Solubilities of Some Cyclohexyl Derivatives of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (Nifedipine Analogues) in Supercritical Carbon Dioxide. Part I

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Equilibrium solubilities of five recently synthesized nifedipine analogues were measured at temperatures ranging from (328 to 348) K for bis(cyclohexyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP1) and bis(cyclohexylmethyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP2) and (338 to 358) K for bis(2-cyclohexylethyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP3), bis(3-cyclohexylpropyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP4), and bis(4-cyclohexylbutyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP5) and in a pressure range from (12.2 to 35.5) MPa in supercritical carbon dioxide. The data were obtained by using a simple static sampling apparatus, which was tested by measuring the solubility of naphthalene in supercritical carbon dioxide. The measured solubilities were correlated using a semiempirical model. The calculated results show satisfactory agreement with the experimental data.

Introduction

Supercritical fluid extraction (SFE) is widely perceived as a technique for the extraction of low to moderately polar compounds. With increasing concern over the use of chemical solvents in the manufacture of pharmaceuticals as well as the need for high-quality products, alternatives to energy-intensive and costly extraction schemes have been sought. The gentle extraction conditions used in SFE compared to those used in more traditional methods such as Soxhlet extraction also provide greater assurance against chemical reaction not taking place during the extraction. This ensures that isolated analytes are representative of the original sample.[1−4] SFE is a potential technique for the purification of pharmaceutical products containing residual solvents. The solubilities of the drugs in supercritical carbon dioxide are being measured as part of a program in which the potential applications of this technology are being investigated.[5]

The 1,4-dihydropyridine (DHP) derivatives, which are well known to be calcium channel blockers, are used for the treatment of cardiovascular diseases such as hypertension, angina pectoris, and other spastic smooth muscle disorders.[6,7] These drugs act directly on the voltage-dependent calcium channels and block the flux of Ca^{2+} to the cell cytoplasm. Some derivatives such as nifedipine, nicardipine, amlodipine, and nitrendipine are now commercially available in drug stores. Very recently, Knuas and co-workers have synthesized new generations of DHP derivatives in which the phenyl substituent at the C-4 position of the DHP ring has been replaced by other aromatic substituents such as imidazolyl and pyridine.[8−12] Recently, some new derivatives of DHP containing a 1-methyl-5-nitro-imidazol-2-yl substituent at the C-4 position and different ester substituents on the C-3 and C-5 positions of the DHP ring have been synthesized.[12−16] The calcium channel antagonist activity of the compounds in Guinea-pig Ileal was determined, and it was found that the activity of some derivatives was higher than that of nifedipine.[12−16] Earlier, we carried out some quantitative structure−activity relationship analysis on these compounds[17−20] and found that lipophilicity and steric and electronic properties are the major factors controlling the binding of these molecules to their receptor.

In the present study, the solubilities in supercritical carbon dioxide were measured for five recently synthesized,[12−16] nifedipine analogues (i.e., bis(cyclohexyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP1), bis(cyclohexylmethyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP2), bis(2-cyclohexylethyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP3), bis(3-cyclohexylpropyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP4), and bis(4-cyclohexylbutyl)-1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP5)) over a wide range of temperature and pressure. The measured solubilities were successfully correlated using a semiempirical model proposed by Bartle.[21]

Experimental Section

Materials. Sabalan (Tehran, Iran) supplied the carbon dioxide used in this work at a purity of 99.99%. HPLC-grade methanol (from Aldrich) was used as received. All of the drugs were synthesized and purified as previously described.[12−16] The purities of the 1,4-dihydropyridine

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Table 1. Physical Properties of the 1,4-Dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates Derivatives (NP1 to NP5)

compound	formula	$(CH_2)_n$−R R = cyclohexyl	MW g·mol^{-1}	T_m K	λ_{max} nm[a]
NP1	$C_{25}H_{34}N_4O_6$	$n = 0$	486	546−548	318.6
NP2	$C_{27}H_{38}N_4O_6$	$n = 1$	514	535−536	320.0
NP3	$C_{29}H_{42}N_4O_6$	$n = 2$	542	488−489	320.2
NP4	$C_{31}H_{46}N_4O_6$	$n = 3$	570	474−475	320.2
NP5	$C_{33}H_{50}N_4O_6$	$n = 4$	598	437−438	319.4

[a] The absorbances of drugs were measured in methanol.

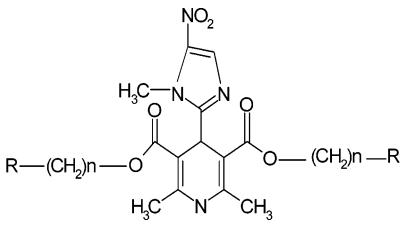

Figure 1. Structure of the dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates.

(DHP) derivatives were confirmed by spectroscopic data and elemental analysis. The purities of the drugs were higher than 99.5 mass %. No further purification was done before their use. However, prior to the measurement of solubilities, small quantities of volatile impurities were extracted by dynamic SFE at 12.2 MPa and 308 K for a duration of 10 min at a supercritical flow rate of 0.3 mL·min^{-1}. The impurities were present only during the extraction of the first (2 to 4)% of the material charged into the extraction vessel. The physical properties of the drugs used are shown in Table 1.

Equipment and Procedure. A Suprex (Pittsburgh, PA) MPS/225 system equipped with a modified static system for solubility determinations in SFE mode was used. A detailed description of the equipment and operating procedures has been given.[22,23] Solubility measurements were accomplished in a pressure range from (12.2 to 35.5) MPa and at temperatures from (328 to 348) K for NP1 and NP2 and from (338 to 358) K for NP3 to NP5 for a period of 20 min. It should be noted that by monitoring the solubility data versus time we found 20 min to be adequate to ensure the attainment of equilibrium. The equilibrium temperature and pressure were measured to accuracies of ±1 K and ±0.1 MPa, respectively. The solid solutes (100 mg) were mixed well with the proper number of glass beads and packed into a 1.0-mL 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, a 176-μL portion of saturated supercritical CO_2 was loaded into an injection loop. Then, the loop was depressurized into the collection vial containing methanol. Finally, the sample loop was washed with methanol, which was collected in the collection vial. The final volume of the solution was 5 mL.

The solubilities of five dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates derivatives (Figure 1) were calculated by absorbance measurements at λ_{max} of each compound (Table 1) using a model 2100 Shimadzu UV−vis spectrophotometer. Stock solutions of each compound (100 μg·mL^{-1}) were prepared by dissolving appropriate amounts of a solid sample in methanol. A set of standard solutions was then prepared by appropriate dilution of the stock solutions. The calibration curves obtained (with regression coefficients better than 0.9999) were used to establish the concentration of the drugs in the collection vial.

Table 2. Solubilities of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (NP1, NP2, NP3, NP4, and NP5) in Supercritical CO_2

T	P	ρ	NP3		NP4		NP5	
K	MPa	kg·m^{-3}	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x
338								
	12.2	396	14.6	3.1	12.2		9.1	
	15.2	561	41.4	6.2	24.3		16.7	
	18.2	654	90.9	11.6	32.1	3.9	26.8	3.1
	21.3	712	124.8	14.7	32.9	4.2	40.7	4.3
	24.3	754	143.2	18.0	37.3	4.9	44.4	5.8
	27.4	786	157.3	19.3	40.8	5.4	58.3	9.1
	30.4	812	164.4	20.1	48.6	5.6	88.6	11.2
	33.4	834	174.3	21.2	52.9	5.9	134.1	13.4
	35.5	848	182.7	22.0	60.7	5.7	169.4	15.1
348								
	12.2	327	14.6	3.7	7.9		11.6	
	15.2	477	37.2	6.5	22.6		15.4	
	18.2	585	83.8	11.9	31.3	4.2	25.5	3.3
	21.3	652	133.3	17.1	34.7	5.1	39.4	4.6
	24.3	702	164.4	21.6	39.9	5.7	571	6.1
	27.4	740	177.1	23.8	45.1	6.5	86.1	11.5
	30.4	772	191.2	26.2	54.6	7.2	149.2	17.0
	33.4	796	198.3	27.7	56.4	7.3	199.7	20.3
	35.5	811	260.5	27.1	76.3	7.5	235.1	23.1
358								
	12.2	287	8.9	2.6			9.1	
	15.2	406	27.3	5.6	5.3		12.8	
	18.2	517	76.7	12.4	20.0	3.8	15.4	2.3
	21.3	593	137.5	19.4	32.9	5.4	22.9	2.9
	24.3	650	175.7	22.6	43.4	6.3	57.0	8.6
	27.4	693	184.1	28.5	48.6	7.3	93.6	14.4
	30.4	728	199.7	31.8	58.1	8.6	166.9	20.7
	33.4	757	264.7	34.0	76.3	9.1	242.7	28.8
	35.5	774	288.8	36.1	93.6	9.6	319.7	34.0

T	P	ρ	NP1		NP2	
K	MPa	kg·m^{-3}	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x
328						
	12.2	516	13.6			
	15.2	657	18.4	2.6	53.5	7.2
	18.2	726	37.3	4.8	94.6	11.5
	21.3	771	73.8	8.9	100.4	11.5
	24.3	804	92.3	10.7	208.5	22.9
	27.4	831	114.0	12.8	245.8	26.1
	30.4	853	151.4	16.6	258.2	26.7
	33.4	872	175.1	18.8	270.6	27.5
	35.5	884	193.2	20.4	312.7	31.2
338						
	12.2	396	10.3			
	15.2	561	12.3	2.0	42.1	7.2
	18.2	654	34.4	4.9	89.9	11.5
	21.3	712	73.0	9.6	110.9	11.5
	24.3	754	93.1	11.5	232.4	22.9
	27.4	786	117.2	13.9	260.2	26.1
	30.4	812	163.8	18.8	303.2	26.7
	33.4	834	185.5	20.8	361.5	27.4
	35.5	848	202.0	22.3	411.3	31.2
348						
	12.2	327				
	15.2	477			15.6	2.9
	18.2	585	57.4	9.1	78.4	11.8
	21.3	652	97.5	14.0	117.6	15.9
	24.3	702	118.0	15.7	249.6	31.4
	27.4	740	157.0	19.9	280.3	40.4
	30.4	772	191.5	23.2	346.3	49.2
	33.4	796	220.9	25.9	399.8	58.0
	35.5	811	238.2	27.5	465.8	62.8

Results and Discussion

The reliability and efficiency of the solubility measurement technique were previously established by measuring the solubility of naphthalene in supercritical CO_2 at 308 K and different pressures.[23,24] The solubilities of the five drugs in terms of equilibrium mole fraction, x, and in grams per liter, s, of the solute along with the temperature, pressure, and density of CO_2 are listed in Table 2. The results represent the average of at least three separate measurements. The maximum deviation between the measurements is ±6% and gives a good indication of the expected precision of the results.

The results obtained in this study indicate that the solubilities of the dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates decrease in the order of NP2 > NP1 > NP3 > NP5 > NP4. Even though a definite correlation between the solubility and the alkyl substituent attached to the molecule is not observed, the differences in solute properties such as molecular weight, polarity, and melting point should be considered while comparing the solubility behavior of dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates derivatives.

An isothermal increase in the pressure increased the solubility of the drugs. The effect of pressure on the solute solubility in the compressed gas follows the expected trends, the solubility increasing with increasing pressure for all temperatures studied. As the pressure rose, the CO_2 density increased, and the mean intermolecular distance of the carbon dioxide moleculars decreased, thereby increasing the specific interaction between the solute and solvent molecules. Another factor affecting the equilibrium solubility of solid substance is the temperature of the system. The temperature influences the solute vapor pressure, the solvent density, and the intermolecular interactions in the fluid phase.

At pressures below the crossover region (for five drugs in the pressure range of (180 to 240) MPa), the solvent density decreases with small increases in temperature. As the density effect is domain in this region, the solubility will decrease with increasing temperature. At higher pressures, the solvent density is only slightly dependent on the temperature, so the increase in solubility occurs primarily because of the higher vapor pressure of the solid.[4] The existence of a crossover pressure in solid−supercritical systems has been suggested as an indication of the reliability and consistency of experimental solubility data.[25]

To predict the trend of measured solubility data, we used a semiempirical model proposed first by Bartle[21]

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

where

$$A = a + \frac{b}{T} \tag{2}$$

and

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

where x is the mole fraction solubility, P is the pressure, P_{ref} is a reference pressure of 1 bar, ρ is the density of pure CO_2 (the computer system of the Suprex MPS/225 will show the density calculations of CO_2 directly according to the Pitzer method[26]), and ρ_{ref} is a reference density for which a value of 700 kg·m^{-3} was used. The other parameters of the above equations have been previously discussed.[22,27]

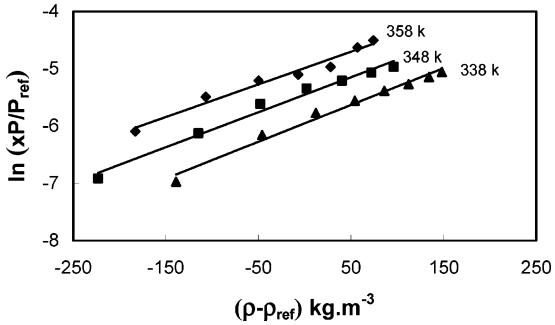

Figure 2. Plots of $\ln(xP/P_{\mathrm{ref}})$ vs $(\rho - \rho_{\mathrm{ref}})$ for NP3 at various temperatures.

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

compound	a	b / K	C / m^3·kg^{-1}	$\Delta_{\mathrm{sub}}H$ / kJ·mol^{-1}	AARD%[a]
NP1	15.88	−7465	0.0106	62	15.0−19.6
NP2	16.40	−7405.9	0.0099	61	12.0−17.1
NP3	10.84	−5598.2	0.0061	46	11.6−14.0
NP4	8.97	−5401.6	0.0060	45	3.1−4.6
NP5	25.07	−10903	0.0135	90	9.0−12.8

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

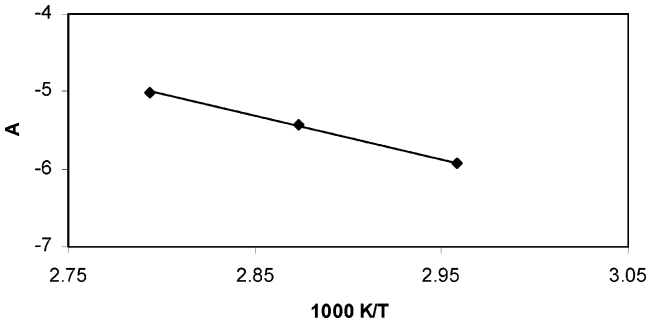

Figure 3. Plot of A against $1/T$ for NP3.

In the first step, $\ln(xP/P_{\mathrm{ref}})$ values were plotted against density (Figure 2), and the values were fit with a straight line by least-squares regression to estimate the C and A parameters. According to eq 1, the plots are expected to be straight lines with similar slopes. (Correlation coefficients, r^2, of the lines lie between 0.9991 and 0.9998.) However, as seen in Figure 2, 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 compound. The plot of A versus $1/T$ for each compound resulted in a straight line (Figure 3), from which the intercept and slope (a and b) were obtained. The resulting a and b values for the compounds are also included in Table 3. Finally, the values of a, b, and C were used to predict the solubility from eq 3. Figure 4 compares the calculated isotherms with the experimental data for NP3. One can see that the Bartle

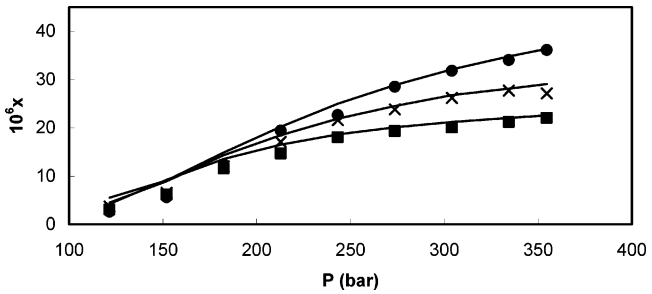

Figure 4. Comparison of experimental (points) and calculated (lines) solubilities for NP3 at various temperatures.

method provided a good fit, with an absolute average relative deviation (AARD) in the range of 3.1% to 19.60% for NP1 to NP5 at different temperatures (Table 3).

Parameter b is approximately related to the enthalpy of sublimation of the solid solutes, $\Delta_{sub}H$, by[27]

$$\Delta_{sub}H = -Rb \tag{4}$$

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

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