and the values are reported in table 1 in terms of equilibrium mol fraction x . Each data point is an average of at least three measurements with percentage relative standard deviations less than 7 %.

Table 1: Solubility of $\Delta 9$ -THC in supercritical carbon dioxide

T = 315 K		T = 327 K		T = 335 K	
P (bar)	$10^4 x$	P (bar)	$10^4 x$	P (bar)	$10^4 x$
118	0.22	141	0.29	141	0.32
118	0.22	142	0.33	158	0.72
119	0.29	144	0.33	183	1.57
135	0.42	145	0.35	205	1.69
199	0.65	152	0.45	227	2.33
209	0.65	155	0.46	240	2.78
236	0.69	158	0.57		
258	0.83	162	0.56		
		167	0.65		
		172	0.69		
		180	0.68		
		182	0.69		
		187	0.70		
		205	1.35		
		226	1.42		
		241	1.99		

Below 150 bar, the solubility is lower than 10^{-4} , and does not vary much with the temperature. At constant pressure higher than 160 bar, the solubility increases with a temperature increase. At constant temperature, the solubility increases with pressure increase. In the pressure range 200-250 bar, and above approximately 325 K, the solubility is higher than 10^{-4} .

The experimental solubility data for $\Delta 9$ -THC was correlated using the following equation proposed by Bartle et al. [5]

$$\ln \left(\frac{xP}{P_{ref}} \right) = A + C(\rho - \rho_{ref}) \quad (1)$$

Where x is the mole fraction solubility, P is the pressure, P_{ref} is a reference pressure of 1 bar, ρ is the density (taken as the density of pure CO_2), ρ_{ref} is a reference density for which a value of 700 kg.m^{-3} is used [5], A is a linear function of temperature and C is a constant. The reason for using ρ_{ref} is to make the parameter A much less sensitive to experimental errors in the solubility data and also, to avoid the large variations caused by extrapolation to zero density. The value of C , which results physically from solvation of the solute by supercritical fluid, is assumed to remain constant over the entire temperature range studied. This has already been reported by Bartle and co-workers. [5, 6]

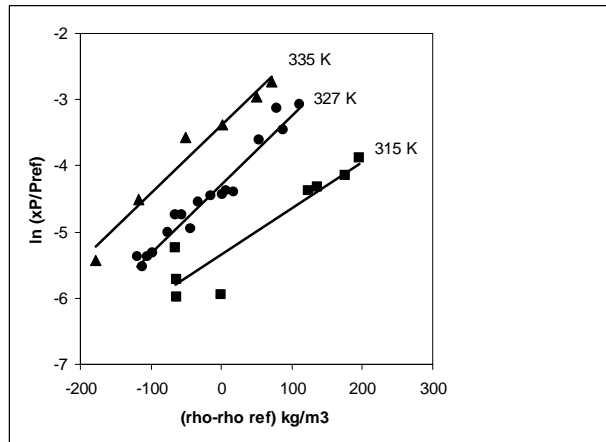


Figure 3: plots of $\ln(xP/P_{ref})$ vs. $(\rho - \rho_{ref})$

The $\ln(xP/P_{ref})$ values were plotted against density difference (Figure 3), and were fitted by least-squares regression to determine A and C. The values of C, obtained from the slopes of the corresponding plots, were averaged to $0.09 \text{ m}^3 \cdot \text{kg}^{-1}$.

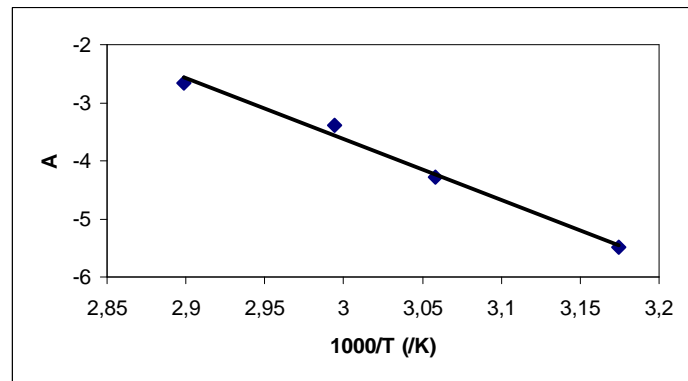


Figure 4: plots of A vs. $1000/T$

A was plotted versus $1/T$ (Figure 4). The values of the intercept and the slope are determined to be 27 and $-10\,000 \text{ K}$ respectively with a linear regression.

Figure 5 compares the calculated isotherms with the experimental data. One can see that the trend of the experimental work and the semi-empirical model are the same. The cross-over region is observed at 135 bar.

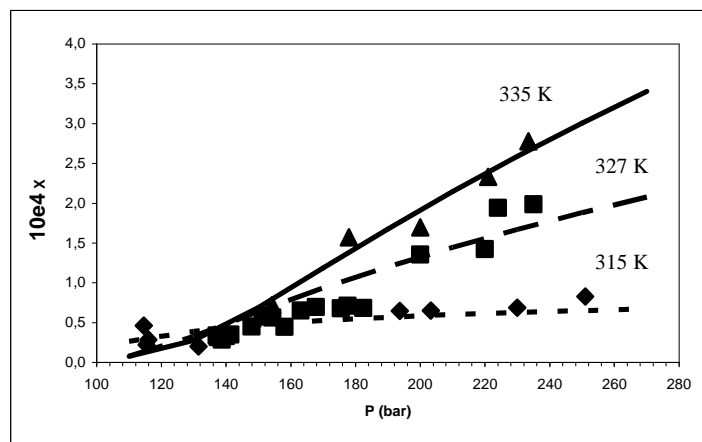


Figure 5: Comparison of experimental (points: \blacklozenge = 315 K; \blacksquare = 327K; \blacktriangle = 335 K) and calculated (lines) solubilities at different temperatures

CONCLUSION

In this work, the solubility of Δ 9-THC in supercritical CO₂ has been measured at 315, 327 and 335 K and at pressures up to 260 bar. To obtain a reasonable solubility – i.e. in the order of 1×10^{-4} - the temperature should be higher than approximately 325 K and the pressure should be higher than 200 bar. The Bartle semi-empirical model was used to show the consistency of the results.

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