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Short communication

Solubilities of phenazopyridine, propranolol, and methimazole in supercritical carbon dioxide

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Abstract

The equilibrium solubilities of three drugs (phenazopyridine, propranolol and methimazole) were determined at temperatures ranging from 308 to 348 K and pressures from 122 to 355 bar in supercritical CO_2 by a simple and reliable static method. The crossover region was observed for phenazopyridine, propranolol and methimazole at 180 bar. The solubilities were correlated using a semi empirical model. Correlation of the results shows good self-consistency of the data obtained.

Keywords: Solubility; Supercritical; Phenazopyridine; Propranolol; Methimazole

1. Introduction

One of the promising fields in separation science during recent three decades is supercritical and specifically supercritical carbon dioxide [1]. Supercritical fluid extraction (SFE) has been widely used to the extraction processes in pharmaceutical industries [2–6]. Besides application of SFE in pharmaceuticals, it has been applied on a wide spectrum of natural products and food industries such as natural pesticides, antioxidants, vegetable oil, flavors, perfumes and etc. The key factor in the successful development of a process involving supercritical fluids in both the laboratory and on the industrial scale is the availability of accurate and reliable solubility data [5].

Information on solubility of pharmaceutical products in supercritical fluids is of vital importance. This is for the possibility of efficient extraction or separation on the basis of supercritical fluids. Present work is undertaken to determine the solubilities of three drugs (phenazopyridine, propranolol, and methimazole) in supercritical carbon dioxide over a wide range of temperatures and pressures. Phenazopyridine is a drug that used in the management of genitourinary tract infections. Propranolol as mixed with hydrochlorthiazide is applied in the cardiovascular drugs and methimazole is an antithyroid drug for the preparation of the hyperthyroid patient for surgery and for the total treatment of hyperthyroidism [7].

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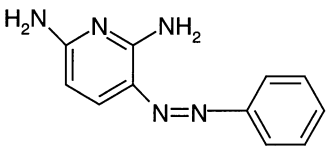
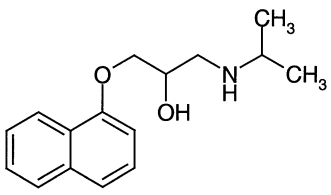
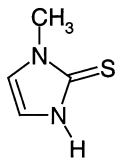
Table 1
Physical properties of the drugs

Compound	Molecular formula	Molecular structure	Melting point (°C)	λ max (nm).
Phenazopyridine	$C_{11}H_{11}N_5$		139	417
Propranolol	$C_{16}H_{21}NO_2$		96	290
Methimazole	$C_4H_6N_2S$		144	257

2. Experimental

2.1. Materials

All of the drugs were obtained (with purities better than 99.5%) from the Food and Drug Quality Control Lab in Tehran, Iran and used without any further purification. Ethanol 96% (Panreac, Barcelona, Spain) was used as received. Pure carbon dioxide (Sabalan, Tehran, Iran 99.99%) was used for all extractions.

2.2. Procedure

The schematic diagram of experimental apparatus and a detailed description of the apparatus and operating procedures are available in the literature [8]. A Suprex (Pittsburgh, PA) MPS/225 integrated SFE/SFC system equipped with a modified static system for the solubility determination in the SFE mode was used. Solubility measurement 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. One hundred milligram of each drug (Table 1) was mixed with proper amounts of glass beads and packed into the extraction vessel. This procedure prevents channeling, increases the contact surface between the sample and supercritical fluid, and consequently reduces the equilibration time. Sintered stainless steel filters (5μm) were used to prevent any carry-over of the drugs.

Supercritical CO_2 was pressurized and passed into the vessel. After equilibrium at the desired temperature and pressure was reached (about 30 min), a 132 μl portion of saturated supercritical carbon dioxide was loaded into an injection loop. Then, loop was depressurized into the collection vial containing ethanol. The sample loop finally was washed with ethanol, which was collected in the collection vial. The final value of the solution was 5 ml. The equilibrium temperature and pressure were measured to an accuracy of ± 1 K and ± 0.5 bar, respectively.

The solutions of phenazopyridine, propranolol, and methimazole were calculated by absorbance measurements at suitable wavelength (λ) for each compound (Table 1) using a model 2100 Shimadzu UV–Vis spectrophotometer with 1-cm pass length quarts cell. The stock solution of each compound (1000 μg ml^{-1}) was prepared by dissolving 10 mg of compound in 10 ml of ethanol. 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 establish the concentration of compounds in the collection vial.

3. Results and discussion

The supercritical carbon dioxide solubilities of the three drugs, phenazopyridine, propranolol and methimazole were determined, and the values are listed in Table 2. Each reported data point is the average of at least three replicate samples. The mole fraction solubilities of the solutes were reproducible within $\pm 3\%$. Examination of the solubility data in Table 2 reveals that the solubilities of drugs increase with an increase in pressure at all temperatures. This may be due to the increase of CO_2 density with increasing pressure since CO_2 density is directly related to the dissolving power of CO_2 [9]. However, despite the decreased density of CO_2 at higher temperatures (at constant pressures) 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 phenazopyridine by a factor of 4.09 at 308 K and a factor of 57.87 at 348 K. Obviously, this is contrast to conventional wisdom stating that the supercritical fluid's density must increase in order to increase the solubility and extraction efficiency [10,11]. The data given in Table 2 clearly reveal that while, at a constant temperature, increasing density (by increasing pressure) enhances the solubility, the increase in density at a constant pressure (by lowering temperature) actual results in diminished solubility. Similar observations have already been reported in the literature [11–13].

From the effect of temperature on solubilities (Table 2) it is found that the retrograde solubility (crossover/pressure effect) behavior for the compounds exists in the supercritical state. At pressure under the crossover region (about 180 bar for

Table 2
Solubilities of phenazopyridine, propranolol and methimazole in supercritical carbon dioxide

T (K)	P (bar)	ρ (kg m^{-3})	Phenazopyridine 10^5X	Propranolol 10^5X	Methimazole 10^5X
308	122	771	1.50	3.67	2.23
	152	818	2.05	6.10	2.31
	182	850	2.63	7.52	2.95
	213	876	3.22	8.53	4.03
	243	897	3.84	9.34	4.49
	273	916	4.44	11.02	5.04
	304	931	4.78	13.08	5.29
	334	946	5.10	15.16	–
	355	955	5.68	15.02	5.99
318	122	661	1.45	5.84	2.13
	152	745	2.13	8.72	2.06
	182	792	3.10	10.57	3.22
	213	826	4.18	12.04	4.02
	243	852	5.16	14.36	5.50
	273	875	6.18	17.51	6.33
	304	893	7.36	21.84	6.95
	334	910	8.09	27.89	–
	355	919	8.76	30.42	8.25
328	122	516	1.12	4.27	1.89
	152	657	1.84	8.21	1.97
	182	726	2.79	12.32	3.54
	213	771	4.42	17.99	5.07
	243	804	5.99	23.53	6.37
	273	831	7.14	30.36	7.39
	304	853	8.69	40.00	9.16
	334	872	9.89	47.39	–
	355	884	10.82	66.39	11.84
338	122	396	0.44	3.58	1.51
	152	561	1.49	8.56	1.73
	182	654	3.16	14.97	3.47
	213	712	5.15	22.56	5.19
	243	754	7.69	31.90	7.67
	273	786	9.99	50.02	8.93
	304	812	12.18	70.22	11.60
	334	834	14.91	90.07	–
	355	848	16.84	116.23	14.86
348	122	327	0.71	4.14	0.54
	152	477	1.18	11.30	1.22
	182	585	2.91	17.13	3.00
	213	652	5.52	30.27	5.25
	243	702	8.84	46.34	8.54
	273	740	12.19	70.80	11.21
	304	772	15.61	95.80	13.78
	334	796	19.31	169.45	–
	355	811	20.21	239.61	18.99

phenazopyridine, propranolol and methimazole) the concentration of the solute in the supercritical phase decreases as temperature is increased. Beyond the crossover region, the solubilities increase with increase of both the temperature and pressure. The different effects of temperature on the solubilities are due to the influences of temperature on the vapor pressure, the density, and the

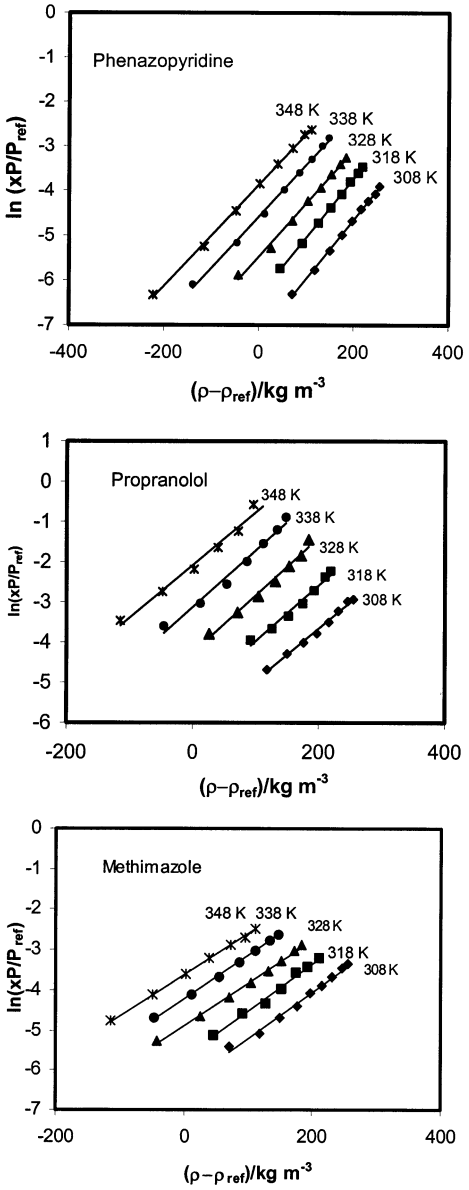


Fig. 1. Plots of $\ln(xP/P_{ref})$ vs. $(\rho-\rho_{ref})$ for phenazopyridine, propranolol and methimazole.

molecular interaction of the supercritical phase. The existence of a crossover pressure in solid supercritical fluid systems has been suggested as on indicated of the reliability and consistency of experimental solubility data [14]. The results obtained in this study indicate that the solubilities of drugs vary in the order propranolol > methimazole > phenazopyridine. The solubilities of propranolol–methimazole and propranolol–phenazopyridine is parallel to the order of their relative melting points (Table 1), i.e. the higher the melting point, the lower the solubility. Similar results reported in literature [15,8]. The melting points of methimazole and phenazopyridine have not shown considerable differences, thus increased solubility of methimazole could be related to the polarities of drugs. On the other hand, observing no change in the UV–Vis spectra (800–200 nm) of the extracted sample in the temperature range of 308–348 K, speak for the stability of these drugs under the given conditions. The experimental solubility data for the drugs were correlated using the following equation proposed by Bartle et al. [12,16]:

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

where:

$$A = a + \frac{b}{T} \quad (2)$$

and:

$$\ln\left(\frac{xP}{P_{ref}}\right) = a + \frac{b}{T} + C(\rho - \rho_{ref}) \quad (3)$$

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 [12], 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. 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 point has already been reported by Bartle and co-workers [12,16]. In the first step, the $\ln(xP/P_{ref})$ values were plotted against density (Fig. 1), and the resulting plots were fitted to a straight line by least-squares regression to estimate A and C values. According to Eq. (1), the plots are expected

Table 3
Solubility constants of a, b and C and the estimated ΔH_{sub} values obtained from the data correlation procedure

Compound	a	b (K)	C (m^3 kg^{-1})	ΔH_{sub} (kJ mol^{-1})	AARD%
Phenazopyridine	22.75	−9257	0.012	76.7	10.4–16.6
Propranolol	30.53	−11 384	0.013	94.6	4.8–23.7
Methimazole	19.36	−8104	0.012	67.4	10.6–18.2

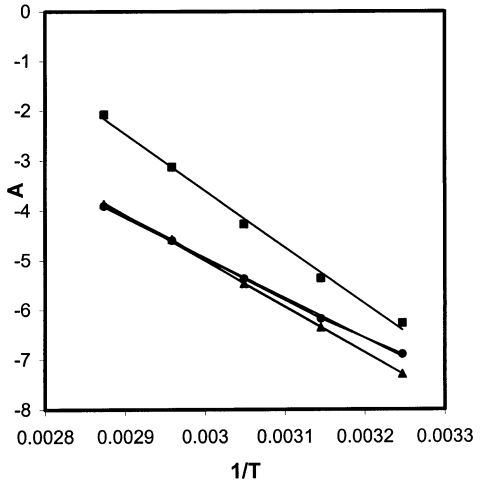


Fig. 2. Plots of A vs. $1/T$ for phenazopyridine (▲), propranolol (■), and methimazole(●).

to be reasonably straight lines with similar slopes. However, 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 (Fig. 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 reported in Table 3.

Finally, having the values of a, b and C parameters and considering the fact that the ρ values are known at any specific temperature and

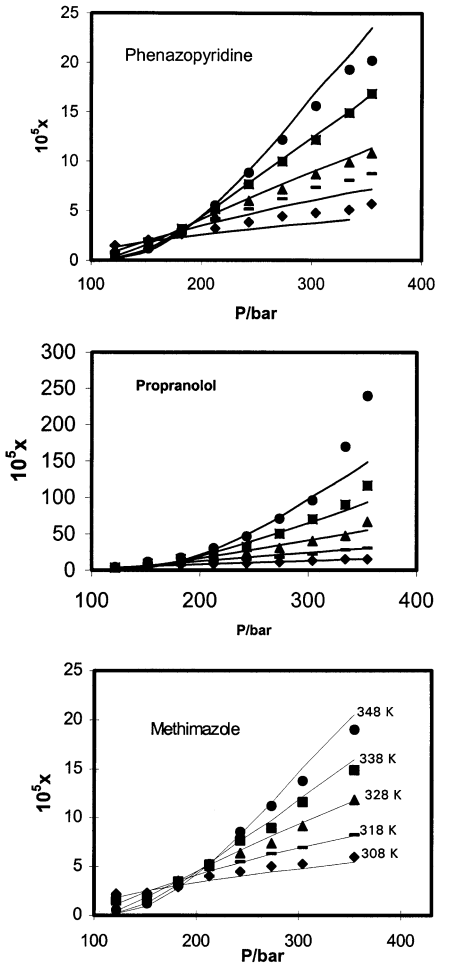


Fig. 3. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for drugs.

pressure, Eq. (3) can be used to evaluate the solubility, x, at any given temperature and pressure. Fig. 3 compares the calculated isotherms with the experimental data for drugs. One can see that, the Bartel method provides a good fit, with

absolute average relative deviation (AARD) in the range of 4.8–23.7% for drugs in different temperatures (Table 3). The poor consistency is mainly limited to the data points obtained at higher pressure limits of the isotherms, which are close to the melting points of the drugs (melting point depression is obtained at higher pressures). Similar results have been observed for anthracene and pyrene [10] and xanthene derivatives [17]. By removing the solubility results at pressures of 122 and 350 bar AARDs% less than 10% is obtained. Thus, in the present work the Bartel method is valid in the pressure range of 150–330 bar.

The parameter b is approximately related to the enthalpy of sublimation of the solid solutes, ΔH_{sub}, (Miller et al. [10]) by:

$$\Delta H_{sub} = -Rb \quad (4)$$

where R is the gas constant. The validity of Eq. (4) relies on the assumption that the enhancement factor $\ln(xP/P_r)$, where P_r is the vapor pressure of the solute, is independent to temperature. This point was found to be nearly true in practice. The estimated ΔH_{sub} values are also included in Table 3.

4. Conclusions

The equilibrium solubilities of phenazopyridine, propranolol, and methimazole are determined at temperatures ranging from 308 to 348 K and pressures from 122 to 355 bar in supercritical CO_2. The observed drugs solubilities ranged from $x = 4.4 \times 10^{-6}$ to 2.0×10^{-4} for phenazopyridine, from 3.6×10^{-5} to 2.4×10^{-3} for propranolol and from $x = 5.4 \times 10^{-6}$ to 1.9×10^{-4} for methimazole. The solubilities are correlated using a semi empirical Bartle model. Results show that the Bartel method is holds in the pressure range of 150–330 bar. Results of this study show that extraction and purification of these drugs is possible using supercritical carbon dioxide.

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