Solubility of the Drugs Bisacodyl, Methimazole, Methylparaben, and Iodoquinol in Supercritical Carbon Dioxide

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Fluids have been used before for the extraction and chromatography of drugs, but only a few literature references are available on drug solubility in supercritical fluids. The objective of this work concerned the experimental determination of the equilibrium solubilities of four compounds used as drugs (bisacodyl, methimazole, methylparaben, and iodoquinol) in supercritical carbon dioxide at temperatures ranging from (308 to 348) K and pressures from (122 to 355) bar. The measurements were performed using a simple and reliable static method. Iodoquinol showed solubilities below the range in which reliable data can be obtained with the used method. Bisacodyl, methimazole, and methylparaben solubilities were successfully correlated using a semiempirical model. Correlation of the results shows good self-consistency of the data obtained. Crossover pressures were observed for all compounds.

1. Introduction

In the past two decades supercritical fluids (SCFs), particularly supercritical carbon dioxide (SC-CO_2), have been proposed as alternatives to organic solvents for many analytical extraction applications. Much of the current interest in using supercritical fluid extraction (SFE) stems from the need to replace conventional liquid solvent extraction methods with sample preparation methods that are faster and more efficient, have better potential for automation, reduce the need for large volumes of potentially hazardous liquid solvents, and also remove rapidly the solvent from the accompanying solute. In this regard, the pharmaceutical and food industries are currently examining the application of supercritical separation processes, since there exists the possibility of employing cheap and safe solvents such as carbon dioxide.[1−3] For the design of these processes, solubility data are needed as fundamental knowledge; and the correlation and extension of existing equilibrium data is an important step in the application and development of such processes. The effect of different physicochemical parameters can be better understood if solubility in the supercritical fluid is known as a function of temperature and pressure.[4]

During the past two decades a number of investigators have published equilibrium solubility data for various pharmaceutical products in SC-CO_2.[5−10] We could not find any reports for the solubility of the drug compounds bisacodyl, methimazole, methylparaben, and iodoquinol (diiodohydroxyquinoline). In the present work, solubilities of these drugs are reported in the range of various temperatures [(308, 318, 328, 338, and 348) K] and pressures [(122 to 355) bar]. From these measurements crossover pressures were observed. This crossover pressure is a phenomenological observation which appears to reflect a property characteristic of the solute−solvent system. The measured solubilities were nicely correlated using a semiempirical model proposed by Bartle et al.[11] and Safa-Ozcan et al.[12] Average deviations of less than 10% between the predicted and experimental values for the crossover pressure are achieved for most of the systems studied.

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2. Experimental Section

2.1. Materials. The carbon dioxide used in this work was supplied by Sabalan (Tehran, Iran) at a purity of 99.99%. HPLC-grade methanol (from Aldrich) was used as received. All of the drugs (with purities better than 99.5%) were obtained from the Food and Drug Quality Control Lab in Tehran, Iran, and used without any further purification except for vacuum-drying. The physical properties of the drugs used are shown in Table 1.

2.2. Equipment and Procedures. A Suprex (Pittsburgh, PA) MPS/225 system modified for the solubility determination in SFE mode was used. Modifications and operation of the instrumental apparatus have been previously described.[6,13] The reliability and efficiency of the experimental apparatus and technique were already checked by measuring the solubility of naphthalene in SC-CO_2.[14] Solubility measurements were accomplished with a 1-mL extraction vessel. The solid samples (150 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. Sintered stainless steel filters (5 μm) were used to prevent any carryover of the solutes. 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 134 μL portion of the saturated supercritical CO_2 was loaded into an injection loop. Then, the loop was depressurized into the collection vial containing methanol. To prevent solvent dispersal, the depressurizing rate of the sample loop was adjusted with a valve. Finally, the sample loop was washed with some methanol, which was collected in the collection vial. The final volume of the solution was 5 mL. The experimental uncertainties in this study are simulated to be ±1 K for temperature and ±0.5 bar for pressure.

The solubilities were determined by absorbance measurements at suitable wavelength (λ) for each compound (Table 1) using a model 2100 Shimadzu UV−Vis spectrophotometer. The stock solutions of the drug compounds were prepared by dissolving appropriate amounts of the solid samples in methanol. A set of standard solutions were

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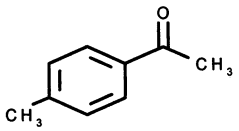
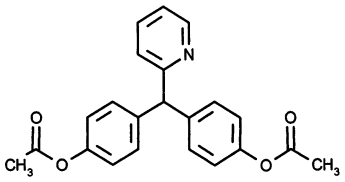
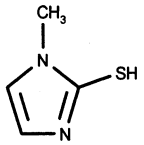
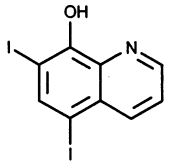
Table 1. Physical Properties of the Drugs Used

Compound	Formula	Structure	MW (g·mol^{-1})	T_m (K)	λ^a_{max} (nm)
Methylparaben	$C_8H_8O_3$		152.15	404	256
Bisacodyl	$C_{22}H_{19}NO_4$		361.40	411	220
Methimazole	$C_4H_6N_2S$		114.17	420	259
Iodoquinol	$C_9H_5I_2NO$		396.95	487	256

[a] Absorbance was measured by using methanol as solvent.

then prepared by appropriate dilution of the stock solutions. The calibration curves obtained (with regression coefficients better than 0.999) were used to establish the concentration of the drugs in the collection vial. The mole fraction compositions of the solutes were generally reproducible within ±3%.

3. Results and Discussion

In preliminary experiments, the solubility of iodoquinol in SC-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 the 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 the drugs bisacodyl, methimazole, and methylparaben at the 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 grams per liter, s, of the solute in supercritical CO_2, given by

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

where

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

and

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

where n_{solute} and n_{CO_2} are millimoles of solute and CO_2 in the sampling loop, C is the concentration of solute ($\mu g \cdot mL^{-1}$) in the collection vial that was obtained from the calibration curve, V_s (mL) and V_l (μL) are the volumes of the collection vial and the sampling loop, ρ (g·L^{-1}) is the density of CO_2 (the computer system of the Suprex MPS/225 shows the density calculations for CO_2 with the Pitzer method[15]), and M_s and M_{CO_2} are the molecular weights of the solute and CO_2, respectively.

Each reported datum is the average of at least two replicate samples. From the data given in Table 2 it is readily seen that the solubility of compounds increases with increasing pressure at constant temperature. 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 the solid samples. The influence of pressure on the solubilities is more pronounced at higher temperatures. For example, raising the pressure from 122 to 355 bar enhanced the solubility of bisacodyl by a factor of 3.9 at 308 K and a factor of 49.2 at 338 K. Obviously, this is in contrast to conventional wisdom stating that the supercritical fluid's density must increase in order to increase the solubility and extraction efficiency.[16,17]

By observing the effect of the temperature on the solubilities, we revealed the existence of a retrograde (crossover pressure effect) behavior for all drugs, as was reported for different organic compounds previously.[6–8,13,14,18] The different effects of temperature on the solubilities are due to the influences of temperature on the solute vapor pressure, the solvent density, and the intermolecular interactions in supercritical fluid phase. At pressures under the crossover region (for bisacodyl and methimazole, 180 bar; for methylparaben, 150 bar), the solvent density is lowered by small increases in temperature and, as the density effect is dominant in this region, the solubility decreases with the raising of temperature. At higher

Table 2. Solubilities of the Drugs Methylparaben, Bisacodyl, and Methimazole in Supercritical CO_2 at Various Temperatures and Pressures

			methylparaben		bisacodyl		methimazole	
T/K	P/bar	ρ/kg·m^{-3}	10^4x	s/g·L^{-1}	10^4x	s/g·L^{-1}	10^4x	s/g·L^{-1}
308	122	771	1.13	0.30	0.36	0.23	0.22	0.04
	152	818	1.35	0.38	0.52	0.37	0.23	0.05
	182	850	1.60	0.47	0.71	0.50	0.29	0.06
	213	876	1.88	0.57	0.81	0.59	0.40	0.09
	243	897	1.94	0.60	1.00	0.74	0.45	0.10
	274	916	2.09	0.66	1.06	0.80	0.50	0.12
	304	931	2.33	0.75	1.20	0.92	0.53	0.13
	355	955	2.56	0.84	1.39	1.09	0.60	0.14
318	122	661	1.13	0.26	0.27	0.17	0.21	0.04
	152	745	1.57	0.40	0.44	0.27	0.21	0.04
	182	792	2.00	0.55	0.71	0.46	0.32	0.07
	213	826	2.48	0.70	0.89	0.60	0.40	0.09
	243	852	2.62	0.77	1.13	0.79	0.55	0.12
	274	875	3.01	0.91	1.39	1.00	0.63	0.14
	304	893	3.45	1.07	1.58	1.16	0.70	0.16
	355	919	3.96	1.26	2.03	1.53	0.83	0.20
328	122	516	1.08	0.19	0.22	0.09	0.19	0.02
	152	657	1.70	0.39	0.37	0.19	0.20	0.03
	182	726	2.37	0.60	0.63	0.38	0.35	0.07
	213	771	3.00	0.80	0.98	0.62	0.51	0.10
	243	804	3.51	0.98	1.45	0.96	0.64	0.13
	274	831	3.95	1.13	1.90	1.30	0.74	0.16
	304	853	4.22	1.25	2.27	1.59	0.92	0.20
	355	884	4.93	1.51	2.97	2.15	1.18	0.27
338	122	396	1.18	0.16	0.09	0.03	0.15	0.01
	152	561	1.73	0.34	0.23	0.11	0.17	0.03
	182	654	2.95	0.67	0.58	0.31	0.35	0.09
	213	712	4.22	1.04	0.96	0.56	0.52	0.10
	243	754	4.51	1.18	1.79	1.11	0.77	0.15
	274	786	5.47	1.48	2.51	1.62	0.90	0.18
	304	812	6.41	1.80	3.09	2.06	1.16	0.24
	355	848	7.19	2.11	4.43	3.09	1.49	0.33
348	122	327	1.35	0.15				
	152	477	1.85	0.31	0.19	0.07	0.12	0.02
	182	585	3.45	0.70	0.54	0.26	0.30	0.04
	213	652	5.03	1.13	1.30	0.70	0.52	0.09
	243	702	6.02	1.51	2.05	1.18	0.85	0.16
	274	740	8.08	2.07	2.82	1.72	1.12	0.22
	304	772	9.60	2.56	4.06	2.58	1.38	0.28
	355	811	12.13	3.40	5.83	3.88	1.90	0.40

pressures, the solvent density is less dependent on temperature so the increase of the solubility is primarily due to the higher vapor pressure of the solute.

The results obtained in this study indicate that the solubilities of the drugs vary in the order methylparaben > bisacodyl > methimazole. 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.[6,7,10,13,14]

The correlations were based on the concept of solubility enhancement,[18] from which the following equations were derived[11,12]

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

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} was used,[11] and A and C are constant values for a given temperature. The reason for using ρ_{ref} is to make the constant A much less sensitive to experimental errors in the solubility data to avoid the large variations caused by extrapolation to zero density. The value of C, which results physically from solvation of the solute by the supercritical fluid, is assumed to remain constant over the entire temperature range studied. This

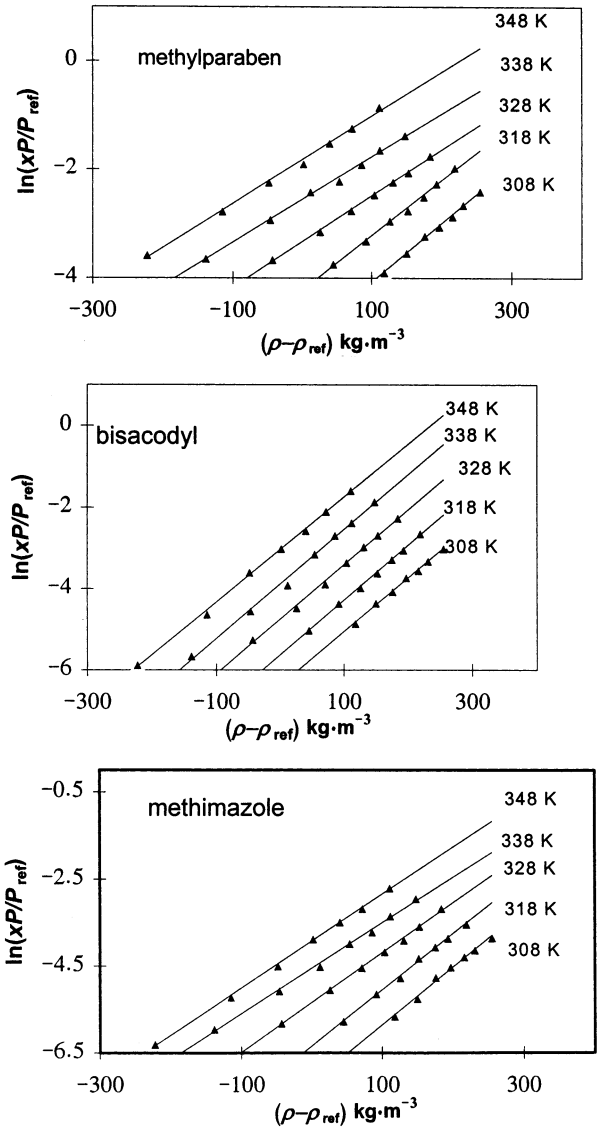


Figure 1. Plots of $\ln(xP/P_{ref})$ versus $(\rho - \rho_{ref})$ for methylparaben, bisacodyl, and methimazole.

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

compound	a	b/K	C/m^3·kg^{-1}	$\Delta_{sub}H$/kJ·mol^{-1}
methylparaben	21.30	−8067	0.009 05	67.0
bisacodyl	22.89	−9043	0.013 30	75.2
methimazole	19.36	−8104	0.011 78	67.4

point has already been reported by Bartle and co-workers.[11,12] While the value of A, which arises from the vapor pressure (fugacity) of the solute, is assumed to obey the equation

$$A = a + b/T \quad (5)$$

where T is the absolute temperature and a and b are constants. Substitution of eq 5 into eq 4 will result in

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

The initial stage is to plot $\ln(xP/P_{ref})$ for each isotherm against density (Figure 1) and fit the plots to a straight line by least squares to obtain A (the value of the fitted line at ρ_{ref}) and C. According to eq 4, these plots are expected to be reasonably straight lines of similar slopes.

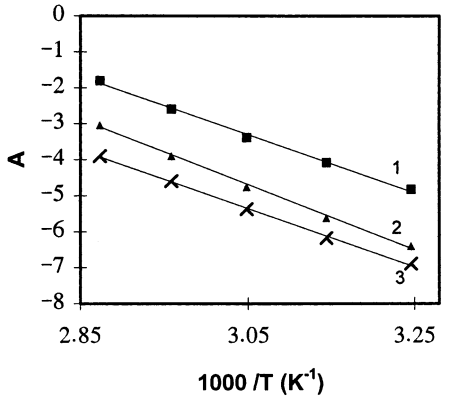


Figure 2. Plots of A versus $1/T$ for methylparaben (1), bisacodyl (2), and methimazole (3).

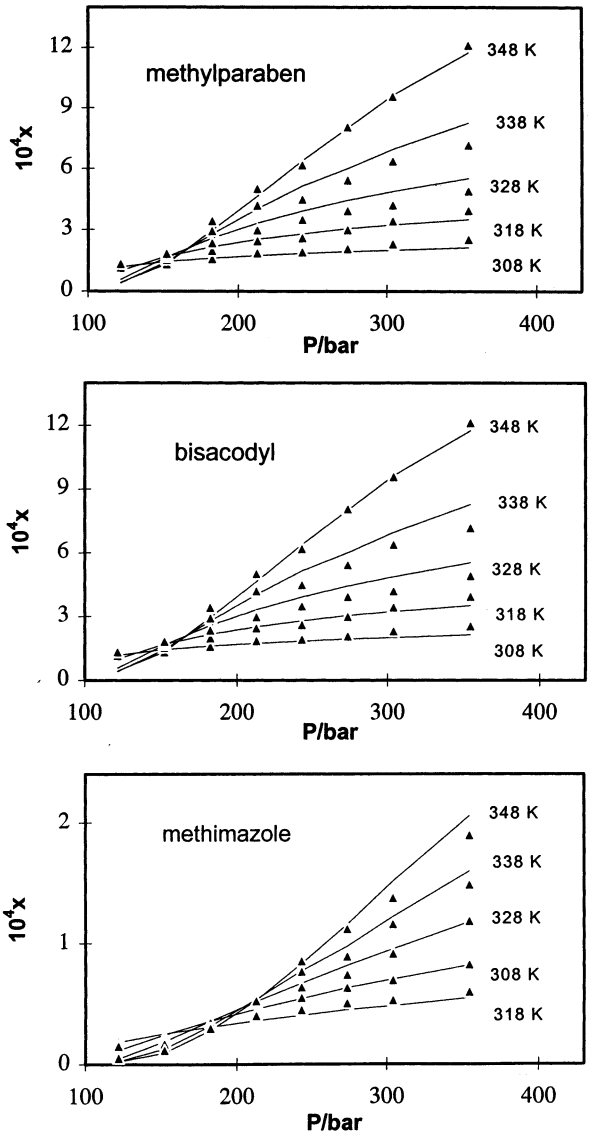


Figure 3. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for methylparaben, bisacodyl, and methimazole.

However, as it is seen from Figure 1, the slopes show a small increase at lower temperatures. Such deviations can be improved by removing the experimental points at lower pressures from the corresponding graphs. The values 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 (Table 3).

Finally, the values of a, b, and C were used to predict solubility from eq 6. Figure 3 compares the calculated isotherms with the experimental data for all three drugs. As seen, the agreement is satisfactory, and the poor consistency is limited to data points obtained at the high-pressure limits of the isotherms, which are close to the melting points of the drugs. Similar results have been observed previously.[13,16]

The parameter b is approximately related to the enthalpy of sublimation of the solid solutes $\Delta_{sub}H$ by[16]

$$\Delta_{sub}H = -Rb \qquad (7)$$

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 $\Delta_{sub}H$ values are also included in Table 3.

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