Solubility of Naproxen in Supercritical Carbon Dioxide with and without Cosolvents

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The solubility of naproxen ((*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid) in supercritical CO_2 was determined at 313.1, 323.1, and 333.1 K. The influence of six polar cosolvents, ethyl acetate, acetone, methanol, ethanol, 1-propanol, and 2-propanol, was studied at concentrations of 1.75, 3.5, and 5.25 mol %. The solubility enhancement with these cosolvents is considerable, and the cosolvent effect increases in the order ethyl acetate, acetone, methanol, ethanol, 2-propanol, 1-propanol. A nonlinear increase in solubility is observed with an increase in cosolvent concentration. The use of the Peng–Robinson and Soave–Redlich–Kwong equations of state to correlate these ternary systems requires the use of negative binary interaction parameters indicating strong interactions between naproxen and the cosolvents. The cosolvent effects cannot be explained by any one physical property of the cosolvents but appear to be influenced by hydrogen bonding ability as determined from solvatochromic parameters as well as the relative distance from the CO_2–cosolvent binary critical point.

Introduction

In recent years, a great deal of research has been carried out in the field of supercritical fluid (SCF) technology. The interest in using this technology for selective extraction or reaction is due to the superior properties that are inherent to this class of fluid, including the ability to vary solvent density and to effect a change in solvent properties by changing either the pressure or temperature. The viscosity of a SCF is much lower than a liquid, and diffusivities can vary between gaslike and liquidlike values. As a result, extraction processes can be carried out more rapidly. Another advantage of using SCF's in separation processes is the relative ease of solvent recovery and the separation of the desirable product(s).

For most high molecular weight, nonvolatile organic compounds, the solubility in SCF's is low requiring high temperatures and pressures for substantial loadings. Thus the capital cost for commercial-scale processes can be prohibitive, and this has been one of the major hindrances to the advance of SCF technology. Carbon dioxide is one of the most common gases used as a SCF mainly because it is an easy gas to handle, it is inert and nontoxic, it is nonflammable, and it has a convenient critical temperature. Although CO_2 is the most common SCF being used, it does have limitations as a result of its lack of polarity and associated lack of capacity for specific solvent–solute interactions which would lead to high loading and/or selectivity for polar organic compounds. Pure SCF's exhibit polarization behavior that is primarily related to the density and SC CO_2 at 308 K and 200 bar only has a solubility parameter approaching that of liquid isopentane (6.5 $(cal/cm^3)^{1/2}$); thus there is a great incentive to improve its polarity. It has been found that the addition of a small amount of cosolvent to a SCF can have dramatic effects on its solvent power.

In recent years, progress has been made toward understanding the interactions involved in dilute supercritical mixtures. It has been shown that near the critical point of a SCF solution, the solvent molecules "cluster" around the relatively large solute molecule to form a local density higher than the bulk density (Eckert et al., 1986; Kajimoto et al., 1988; Cochran and Lee, 1989; Debenedetti, 1987; Debenedetti et al., 1989; Petsche and Debenedetti, 1989, 1991; Brennecke et al., 1990; Morita and Kajimoto, 1990). When a cosolvent is added, the situation is further complicated by the differences in local and bulk compositions (Kim and Johnston, 1987a; Yonker and Smith, 1988). Frye et al. (1987) also indicated a change in composition of the cybotactic region (a region in the vicinity of the solute) in a cosolvent-modified SCF.

The increase in solubility due to the addition of cosolvent is the result of additional interactions between the solute and the cosolvent. Considering the interactions possible, these cosolvent effects could be the result of several mechanisms. The addition of a cosolvent will generally increase the mixture density which will contribute to the overall solubility enhancement as will physical interactions like dipole–dipole, dipole–induced dipole, and induced dipole–induced dipole interactions. However, when using a polar cosolvent for polar solutes, the largest increase in solubility would be expected to be a result of specific chemical interactions like hydrogen bonding or charge transfer complex formation.

There are relatively few reported studies of solid–SCF cosolvent solubility to date (Dobbs et al., 1986; Schmitt and Reid, 1986; Wong and Johnston, 1986; Van Alsten, 1986; Larson and King, 1986; Dobbs et al., 1987; Schaeffer et al., 1988; Lemert and Johnston, 1989, 1991; Tavana et al., 1989; Cygnarowizc et al., 1990; Hollar and Ehrlich, 1990; Smith and Wormald, 1990; Gurdial et al., 1993; Ekart et al., 1992). Overall, only two SCF's have been used, ethane and CO_2—whereas a multitude of cosolvents have been used ranging from nonpolar gases to polar liquids.

In this work, the flow technique coupled with gravimetric analysis was used to measure the solubility of naproxen, (*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid (a nonsteroidal antiinflammatory drug), in pure SC CO_2 and also in various SC CO_2–cosolvent mixtures. The cosolvents chosen were all polar and could either exhibit self-association (alcohols) or not (ketone and ester). For all the cosolvents studied, three concentrations ranging from 1.75 to 5.25 mol % were investigated at 333.1 K. This was to enable the study of the effect of concentration together

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Table I. Source and Purity of Materials

compound	source	purity
naproxen	Sigma Chemicals	99+%
carbon dioxide	Liquid Air	liquid withdraw grade, 99.8+%
acetone	BDH	HiPerSolv grade, 99.8% by HPLC
ethyl acetate	Aldrich	99.9+% by GLC
methanol	BDH	HiPerSolv grade, 99.8% by GLC
ethanol	BDH	AnalaR grade, 99.7% v/v
1-propanol	BDH	HiPerSolv grade, 99.8% by GLC
2-propanol	BDH	HiPerSolv grade, 99.8% by GLC

with the functionality of the cosolvent. Experiments were also carried out at 323.1 and 318.1 K with acetone cosolvent and 323.1 K with methanol, ethanol, and 2-propanol cosolvents.

Materials

The sources and purities of the various compounds used are given in Table I. These materials were used without further purification.

Experimental Section

Binary System. A schematic diagram of the equipment used is shown in Figure 1. The syringe pump used was an Isco Model 260D, with constant pressure operating capability, equipped with an external jacket for heating or cooling purposes. In the study of the solubility of naproxen in pure SC CO_2, the equilibrium cells consisted of two 6-in. by 0.5-in. o.d. stainless steel tubes and a Jerguson sight gauge. For the cosolvent studies a slight modification was made to the overall equipment setup used for solubility measurements in pure CO_2. Because of the anticipated higher solubility involved, the equilibrium cells were replaced with a 300-mL bomb half-filled with naproxen. The system temperature was monitored by a platinum resistance thermometer accurate to ±0.1 K, and the system pressure was measured by a Druck pressure transducer (Model TJE), with an accuracy of ±5 psi, located just after the sight gauge. The equilibrium cells and sight gauge were placed in a water bath which was regulated to ±0.1 K.

The equilibrium cells were packed with naproxen, and each end was plugged with glass wool to prevent the fine naproxen powder from plugging the smaller 1/8-in. o.d. interconnecting stainless steel tubing. Similarly, the sight gauge was three-quarters filled with naproxen and also plugged loosely with glass wool to prevent entrainment. The sight gauge provided a means of determining the physical state of the mixture (i.e., to detect potential melting of the solid). A 7-μm Nupro inline filter, F1, was placed after the pressure transducer to prevent any further entrainment of solid particles of naproxen. The pressure drop through the saturators was less than 0.5 bar.

The method used in this study is similar to that used by Gurdial and Foster (1991). Initially, the system was purged with carbon dioxide at low pressure and then brought up to the required system pressure and temperature. After equilibrating for several hours, the system was purged with SC CO_2 equivalent to 520 cm^3 or two syringes of liquid CO_2 at room temperature and system pressure which corresponded to at least three complete system volumes. For operation, the metering valve, V5 (Whitey 32RS4 with lubricant removed), was first closed and V4 was slowly opened and the system was allowed to equilibrate further at system pressure and temperature for 15–30 min. The experiment was then started by opening valve V5, which was heated by a 100-W lamp. The flow rate was normally maintained to within 10 dm^3/h CO_2 at ambient conditions. Consistent results could still be obtained when this flow rate was halved indicating that equilibrium was achieved. The solute which precipitated on expansion through valve V5 was collected in a 0.5-μm Nupro inline filter, F2. The total volume of CO_2 at ambient conditions, after passing through a water saturator, was measured by a wet test meter (Type DM3A, Alexander Wright & Co.).

At the end of each run, V4 was closed and the section between V4 and V5 was allowed to depressurize through V5. The valve V4 was located outside the constant-temperature water bath so that V5 together with the section of tubing connecting to V4 could be disconnected. As V4 was located outside the water bath, its temperature was controlled with a heating tape to that of the bath temperature. The solute collected in the valve and the connecting tubing was flushed with high-purity acetone (99% or better) into a Petri dish. The acetone was then evaporated until a constant mass was obtained. The Petri dish and the filter were then weighed and the mass difference was recorded. The reproducibility and uncertainty of the solubility data obtained using this method were within ±5%.

Ternary Systems. To ensure that the solvent–cosolvent mixtures were supercritical at the chosen operating conditions, the critical locus for each system was determined for the concentration range of interest. A rigorous technique to determine the critical locus is via a vapor–liquid equilibrium (VLE) experiment. However, the method proposed by Gurdial et al. (1991a,b) provides a quick technique for the determination of critical loci of binary mixtures. The critical loci for CO_2–acetone, CO_2–methanol, CO_2–1-propanol, and CO_2–2-propanol have been established using this technique (Gurdial, 1991a,b). As no CO_2–ethyl acetate critical locus data in the concentration range of interest were available, the critical locus was determined using the above method. The data obtained are shown in Figure 2. As expected with these dilute systems, the variations of critical temperatures and pressures are linear with composition. It can be seen that for the ethyl acetate–CO_2 system, at 5.25 mol % ethyl acetate, the critical temperature and pressure are approximately 330 K and 97 bar, respectively, and thus all work done at this concentration was carried out above these conditions.

To prepare the cosolvent mixtures, the barrel of the syringe pump was used as a mixing bomb. The syringe volume was calibrated with N_2 at ambient temperature and at various pressures and was found to be 265 ± 5 cm^3. The maximum volume readout on the pump was found to be reliable and was close to the calibrated volume. The mixture was prepared by raising the head of the piston as far up as possible and then purging with CO_2. The required amount of cosolvent was injected directly into the pump via T1 as shown in Figure 1. The barrel of the pump was then cooled by circulating chilled water through the water jacket. The three-way valve, V2, was switched to the liquid CO_2 cylinder, and at the same time the piston was drawn down. The temperature was set at 274 K primarily because at this temperature and around 50–60 bar (CO_2 cylinder pressure) CO_2 exists only as a liquid. A secondary consideration was that, at this temperature, the density of liquid CO_2 is not too sensitive to small variations in pressure (±5 bar). With these parameters set, the required amount of CO_2 to be added could be determined by setting the pressure. No account was made for excess volume of mixing. When the desired pressure (e.g., 52 bar) was

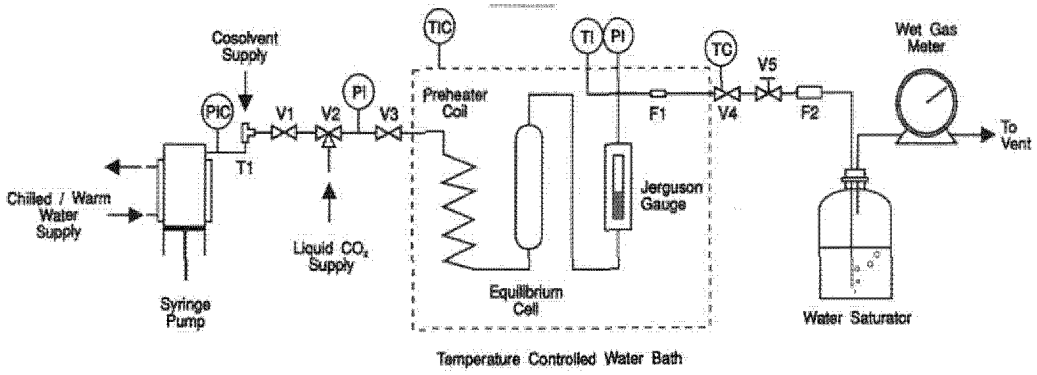

Figure 1. Flow apparatus for solubility measurements in pure and cosolvent modified SCF's.

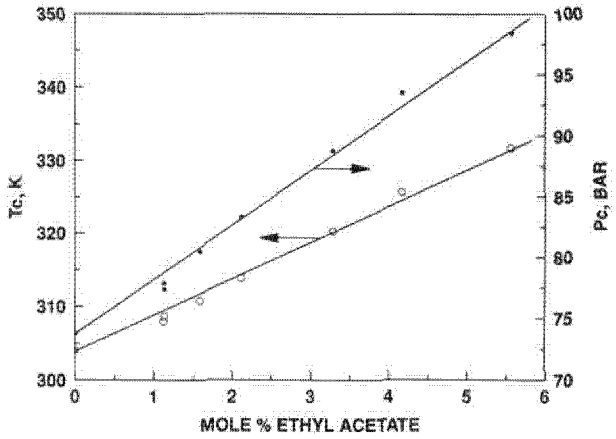

Figure 2. Binary critical locus for the ethyl acetate–CO_2 system.

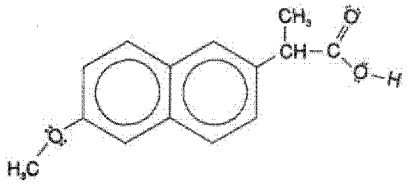

Figure 3. Structure of naproxen.

reached, V1 was closed and warm water (313.1–323.1 K) was circulated through the outside water jacket to provide thermal mixing of the solvent mixture. The mixture was allowed to equilibrate for about 15 min and then cooled and reheated to enhance the mixing process.

The homogeneity of the CO_2–acetone mixture was checked by using an UV detector equipped with a high pressure flow cell. The solvent mixture was prepared as described above, and the whole syringe was pumped through the UV detector to check for the consistency of the baseline. Our results showed a reasonably stable baseline with respect to the volume of the solvent mixture passed through, indicating a homogeneous solvent mixture along the length of the syringe. This was further confirmed by the reproduciblity of the solubility data.

Prior to each change in cosolvent concentration and each change over to an entirely new cosolvent, the whole system was purged with at least two syringes of the cosolvent mixtures at the required conditions to ensure consistent results.

The procedure was similar to that stated earlier. However, more care was taken to ensure any collected cosolvent was removed from the filter, F2. This was done by placing the filter and the Petri dish containing the solute, cosolvent, and acetone in a vacuum oven. Although the solute was not analyzed, no change in appearance was observed after depressurization which implies that none of the cosolvents chemically reacted with naproxen. For these ternary systems, the reproducibilities were slightly better than with the pure studies because of the higher solubilities involved.

Choice of Cosolvents

The choice of cosolvents used was based on availability in high purity, toxicology, and physical and chemical characteristics. The functionality of the cosolvents was chosen such that they might interact differently with naproxen, whose structure is shown in Figure 3. As naproxen has an acid group, it was expected that interactions with cosolvents via hydrogen bonding might play an important role in solubility enhancement. Thus all the cosolvents chosen in this study have hydrogen bond accepting capability.

Various workers have provided methods for cosolvent selection. Sunol et al. (1985) divided solvents into various classes according to their potential to form hydrogen bonds. These workers also listed the likelihood of hydrogen bond formation when two separate classes of solvent were mixed, and cosolvent was chosen based on this. Walsh et al. (1987, 1989) used a similar concept for choosing cosolvents for SCF systems. Tavana et al. (1989) used the ability of the cosolvent to reduce retention time of the solute in packed GC columns as a method for scanning potential cosolvents. In this work, the Kamlet–Taft solvatochromic solvent scale of acidity (α), basicity (β), and polarity/polarizability (π^*) (Kamlet and Taft, 1976a,b; Kamlet et al., 1977, 1983) was one tool used as a measure of hydrogen bonding capability. Perhaps a more quantitative measure of solvent power is the Hilderbrand solubility parameter (Hildebrand and Scott, 1950). This parameter can be partitioned into a dispersion (δ_d), polar (δ_p), and hydrogen bonding (δ_h) components (Hansen, 1967a,b, 1969; Hansen and Beerbower, 1971) which again provides a convenient tool for classifying solvent strength. The Kamlet–Taft α, β, and π^* along with the Hansen δ_h for the cosolvents used are given in Table II.

The dipole moment for the various cosolvents are also included in Table II. The dipole moment largely determines the orientation of a solvent around an organic solute molecule (Keesom forces) in the absence of specific solute–solvent interactions. In turn, the dissolving power of a solvent also depends on the effectiveness of this electrostatic solvation.

The polarizability α^* of neighboring molecules is fundamental in accounting for the strength of both Debye and London forces between them. The α^* values for all the cosolvents and naproxen were estimated and are listed in Table II. However, the effectiveness of these attraction forces also depends on molecular size as suggested by Grant

Table II. Solvatochromic and Solubility Parameters for All Compounds

cosolvent	π^{*} [a]	α [a]	β [a]	μ [b] (D)	α^{*} [c] ($cm^3 \times 10^{25}$)	$\alpha^{*}/\bar{v}$	v (cm^3/mol)	δ^d ($MPa^{1/2}$) δ_d	δ_p	δ_h	δ_{total}
acetone	0.71	0.06	0.48	2.9	64.1	0.0525	74.0	15.5	10.4	7.0	20.0
ethyl acetate	0.55	0.00	0.45	1.9	88.3	0.0543	98.5	15.8	5.3	7.2	18.1
methanol	0.60	0.93	0.62	1.7	32.3	0.0485	40.7	15.1	12.3	22.3	29.6
ethanol	0.54	0.83	0.77	1.7	51.2	0.0528	58.5	15.8	8.8	19.4	26.5
1-propanol	0.52	0.78		1.7	69.5	0.0559	75.2	16.0	6.8	17.4	24.5
2-propanol	0.48	0.76	0.95	1.7	69.9	0.0550	76.8	15.8	6.1	16.4	23.5
naproxen					252.5	0.0850	178.3 [b]	10.0 [f]	6.9 [g]	20.0 [h]	23.4 [e]
CO_2				0	27.4						

[a] Kamlet et al. (1983). [b] Reid et al. (1988). [c] Estimated using eq 2.132-3, Grant and Higuchi (1990). [d] Barton (1983). [e] Fedors group contribution method (Fedors, 1974). [f] Koenhen and Smolders (1975). [g] Group molar attraction constants (Hoy, 1970). [h] $\delta_h = (\delta_t^2 - \delta_d^2 - \delta_p^2)^{1/2}$ (Hansen, 1971).

Table III. Solubility of Naproxen in Pure SC CO_2

press. (bar)	mole fraction naproxen × 10^5 313.1 K	323.1 K	333.1 K
89.6	0.20		
100.0		0.19	
110.3	0.83	0.43	
124.1			0.70
131.0	1.29	1.20	
137.9			1.08
144.8		1.77	
151.7	1.72		1.56
165.5			2.33
172.4	2.08	2.32	
179.3			2.71
193.1	2.43	2.91	3.18

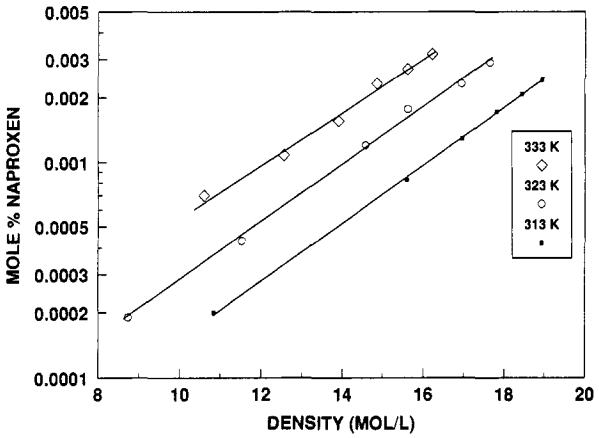

Figure 4. Solubility of naproxen in pure supercritical carbon dioxide. Solid line represents line of best fit.

and Higuchi (1990). A useful measure of the relative potential of these kind of interactions would be to divide the polarizability α^{*} by the mean volume $\bar{v}$ of the molecule. The $\alpha^{*}/\bar{v}$ ratios for all the cosolvents and naproxen are listed in Table II. The molar volume, v, was used instead of the mean molecular volume. The units used were such that this ratio remains a dimensionless entity.

Acetone and ethyl acetate do not self-associate and are solely hydrogen bond acceptors. However, they vary greatly in terms of dipole moment, dielectric constant, molecular size, and critical properties. Alcohols on the other hand are able to be both hydrogen bond donors and acceptors. They also tend to self-associate even in SCF's (Fulton et al., 1991a,b). Because of the similarities in the chemical and physical behavior of compounds in a homologous series, their use as cosolvents could contribute to a further understanding of their contributions to solubility enhancement. The alcohols used are methanol, ethanol, 1-propanol, and 2-propanol. The reason for including 2-propanol was to study possible steric effects.

Table IV. Solubility of Naproxen in SC CO_2 with Acetone Cosolvent

press. (bar)	mole fraction naproxen × 10^5 333.1 K 1.75[a]	3.5[a]	5.25[a]	323.1 K 3.5[a]	318.1 K 3.5[a]
89.6					2.45
96.5					3.17
110.3	0.67	2.03	4.55	3.25	4.66
124.1	1.49	3.42	7.88	4.78	5.22
137.9	2.67	5.37	10.68	5.84	6.05
151.7	3.91	6.96	13.14	7.05	6.79
165.5	5.05	8.55	15.07	7.91	7.18
179.3	6.09	10.8	16.97	8.98	7.63
193.1	5.75				

[a] Cosolvent composition in mol % (solute free).

Table V. Solubility of Naproxen in SC CO_2 with Ethyl Acetate Cosolvent at 333.1 K

press. (bar)	mole fraction naproxen × 10^5 1.75[a]	3.5[a]	5.25[a]
110.3	0.64	2.10	5.32
124.1	1.32	3.43	7.38
137.9	2.36	5.27	9.64
151.7	3.26	6.55	11.60
165.5	4.15	7.18	13.11
179.3	5.26	9.75	14.33

[a] Cosolvent composition in mol % (solute free).

Results and Discussion

Pure Component Solubility. The solubility of naproxen in pure SC CO_2 was obtained at 313.1, 323.1, and 333.1 K and is shown in Table III. As indicated by Figure 4, the logarithm of the experimental solubility data gave a good linear correlation with respect to pure CO_2 density. This was expected as shown by various workers (Chrastil, 1982; Kumar and Johnston, 1988; Gurdial et al., 1989; Wells et al., 1990; Gurdial and Foster, 1991) and provides a check on the internal consistency of the data.

Cosolvent Effect. The introduction of cosolvents resulted in a marked increase in solubility for all the cosolvents used in this study. These solubility data are given in Tables IV–IX. The shapes of the isotherms were similar to those obtained with pure CO_2, with each concentration offset by almost a constant distance from the previous one. The solubility isotherms are also linear on a log solubility–mixture density plot as represented in Figure 5 for the CO_2–methanol system. Mixture densities were determined as described in the Effect of Density section. Thus the solubility behavior in SC CO_2–cosolvent mixtures is similar to that in pure CO_2 under the conditions studied. Some workers have observed a significant shift of the crossover pressure (Gurdial, 1992; Dobbs et al., 1986) when cosolvents were added, however this shift is not significant with naproxen and the cosolvents studied.

Table VI. Solubility of Naproxen in SC CO_2 with Methanol Cosolvent

	mole fraction naproxen × 10^5			
	333.1 K			323.1 K
press. (bar)	1.75[a]	3.5[a]	5.25[a]	3.5[a]
110.3	0.87	3.29	8.11	8.69
124.1	1.95	7.27	15.63	11.37
137.9	3.53	12.22	22.99	14.75
151.7	5.64	16.54	30.25	16.31
165.5	7.76	20.39	35.90	19.52
179.3	9.53	23.56	41.61	22.46
193.1		28.54		24.05

[a] Cosolvent composition in mol % (solute free).

Table VII. Solubility of Naproxen in SC CO_2 with Ethanol Cosolvent

	mole fraction naproxen × 10^5			
	333.1 K			323.1 K
press. (bar)	1.75[a]	3.5[a]	5.25[a]	3.5[a]
110.3	1.26	4.76	12.78	8.13
124.1	2.69	9.62	21.47	11.42
137.9	4.42	14.17	29.87	14.21
151.7	6.26	18.16	36.43	15.24
165.5	8.09	22.19	42.58	16.82
179.3	9.55	25.61	47.78	19.18

[a] Cosolvent composition in mol % (solute free).

Table VIII. Solubility of Naproxen in SC CO_2 with 1-Propanol Cosolvent at 333.1 K

	mole fraction naproxen × 10^5		
press. (bar)	1.75[a]	3.5[a]	5.25[a]
110.3	2.23	8.66	25.17
124.1	3.86	14.34	34.65
137.9	5.88	19.30	42.34
151.7	7.35	23.18	50.40
179.3	11.20	31.58	61.82

[a] Cosolvent composition in mol % (solute free).

Table IX. Solubility of Naproxen in SC CO_2 with 2-Propanol Cosolvent

	mole fraction naproxen × 10^5			
	333.1 K			323.1 K
press. (bar)	1.75[a]	3.5[a]	5.25[a]	3.5[a]
110.3	1.37	7.01	19.71	9.54
124.1	3.20	11.80	28.09	13.80
137.9	5.32	16.83	36.33	15.85
151.7	7.22	21.67	43.82	18.31
165.5	8.91			21.64
179.3	10.84	28.11	56.60	22.00

[a] Cosolvent composition in mol % (solute free).

In order to illustrate the enhancement as the result of the introduction of cosolvent more clearly, the *cosolvent effect* is defined as the ratio of the solubility obtained with cosolvent to that obtained without cosolvent. The cosolvent effects as a function of cosolvent composition on a solute-free basis at 333.1 K and 179.3 bar for all the cosolvent systems are shown in Figure 6. Ekart et al. (1992) observed that the cosolvent effect for most of the systems they studied varied almost linearly with cosolvent compositions. They studied the cosolvent effects of a wide selection of cosolvents on a variety of organic compounds in SC ethane using SCF chromatography. However, as can be seen in Figure 6, the naproxen solubility varied nonlinearly with composition and the cosolvent effect increases more rapidly at higher concentration. This may be indicative of higher order interactions between the solute and the cosolvent.

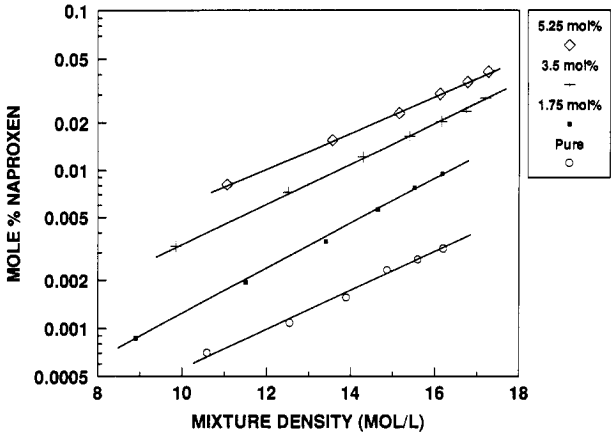

Figure 5. Solubility of naproxen in supercritical carbon dioxide–methanol mixtures at 333.1 K. Solid line represents line of best fit.

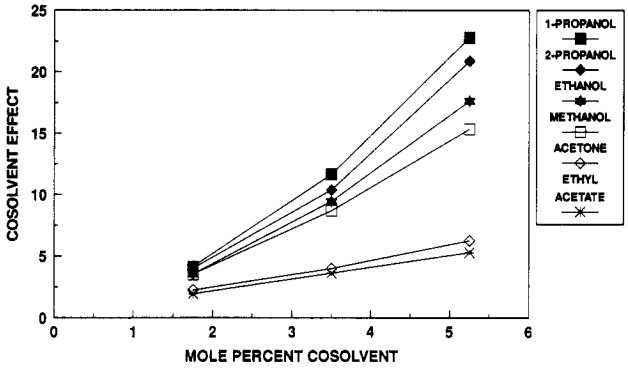

Figure 6. Cosolvent effect as a function of cosolvent concentration at 333.1 K and 179.3 bar.

Effect of Density. The addition of a cosolvent generally increases the bulk density of the fluid mixture which would contribute to solubility enhancement. A large variation in density would be anticipated close to the critical point where the isothermal compressibility is largest. However, at pressures and temperatures further away from this region, where the fluid is less compressible, the increase in bulk density is not expected to be very significant and should be within a few percent (0–3% for $P > 180$ bar) for the cosolvent concentration range between 1 and 5 mol %.

The magnitude of the density contribution to the cosolvent effect was estimated using the Peng–Robinson equation of state (PR EOS). In order to obtain a reasonable estimate of the mixture density, the following procedure was used. First, the ratio of the calculated mixture density to the calculated pure SC CO_2 density was obtained using the PR EOS. This ratio was then multiplied by the actual CO_2 density (Wells, 1991) to give the estimated density. This procedure will help the density curves fit the shape of pure CO_2 isotherms. The binary interaction parameters necessary were obtained by fitting the EOS to binary vapor–liquid equilibrium data as described later. This procedure gives binary cosolvent–CO_2 density estimates accurate to within 20% and will in general overpredict the correct value based on the limited density data available (Dobbs et al., 1987; Tilly, 1992).

On the basis of the calculated mixture densities, the density contribution to the overall enhancement was estimated by determining the increase in naproxen solubility in pure SC CO_2 at the same temperature and density as the CO_2–cosolvent mixture. The contribution of the bulk density increase to the overall cosolvent effect for the methanol system at 333.1 K is shown in Figure 7. At

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