Solubilities of the Drugs Benzocaine, Metronidazole Benzoate, and Naproxen in Supercritical Carbon Dioxide

Aziz Garmroodi, Jalal Hassan, and Yadollah Yamini*

Department of Chemistry, Tarbiat Modarres University, Tehran, Iran

The solubilities of the drugs benzocaine, metronidazole benzoate, and naproxen in supercritical carbon dioxide were measured at pressures ranging from (122 to 355) bar and temperatures ranging from (308 to 348) K. These drugs have mole fraction solubilies between 1.0×10^{-5} and 1.2×10^{-2}, which are high enough to make the supercritical impregnation process a feasible alternative to impregnation employing organic solvents. Crossover pressures of (150, 180, and 150) bar were found for benzocaine, metronidazole benzoate, and naproxen, respectively. The solubility data were correlated with a semiempirical model.

Introduction

Conventional pharmaceutical processing involves extensive use of organic solvents for recrystallizing drugs from solutions, as reaction media for the synthesis of drugs, or as extraction agents for selectively isolating drugs from solid matrices. A major research focus in this regard has been the investigation of processes in which the traditional solvents are replaced with supercritical carbon dioxide. Among the reported applications are the formation of drug particles using dense carbon dioxide either as a solvent or nonsolvent and the "clean" synthesis of drug compounds using carbon dioxide as a reaction medium.[1,2] Supercritical fluid exctraction (SFE) is also applied on a laboratory scale as a preliminary step to drug analysis by various techniques such as spectrophotometry[3] and chromatography.[4−6]

For all of these processes, knowledge of solubility of drugs in supercritical fluids is important. Numerous research groups have measured the solubility of pharmaceutical products in different supercritical fluids.[7−11] In this work, the solubilities of benzocaine, metronidazole benzoate, and naproxen in supercritical carbon dioxide were measured over the temperature range of (308 to 348) K and at pressures from (122 to 355) bar. From these measurements, crossover pressures were ascertained. Modeling of the resultant data was carried out using a density-based correlation proposed by Bartle et al.[12]

Benzocaine is a chemical used in medicinal preparations to alleviate pain caused by skin burns.[13] Metronidazol is used for the treatment of symptomatic trichomoniasis in females and males where the presence of the trichromonad has been confirmed by appropriate laboratory procedures. Naproxen is used for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. It also provides relief of mild to moderate pain and is used for the treatment of primary dysmenorrheal.[14] To the best of our knowledge, there is no any report about the solubility of benzocaine and metronidazole benzoate in supercritical CO_2. On the other hand, the solubility of naproxen in pure and modified supercritical CO_2 was determined at temperatures of (313, 323, and 331) K and pressure range of (89.6−193.1) bar by Foster et al.[15] In the present work, solubilities of naproxen are reported at different pressures and temperatures than that reported in ref 15.

* To whom correspondence may be addressed. E-mail: yyamini@modares.ac.ir.

Experimental Section

Equipment and Procedure. A Suprex (Pittsburgh) MPS/225 integrated SFE/supercritical fluid chromatography (SFC) system, equipped with a static system for the solubility determination in the SFE mode, was used. A detailed description of the apparatus and experimental procedure is given elsewhere.[16,17] In this system, contact between the species and the fluid is established. After the equilibrium is reached, a known volume of the saturated fluid of the species is chosen and the amount of the solute is measured. Then the solubility is calculated. The solid solutes (100 mg) were mixed well with glass beads and packed into the 1-mL extraction vessel. Supercritical CO_2 was then pressurized and passed into the extraction vessel. After equilibrium was attained at the desired temperature and pressure (for about 30 min), a 143-μL aliquot of the supercritical CO_2 solution was loaded into an injection loop. The loop was then depressurized into the collection vial containing methanol as solvent. Finally, the same sample loop was washed with the identical solvent, which was charged into the collection vial. The final volume of the resultant solution was 5 mL.

The solubilities of drugs were calculated by absorbance measurements at suitable wavelengths for each compound (Table 1) using a Model 2100 Shimadzo UV−Vis spectrophotometer (Shimadzo Co., Japan) with 1-cm length quartz cell. The stock solution of the drug compound (100 $\mu g \cdot mL^{-1}$) was prepared by dissolving appropriate amounts of pure solid samples in methanol. A set of standard solutions was then prepared by appropriate dilution of stock solutions. The calibration curves obtained (with regression coefficients better than 0.999) were used to establish the concentrations of drugs contained in the collection vial. The mole fraction composition of the solutes was generally reproducible within ±4% (given a standard deviation on at least three replicated measurements).

Materials. All of the drugs, benzocaine, metronidazol benzoate, and naproxen (with purities better than 99 mass %), were obtained from the Food and Drug Quality Control Lab in Tehran, Iran and used without further purification.

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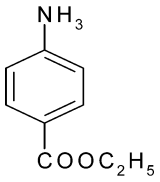
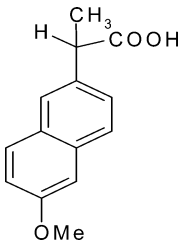
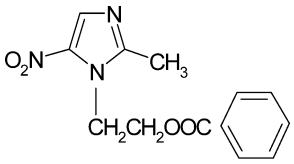
Table 1. Physical Properties of the Drugs Used

compound	formula	structure	MW/g·mol^{-1}	T_m/K	λ/nm
benzocaine	$C_9H_9NO_2$		165.1	365.15	290
naproxen	$C_{14}H_{14}O_3$		230.3	392.45	232
metronidazole benzoate	$C_{13}H_{13}N_3O_4$		275	375.15	312

Absorbance was measured by using methanol as solvent.

HPLC-grade methanol (Merck) was used as received. Pure carbon dioxide (Sabalan, Tehran, 99.99 %) was used for all extractions.

Results and Discussion

Theory. 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, y, of the solute and s (in g·L^{-1}) of the solute in supercritical CO_2. Each reported value is the average of at least three replicate samples. The mole fraction of the solutes was reproducible within ±4%.

The measurement solubilities were correlated with the following equation

$$\ln(yP/P_{ref}) = A + C(\rho - \rho_{ref}) \quad (1)$$

where

$$A = a + b/T \quad (2)$$

yielding

$$\ln(yP/P_{ref}) = a + b/T + C(\rho - \rho_{ref}) \quad (3)$$

Here, P_{ref} is a standard pressure of 1 bar and ρ_{ref} is a reference density for which a value of 700 kg·m^{-3} was used. The reason for using ρ_{ref} is to make the constant A much less sensitive to experimental errors in the solubility data and to avoid the large variations caused by extrapolation to zero density.[12] The other terms in the above equations have already been discussed.[12,16]

From the experimental data, each solubility isotherm was fitted to eq 1 to obtain the values of A and C (Figure 1). The values of C were then averaged for each compound (Table 3). The values of A were then plotted against $1/T$ for each drug (Figure 2), and the values of a and b were obtained from eq 2 and are given in Table 3. Finally, the values of a, b, and C were used to predict the drug's solubility from eq 3. Figure 3 compares the calculated isotherms with the experimental data for all drugs. One can see the agreement between the calculated and experimental values for these drugs is good. Therefore, the Bartle equation provides a good fit of the experimental data yielding average absolute relative deviations in the range of 5−21 (Table 3). It should be noted that the parameter b is approximately related to the enthalpy of sublimation of the solid solutes $\Delta_{sub}H$ by[18]

$$\Delta_{sub}H = -Rb \quad (4)$$

where R is the gas constant. The estimated $\Delta_{sub}H$ values are included in Table 3.

Discussion. Table 2 shows the temperature and pressure effects on solubility. Increasing the pressure of the supercritical CO_2 at a constant temperature results in increasing its density and thereby its solvent strength. One way of justifying this observation is to use a modified version of the Hildebrand equation (eq 5), which gives the solvent strength (Hildebrand solubility parameters, δ) as a function of the reduced density of the supercritical fluid (ρ_{SF}) with respect to the reduced density of a typical fluid in liquid stage (ρ_L) and the critical pressure of the fluid (P_c)[19]

$$\delta = 1.25P_c^{1/2}(\rho_{SF}/\rho_L) \quad (5)$$

Since theoretically, as the density of the supercritical CO_2 is raised, the solubility of solid solutes is increased. Thus, the maximum solubility of the analyte is achieved when the density of the supercritical CO_2 is equivalent to the density of the target analyte. It is worthy to note that in our experimental conditions the density of supercritical CO_2 is far from the density of the target analyte.

The temperature also influences the solute vapor pressure, the solvent density, and the intermolecular interactions in the fluid phase. When the pressure of the supercritical CO_2 is constant and temperature is increased, the effect on solvent strength depends on the density. If this pressure is below the crossover region (for bezocaine and

Table 2. Solubilities of the Drugs Benzocaine, Naproxen, and Metronidazole Benzoate in Supercritical Carbon Dioxide

		benzocaine		naproxen		metronidazole benzoate	
P	ρ		s		s		s
bar	kg·m^{-3}	$10^4\,y$	g·L^{-1}	$10^4\,y$	g·L^{-1}	$10^4\,y$	g·L^{-1}
			$T = 308$ K				
122	771	10.30	2.98	0.10	0.05	4.90	2.38
152	818	10.60	3.27	0.20	0.08	5.40	2.76
182	850	12.80	4.10	0.20	0.09	6.10	3.23
213	876	13.80	4.56	0.20	0.09	7.00	3.86
243	897	14.70	4.96	0.20	0.11	8.40	4.73
274	916	16.40	5.64	0.30	0.13	9.50	5.44
304	931	17.60	6.26	0.30	0.15	10.80	6.31
355	955	20.00	7.18	0.40	0.19	13.90	8.34
			$T = 318$ K				
122	661	10.60	2.63	0.20	0.06	2.70	1.11
152	745	12.10	3.39	0.20	0.08	3.70	1.75
182	792	15.30	4.55	0.20	0.10	7.20	2.57
213	826	18.10	5.62	0.30	0.12	6.90	3.59
243	852	18.20	5.83	0.30	0.15	8.80	4.70
274	875	20.30	6.69	0.40	0.17	10.80	5.93
304	893	22.80	7.64	0.40	0.19	12.70	7.09
355	919	22.50	7.78	0.50	0.23	14.70	8.44
			$T = 328$ K				
122	516	8.30	1.61	0.10	0.03	1.50	0.48
152	657	13.40	3.31	0.20	0.06	3.50	1.45
182	726	18.90	5.15	0.20	0.09	5.60	2.53
213	771	25.10	7.27	0.30	0.12	8.20	3.97
243	804	28.30	8.56	0.40	0.17	10.50	5.28
274	831	34.60	10.84	0.50	0.20	12.50	6.49
304	853	36.00	11.56	0.50	0.24	14.40	7.68
355	884	39.00	12.99	0.80	0.35	17.70	9.80
			$T = 338$ K				
122	396	3.90	0.58	0.20	0.03	0.70	0.16
152	561	12.70	2.68	0.20	0.06	2.40	0.83
182	654	23.00	5.67	0.30	0.10	5.10	2.10
213	712	31.30	8.39	0.40	0.15	8.70	3.86
243	754	42.60	12.12	0.60	0.23	12.60	5.93
274	786	56.00	16.61	0.70	0.28	16.20	8.00
304	812	64.40	19.74	0.80	0.34	22.70	11.57
355	848	78.20	25.06	1.10	0.51	27.90	14.87
			$T = 348$ K				
122	327	2.70	0.33	0.10	0.02	1.60	0.32
152	477	9.60	1.73	0.20	0.04	4.07	1.40
182	585	20.30	4.47	0.30	0.09	5.50	2.03
213	652	33.00	8.10	0.50	0.16	11.80	4.83
243	702	49.30	13.06	0.70	0.25	17.50	7.68
274	740	73.70	20.61	1.00	0.40	22.90	10.62
304	772	86.50	25.28	1.30	0.52	30.20	14.63
355	811	121.20	37.35	2.00	0.84	45.50	23.17

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

		b	C	$\Delta_{sub}H$	AAPD[a]
compound	a	K	m^3·kg^{-1}	kJ·mol^{-1}	%
benzocaine	24.1	−8325	0.0093	69	5−12
naproxen	20.5	−8519	0.0102	71	8−20
metronidazole benzoate	22.6	−8221	0.0121	68	16−21

[a] AARD = $(100/N)\{\sum(y^{exp} - y^{cal})/y^{cal}\}$, where y^{exp} and y^{cal} are the experimental and calculated solubility values and N is the number of data points.

naproxen, 150 bar, and for metronidazol benzoate, 180 bar), increasing the temperature leads to lower solvent strength of the CO_2 due to a decrease in fluid density. Above the crossover region, an increase in temperature usually improves the extraction efficiency despite the decrease in fluid density, since the vapor pressure of the analyte is increased. The crossover region depends on the solute−

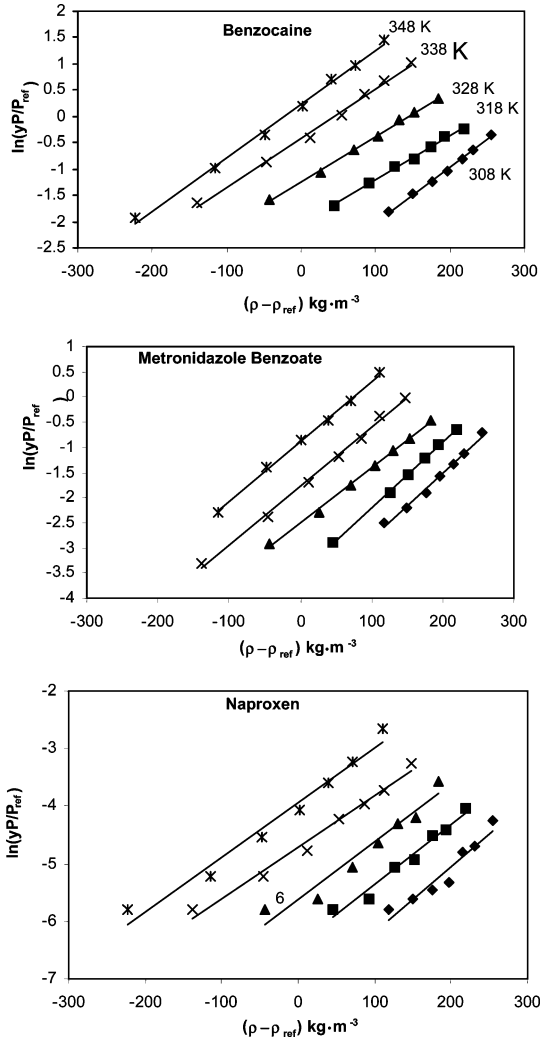


Figure 1. Plots of $\ln(yP/P_{ref})$ vs $(\rho-\rho_{ref})$ for benzocaine, metronidazole benzoate, and naproxen.

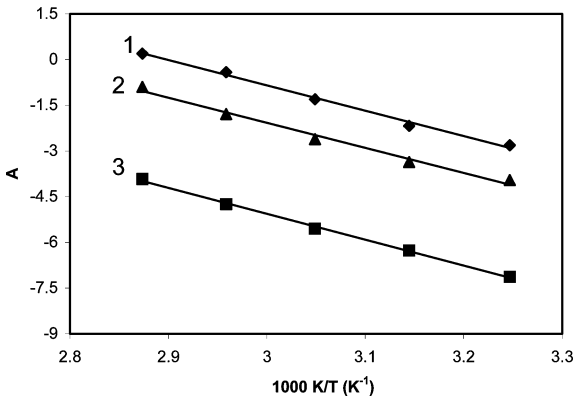


Figure 2. Plots of A vs $1/T$ for benzocaine (1), metronidazole benzoate (2), and naproxen (3).

supercritical CO_2 interaction and has been reported for numerous organic compounds in the literature.[1,8,16,17,20,21]

The results obtained in this study indicate that the solubilities of drugs vary in the order: benzocaine > metronidazole benzoate > naproxen. These solubilities parallel the order of the relative melting points of the solutes; the higher the melting point, the lower the solubility. Similar trends have been reported in the literature.[8,17,20]

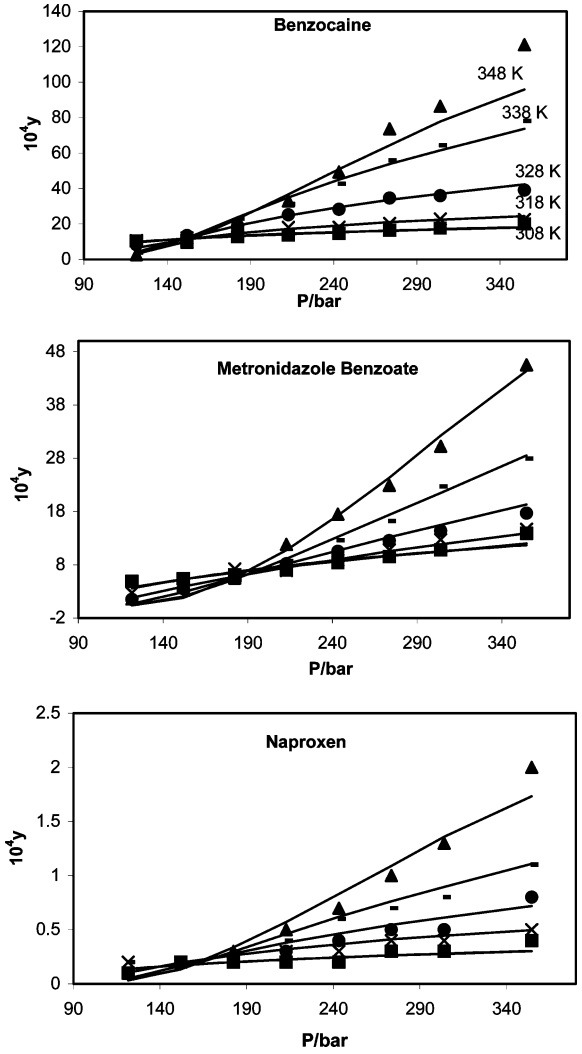


Figure 3. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for benzocaine, metronidazole benzoate, and naproxen.

Conclusion

The equilibrium solubilities were measured for benzocaine, metronidazole benzoate, and naproxen in supercritical CO_2 at (308, 318, 328, 338, and 348) K in the pressure range of (122 to 355) bar were determined. The observed drug solubilities ranged from $y = 2.7 \times 10^{-4}$ to 121.2×10^{-4} for benzocaine, from $y = 0.7 \times 10^{-4}$ to 45.5×10^{-4} for benzocaine, and from $y = 0.1 \times 10^{-4}$ to 2.0×10^{-4} for naproxen. The solubilities are correlated using a semiempirical Bartle model. Results show that the Bartle method holds in the pressure range of (120 to 350) bar. Results of this study show that extraction and purification of these drugs is possible using supercritical carbon dioxide.[12]

Note Added after ASAP Posting. This article was released ASAP on 4/9/2004. In Figure 1, the top portion was replaced to reflect the data for benzocaine. The paper was reposted on 4/14/2004.

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