Solubilities of Some Nitrogen-Containing Drugs in Supercritical Carbon Dioxide

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The equilibrium solubilities of five nitrogen-containing drugs carbamazepine, diazepam, codeine, atropine, and lorazepam have been measured in supercritical carbon dioxide using a simple and reliable static method. The measurements were performed in the pressure range (122 to 355) bar at the temperatures (308, 318, 328, 338, and 348) K. The measured solubilities were correlated using a semiempirical model. The calculated results show satisfactory agreement with experimental data.

1. Introduction

Recently, interest in using supercritical fluids as an alternative to conventional extraction methods has grown. The conventional extraction consumed large amounts of solvents, required lots of time, and polluted the environment. Supercritical fluid extraction (SFE) has been widely applied to the extraction processes in food processing and pharmaceutical industries.[1−5] CO_2 has so far been the most widely used supercritical fluid because it evaporates upon decompression at the restrictor outlet, which facilitates off-line collection of extracts. On the other hand, CO_2 is not only a powerful solvent for a wide range of compounds but also relatively inert, inexpensive, nontoxic, nonflammable, recyclable, readily available in high purity, and it leaves no residues.

Information on solubilities of pharmaceutical products in supercritical fluids is of vital importance for the efficient design of the extraction and purification process on the basis of supercritical fluids. Numerous research groups have measured the solubility of pharmaceutical products in different supercritical fluids.[6−11] This work was undertaken to determine the solubilities of five compounds used as drugs (atropine, diazepam, codeine, carbamazepine, and lorazepam) in supercritical carbon dioxide over a wide range of temperatures and pressures. Atropine is a tertiary amine that has become the prototype and most widely used of antimuscarinic drugs. Diazepam, lorazepam, and carbamazepine all are benzodiazepine. Diazepam is indicated for the symptomatic relief of tension and anxiety and acute alcohol withdrawal adjunct therapy in skeletal muscle spasms and is preferred by many clinicians for the management of status epileptics. Lorazepam is mainly promoted as an antianxiety agent, but also is approved for treatment of insomnia. Carbamazepine is an anticonvulsant drug that is useful in complex partial seizures (temporal lob, psychomotor) and generalized tonic-clinic seizures, particularly in patients who have not responded to other less toxic anticonvulsants. Codeine is a cough suppressant, antidiarrhoeal, and analgesic.[12,13] To the best of our knowledge, there is not any report about the solubility of these drugs.

2. Experimental Section

2.1. Experimental and Procedure. A Suprex MPS/225 integrated SFE/SFC system equipped with a modified static system for the solubility determination in the SFE mode was used. A detailed description of the apparatus and operating procedures is given elsewhere.[8,9,14] Solubility measurements were accomplished with a 1-mL extraction vessel in the pressure range from (122 to 355) bar at temperatures (308, 318, 328, 338, and 348) K for a duration of 30 min. It should be noted that, when the solubility data versus time was monitored, 30 min was found adequate to ensure the attainment of equilibrium. The solid solutes (100 mg) were mixed well with glass beads and packed into the extraction vessel. This procedure prevents channeling, increases the contact surface between the sample and the supercritical fluid, and consequently, reduces the equilibration time. Supercritical CO_2 was pressurized and passed into the extraction vessel. After equilibrium at the desired temperature and pressure was reached (for about 30 min) a 145-μL portion of the saturated supercritical CO_2 was loaded into an injection loop. Then, the loop was depressurized into the collection vial containing suitable solvent (Table 2). Finally, the sample loop was washed with the same solvent, which was collected in the collection vial. The final volume of the solution was 5 mL.

The solubilities of carbamazepine, diazepam, codeine, and lorazepam were calculated by absorbency measurements at suitable λ for each compound (Table 1) using a model 2100 Shimadzo UV−Vis spectrophotometer with 1-cm pass length quartz cells.

The solubilities of atropine were determined by the addition of picric acid into atropine solution and absorbance measurements of the resulting atropine−picric acid charge tansfer complex at 420 nm. The stock solution of the drug compound (100 μg mL^{-1}) was prepared by dissolving appropriate amounts of solid sample in the proper solvent (Table 1). A set of standard solutions was prepared by appropriate dilution of the stock solutions. The calibration curves obtained (with regression coefficients better than 0.999) were used to estabilish the concentration of the drugs in the collection vial. The mole fraction composition of the solutes were generally reproducible within ±3%.

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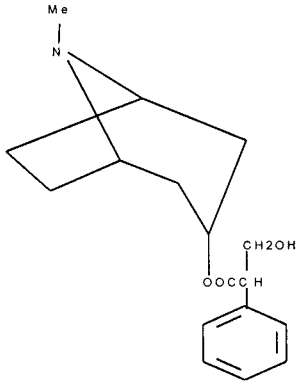
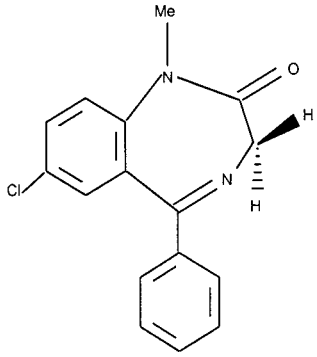
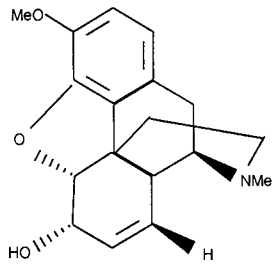
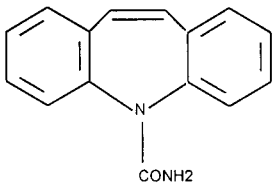
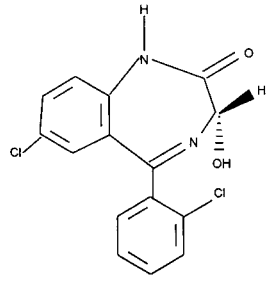
Table 1. Physical Properties of the Solutes[a]

Compound	Formula	Structure	MW/g.mol^{-1}	T_m/K	Solvent	λ /nm
Atropine	$C_{15}H_{23}NO_3$		289.38	115	$CHCl_3$	420 *
Diazepam	$C_{16}H_{13}ClN_2O$		284.76	126	CH_3OH	314
Codeine	$C_{18}H_{21}NO_3$		299.36	155	H_2O	210
Carbamazepine	$C_{15}H_{12}N_2O$		236.26	205	CH_3OH	285
Lorazepam	$C_{15}H_{10}ClN_2O_2$		321.16	167	CH_3OH	318

[a] The asterisk indicates that λ is obtained for an atropine−picric acid charge-transfer complex.

Table 2. Solubilties of Drugs Atropine, Diazepam, Codeine, and Carbamazepine in Supercritical Carbon Dioxide

			atropine		diazepam		codeine		carbamazepine	
T	P	ρ	s	x	s	x	s	x	s	x
K	bar	kg m^{-3}	g L^{-1}	10^4	g L^{-1}	10^4	g L^{-1}	10^4	g L^{-1}	10^5
308										
	122	771	0.32	0.6	0.88	1.8	0.53	1.0		
	152	818	0.47	0.9	1.07	2.0	0.69	1.2		
	182	850	0.53	0.9	1.31	2.4	1.05	1.8		
	213	876	0.58	1.0	1.39	2.5	1.13	1.9		
	243	897	0.80	1.4	1.77	3.1	1.45	2.4	0.05	1.1
	274	916	0.81	1.4	1.82	3.1	1.56	2.5	0.06	1.3
	304	931	0.92	1.5	1.99	3.3	1.87	3.0	0.07	1.4
	334	946	0.87	1.4	2.30	3.8	1.96	3.0	0.07	1.5
	355	955	0.75	1.2	2.40	3.9	2.40	3.7	0.08	1.6
318										
	122	661	0.52	1.2	0.68	1.6	0.28	0.6	0.02	0.6
	152	745	0.87	1.8	1.05	2.2	0.62	1.2	0.03	0.8
	182	792	1.09	2.1	1.36	2.6	1.08	2.0	0.05	1.1
	213	826	1.37	2.5	1.66	3.1	1.43	2.5	0.07	1.5
	243	852	1.96	3.5	1.87	3.4	1.67	2.9	0.08	1.7
	274	875	2.28	4.0	2.34	4.1	2.00	3.4	0.09	2.0
	304	893	3.72	6.3	2.71	4.7	2.09	3.4	0.11	2.2
	334	910	2.70	4.5	3.17	5.4	2.44	3.9	0.12	2.4
	355	919	3.19	5.3	3.35	5.6	2.65	4.2	0.14	2.8
328										
	122	516	0.6	1.9	0.54	1.6	0.29	0.8	0.01	0.3
	152	657	0.74	1.7	0.84	2.0	0.65	1.5	0.02	0.7
	182	726	1.07	2.2	1.27	2.7	1.15	2.3	0.04	1.0
	213	771	1.25	2.5	1.61	3.2	1.54	2.9	0.05	1.3
	243	804	2.30	4.3	2.11	4.1	1.85	3.4	0.08	1.9
	274	831	2.75	5.0	2.63	4.9	2.45	4.3	0.11	2.4
	304	853	2.91	5.2	2.94	5.3	2.71	4.7	0.13	2.8
	334	872	3.53	6.2	3.79	6.7	3.03	5.1	0.16	3.3
	355	884	3.75	6.5	4.04	7.1	3.53	5.9	0.17	3.6
338										
	122	396	0.3	1.0	0.42	1.6	0.44	1.6	_	_
	152	561	0.63	1.7	0.75	2.1	0.48	1.2	0.01	0.4
	182	654	1.37	3.2	1.16	2.7	0.92	2.1	0.03	1.0
	213	712	2.13	4.5	1.76	3.8	1.36	2.8	0.07	1.9
	243	754	3.24	6.5	2.31	4.7	2.17	4.2	0.10	2.6
	274	786	4.25	8.2	3.03	6.0	2.73	5.1	0.14	3.4
	304	812	4.59	8.6	3.78	7.2	3.25	5.9	0.20	4.5
	334	834	5.39	9.8	4.48	8.3	3.78	6.7	0.25	5.5
	355	848	5.51	9.9	4.95	9.0	4.85	8.4	0.32	7.1
348										
	122	327	0.2	0.8	0.39	1.8	0.10	0.4	_	_
	152	477	0.56	1.8	0.62	2.0	0.30	0.9	0.06	2.4
	182	585	1.70	4.4	1.11	2.9	0.78	2.0	0.06	2.0
	213	652	2.86	6.7	1.66	3.9	1.51	3.4	0.06	1.7
	243	702	4.21	9.1	2.38	5.2	2.75	5.8	0.10	2.7
	274	740	5.38	11.0	3.19	6.7	3.66	7.3	0.17	4.2
	304	772	6.69	13.2	4.04	8.1	4.71	9.0	0.23	5.6
	334	796	7.99	15.2	4.99	9.7	5.22	9.6	0.32	7.5
	355	811	8.92	16.7	5.82	11.1	7.97	12.3	0.41	9.4

2.2. Materials. All of the drugs (Table 1) were obtained in pure form from the Food and Drug Quality Control Lab in Tehran, Iran and used without any further purification. HPLC-grade methanol and ethanol-stabilized chloroform (Merck) were used as received. Reagent-grade picric acid (Merck) was used without any further purification expect for vacuum-drying. Doubly distilled water was used as the solvent for codeine. Pure carbon dioxide (Sabalan, Tehran, 99.99%) was used for all extractions.

3. Results and Discussion

In preliminary experiments, the solubility of lorazepam in supercritical CO_2 was found to be very low; its mole fraction solubility (x) at 348 K and 355 bar was $<10^{-6}$. Thus, because of high uncertainty of the solubility due to the low values, the solubility experiments were not performed at other experimental conditions. Table 2 represents the solubilities of drugs at temperatures (308, 318, 328, 338, and 348) K over a pressure range from (122 to 355) bar. The resulting solubilities are reported in terms of equilibrium mole fraction, x, of the solute and in g L^{-1}, s, of the solute in supercritical carbon dioxide.

$$x = n_{\text{solute}}/(n_{\text{solute}} + n_{CO_2}) \quad (1)$$

where

$$n_{\text{solute}} = [C(\mu\text{g/mL}) \times V_s(\text{mL}) \times \text{mg}/1000\ \mu\text{g}\ ]/[M_s(\text{g/mol})] \quad (2)$$

and

$$n_{CO_2} = [V_l(\mu\text{L}) \times \rho(\text{g/L}) \times \text{mL}/1000\ \mu\text{L}]/[M_{CO_2}(\text{g/mol})] \quad (3)$$

where n_{solute} and n_{CO_2} are milimoles of solute and CO_2 in sampling loop, C is the concentration of solute (μg mL^{-1}) in the collection vial that was obtained from the calibration curve, V_s (mL) and V_l (μL) are volumes of the collection vial and sampling loop, and M_s and M_{CO_2} are molecular weights of the solute and CO_2, respectively.

Each reported datum is the average of at least three replicate samples. The mole fractions of the solutes were reproducible within ±3%.

Table 2 shows the temperature and pressure effects on solubility. The effect of pressure on the solute solubility shows the usual trend. As the pressure is raised, the carbon dioxide density increases and the mean intermolecular distance of the carbon dioxide molecules decreases, thereby increasing the specific interaction between the solute molecules which increases the solubility of solid solutes.

The temperature influences the solute vapor pressure, the solvent density, and the intermolecular interactions in the fluid phase. At pressures under the crossover region (for atropine, diazepam, codeine, 150 bar and for carbamazepine, 180 bar), the solvent densities are lowered by small increases in temperature; as the density effect is dominant in this region, the solubility will decrease with the raising of temperature. At higher pressures, the solvent density is less dependent on temperature so the increase in solubility is primarily due to the higher vapor pressure of the solid. A similar retrograde solubility (crossover/pressure effect) behavior for the solubility of organic compounds in supercritical CO_2 has been reported in the literature.[7,9−11,14,15] It is interesting that, in all cases, for a given pressure above the crossover points, the highest solubility values were observed at the lowest density for the drugs (i.e., highest temperatures). On the other hand, observing no change in the UV−Vis spectra (800−200 nm) of the extracted samples in the temperature range of (308−348) K, speak for the stability of these drugs under the given conditions.

The results obtained in this study indicate that the solubility of the drugs vary in the order: atropine > diazepam > codeine > carbamazepine. The solubilities parallel the order of the relative melting point: the higher the melting point, the lower the solubility. Similar results have been reported in the literature.[10,14]

The experimental solubility data for the drugs were correlated using the following equation proposed by Bartle et al.:[16,17]

$$\ln(xP/P_{\text{ref}}) = A + C(\rho - \rho_{\text{ref}}) \quad (4)$$

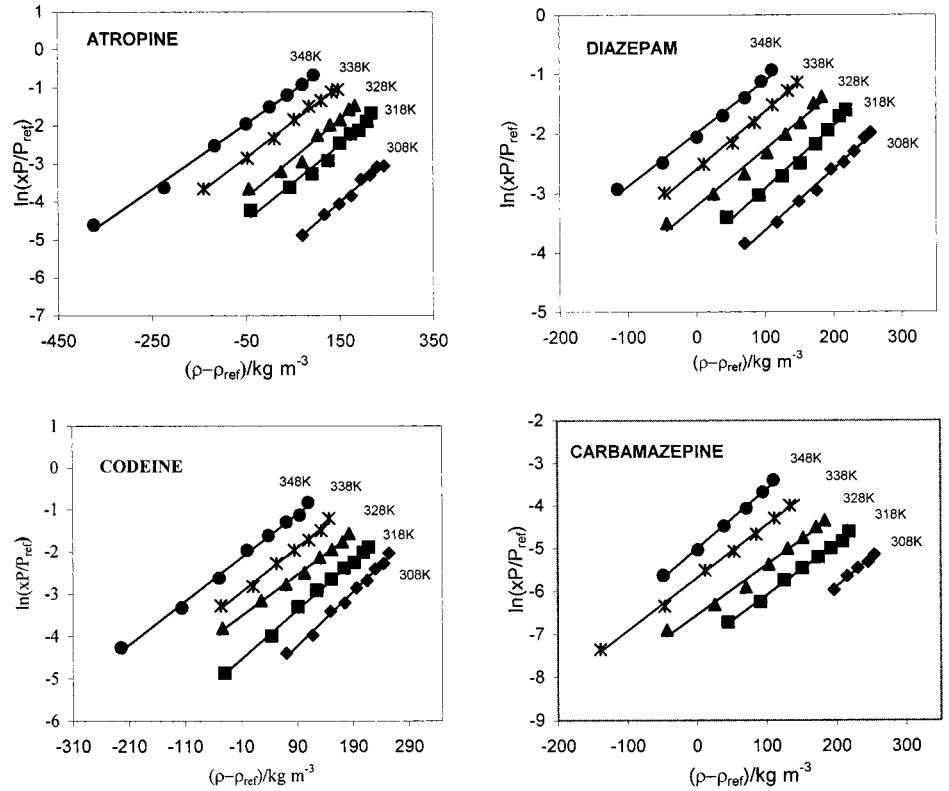


Figure 1. Plots of $\ln(xP/P_{ref})$ versus ρ for atropine, diazepam, codeine, and carbamazepine at various temperatures.

Table 3. Solubility Constant *a*, *b*, and *C* and Estimated $\Delta_{vap}H$ Values Obtained from the Data Correlation Procedure

compound	*a*	*b* / K	*C* / $m^3\ kg^{-1}$	$\Delta_{vap}H$ / kJ mol^{-1}
atropine	28.94	−10583	0.0097	88
diazepam	17.46	−6785	0.0097	56
codeine	20.62	−7923	0.011	66
carbamazepine	21.63	−9258	0.013	77

where

$$A = a + b/T \tag{5}$$

and

$$\ln(xP/P_{ref}) = a + b/T + C(\rho - \rho_{ref}) \tag{6}$$

parameteres of above eqution already were discussed.[14,16,17]

In the first step, the $\ln(xP/P_{ref})$ values were plotted against density (Figure 1), and the resulting plots were fitted to a straight line by least-squares regression to estimate *C* and *A* values. According to eq 4, the plots are expected to be reasonably straight lines of similar slopes. The value of *C* obtained from the slopes of the corresponding plots were then averaged for each compound (Table 3).

By holding *C* at its average value, the experimental solubility data were then used to evaluate the *A* values at various temperatures for each drug. The plots of *A* versus $1/T$ for each compound resulted in a nice straight line (Figure 2) from the intercept and slope of which the values of *a* and *b* were obtained, respectively. The resulting *a* and *b* values for compounds are also included in Table 3. Finally, the values of *a*, *b*, and *C* were used to predict solubility from eq 6. Figure 3 compares the calculated isoterms with the experimental data for diazepam. As seen, the agreement is satisfactory.

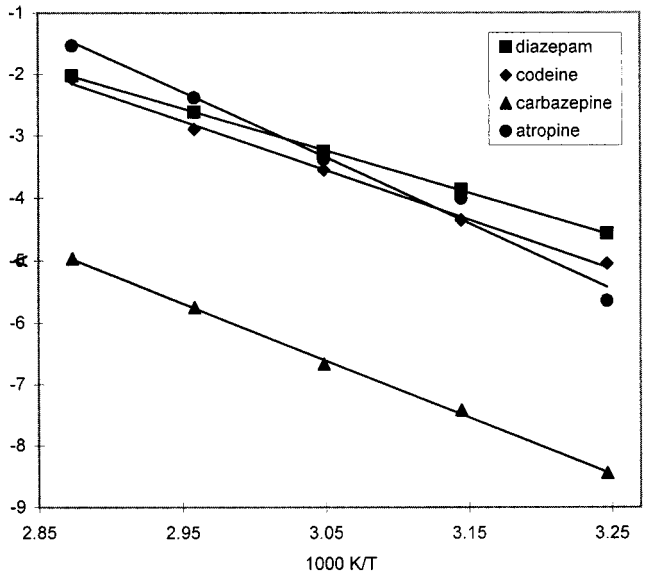


Figure 2. Plots of *A* versus $1/T$ for atropine, diazepam, codeine, and carbamazepine.

The parameter *b* is approximately related to the enthalpy of vaporization of the solid solutes $\Delta_{vap}H$ by[18]

$$\Delta_{vap}H = -Rb \tag{7}$$

where *R* is the gas constant. The validity of eq 7 relies on the assumption that the enhancement factor $\ln(xP/P_v)$, where P_v is the vapor pressure of the solute, is independent of temperature,which was found to be nearly true in practice. The estimated $\Delta_{vap}H$ values are included in Table 3.

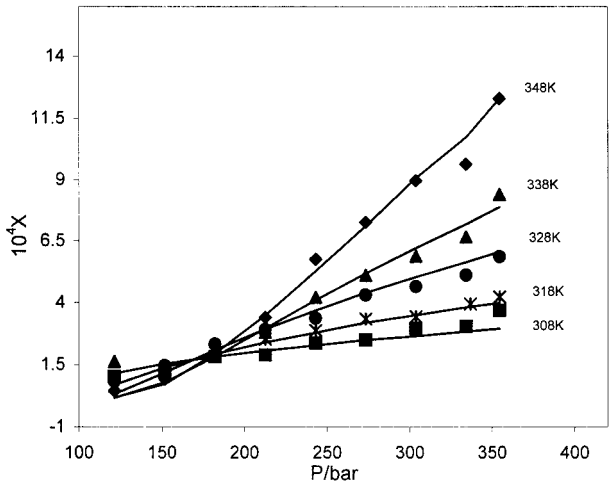


Figure 3. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for codeine.

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