Solubility of Three Veterinary Sulfonamides in Supercritical Carbon Dioxide by a Recirculating Equilibrium Method

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The equilibrium solubility of three pure sulfonamides in supercritical carbon dioxide (SC-CO_2) was determined by use of a recirculating flow method. Overall, solubilities were in the part per million range. Solubilities were measured at two temperatures (40 and 60 °C) and at pressures from 131 to 488 bar. Sulfamerazine (SME) was slightly more soluble than either sulfamethazine (SMZ) or sulfadimethoxine (SDM). The maximum solubility determined for the three sulfonamides was at 60 °C (472 to 488 bar), and their solubility range was 6.50×10^{-5} to 10.14×10^{-5} mol·L^{-1}. The data for SMZ and SDM at 40 °C were compared with published data that showed slight differences in the mole fraction versus pressure curve. Our results provide experimental validation that mole fraction solubility increases with pressure above the critical pressure.

Introduction

A major public health concern of the 1990s is the presence of drug and pesticide residues in animal tissues destined for human consumption. Federal regulations (Code of Federal Regulations, 1989) have established maximum tolerances for these residues. Sulfonamides, as an example, are a class of drugs administered to cattle, swine, and poultry as bacteriostats to prevent microbial infections and to promote growth (Riviere et al., 1991). Sulfamethazine (SMZ) is probably the most widely used sulfonamide in veterinary practice and, therefore, was chosen for study along with two close SMZ derivatives, sulfamerazine (SME) and sulfadimethoxine (SDM). Current analytical methods designed to measure sulfonamide residues in animal tissue generally require the use of organic solvents. Today, however, there is an increasing awareness of the health hazards associated with organic solvents and of the cost of their disposal. Consequently, supercritical fluids (SFs), particularly supercritical carbon dioxide (SC-CO_2), have been proposed as alternatives to organic solvents for many analytical extraction applications (Hawthorne, 1990).

Several review articles and books have described supercritical fluid extraction (SFE) techniques (Randall, 1982; Rizvi et al., 1986; McHugh and Krukonis, 1986; Charpentier and Sevenants, 1988). Although SFE has developed mainly in the past two decades, it still is working its way toward standardization. Government laboratories, however, must have standardized methods for residue-monitoring programs and newer methods are needed for detecting drug residues at or below the tolerance level in target animal tissue, for example, kidney, liver, muscle. New analytical methods, developed in our laboratory using SFE, show promise for drug residue analysis in animal tissue. However, prior to the use of such methods, it is often necessary to measure the solubilities of the pure veterinary compounds in SC-CO_2. A previous report (Hampson, 1996) described a recirculating equilibrium procedure in SC-CO_2 that was developed primarily to measure the solubility of such compounds in supercritical fluids. Research in this laboratory directed toward the development of SFE methods for the isolation of trace level (ppb to ppm) veterinary drugs from biological matrixes has used SF solubility data to develop new analytical methods to determine sulfonamide residues in fortified animal tissues. Parks and Maxwell (1994) used SFE for the isolation of sulfonamides (SMZ, SDM, and sulfaquinoxaline) from fortified chicken tissues both off-line and in-line. Results with in-line traps were superior to the use of off-line traps. Maxwell and Lightfield (1998) used SFE for multiresidue recovery of low ppb levels of sulfonamides (SMZ, SDM, and sulfaquinoxaline) from fortified chicken liver. Results showed recoveries of 71.6 to 88.2% for these three drugs at the 50 ppb level.

SFs have been used before for the extraction and chromatography of drugs, but only a few literature references are available on drug solubility in SFs. Ko et al. (1991) measured the solubility of Penicillin V in SC-CO_2 and found a maximum solubility of 1.1×10^{-2} mol·L^{-1} at 280 bar and 62 °C. Maxwell et al. (1992) measured the solubility of some polyether antibiotics in SC-CO_2 and found a range of solubilities from 1.4×10^{-3} to 2.3×10^{-4} mol·L^{-1} at 390 bar and 80 °C. Recently, Ashraf-Khorassani et al. (1997), using a laboratory assembled apparatus, measured the solubility of SMZ and SDM in SC-CO_2 as well as in supercritical fluoroform and subcritical Freon 134A. They found that SMZ and SDM had maximum solubilities in SC-CO_2 of 4.6 and 4.9×10^{-5} mol·L^{-1}, respectively, at 400 bar and 40 °C. However, their data at 40 °C show mole fraction solubilities for SMZ and SDM in SC-CO_2 at 100 bar that are slightly higher than those at 400 bar, which is a trend that differs from that of studies of other compounds, for example, Ko et al. (1991). Mole fraction solubility above the critical pressure usually increases to a maximum rather than declining slightly (Hampson, 1996).

SC-CO_2 solubility data in our report were obtained with a commercial apparatus and are compared with the published SC-CO_2 data for SMZ and SDM at 40 °C. Our

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Table 1. Properties of Three Sulfonamides

	SME	SMZ	SDM
molecular formula	$C_{11}H_{12}N_4O_2S$	$C_{12}H_{14}N_4O_2S$	$C_{12}H_{14}N_4O_4S$
molecular mass/g·mol^{-1}	264.3	278.3	310.3
melting point range/°C	234−238	176−179	201−203
sublimation pressure[a]/mmHg			
at 40 °C	2.69×10^{-9}	1.61×10^{-9}	2.45×10^{-10}
at 60 °C	1.21×10^{-7}	6.70×10^{-8}	1.22×10^{-8}
UV standard curve[b]	Abs = 3.57*X*	Abs = 3.25*X*	Abs = 3.095*X* (in acetonitrile)
max wavelength in methanol[b]/nm	269.0	269.0	269.9
residue limits in animal tissue[c]/ppm	not specified	0.1	0.1

[a] Estimated values (Watson, 1990; Miller, 1990; Lydersen, 1990). [b] Measured in this work: Abs (absorbency maxima); X = concentration of solute in methanol in mg·L^{-1}; 1 cm cell. [c] According to U.S. federal regulations (Code of Federal Regulations, 1989).

report also provides new solubility data for SMZ and SDM in SC-CO_2 at 60 °C. Additionally, new solubility data in SC-CO_2 at 40 and 60 °C for SME, a close derivative of SMZ, are also provided.

Drug solubilities in SC-CO_2 are difficult to predict, and the solubility of most drugs, if not completely determined experimentally, must be obtained by fitting equations, for example, the Peng−Robinson equation of state, to existing experimental data. Thus, the major objective of this work is to report the experimentally determined solubility data for three sulfonamides in SC-CO_2 at two temperatures and pressures up to 488 bar. Such data can then be used to set experimental parameters for the further optimization of sulfonamide extractions from animal tissue with SC-CO_2.

Experimental Section

Materials. Sulfamethazine, sulfamerazine, and sulfadimethoxine were 99% pure and obtained from Sigma Chemical Company (St. Louis, MO). Carbon dioxide, SFC grade with a dip tube, was obtained from Scott Specialty Chemical (Plumsteadville, PA). Organic solvents (methanol, acetonitrile) were HPLC grade and obtained from Burdick and Jackson Laboratories (Muskegon, MI). Glass beads (0.25−0.32 mm) were obtained from Thomas Scientific (Swedesboro, NJ).

Method. Solubility measurements were performed using a sample preparation accessory (SPA) SFE apparatus from LDC Analytical (Riviera Beach, FL). Procedures for operating the instrument and quantitation by off-line UV analysis were described previously (Hampson, 1996). Equilibrium solubility was obtained in 30 min. The sensitivity of the method for sulfonamide was in the range 1−4 mg·L^{-1} of carbon dioxide.

Results and Discussion

The structural formulas of the three sulfonamides whose solubilities were measured are illustrated in Figure 1. The three sulfonamides studied in this work are derivatives of sulfadiazine with the pyrimidine ring containing substitutions of methyl, dimethyl, or dimethoxy groups in the 4 and 6 positions. The sulfonamide formulas and some properties and residue limits are listed in Table 1. The molecular mass range is 264.3−310.3 g·mol^{-1}. The sulfonamides have melting points in the range 176−238 °C. The sublimation pressure was estimated by using approximate methods (Watson, 1990; Miller, 1990; Lydersen, 1990). Two sulfonamides (SME, SMZ) are readily soluble in methanol while the third (SDM) is readily soluble in acetonitrile. The sulfonamides had at least one peak maximum in the UV spectrum. The correlation coefficients for the UV standard curves were all >0.998. The sulfonamides are used primarily as antibacterials with tolerance residues in animal tissue limited to 0.1 ppm.

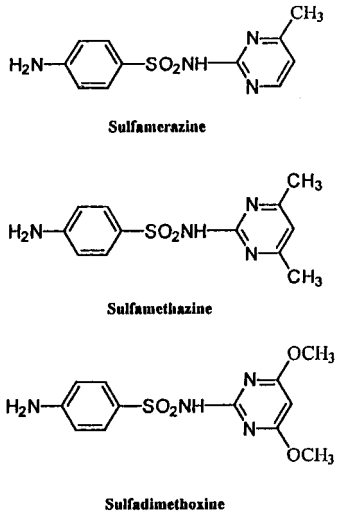

Figure 1. Sulfonamide structural formulas.

Table 2. Solubility *S* of Sulfamerazine (SME) in Supercritical Carbon Dioxide at 40 °C and 60 °C

P/bar	$\rho(CO_2)$/(mol·L^{-1})	*S*[a]/(mol·L^{-1})	*y*
		t = 40 °C	
151	17.80	$5.79\ (2.81) \times 10^{-6}$	3.25×10^{-7}
188	18.85	$2.03\ (0.52) \times 10^{-5}$	1.08×10^{-6}
236	19.80	$3.23\ (0.88) \times 10^{-5}$	1.63×10^{-6}
292	20.60	$4.55\ (1.14) \times 10^{-5}$	2.21×10^{-6}
327	21.00	$4.92\ (0.65) \times 10^{-5}$	2.34×10^{-6}
362	21.40	$5.25\ (0.31) \times 10^{-5}$	2.45×10^{-6}
407	21.80	$5.41\ (0.10) \times 10^{-5}$	2.48×10^{-6}
433	22.25	$6.02\ (0.38) \times 10^{-5}$	2.71×10^{-6}
474	22.35	6.22×10^{-5}	2.78×10^{-6}
		t = 60 °C	
202	16.50	3.30×10^{-6}	2.00×10^{-7}
224	17.20	$1.67\ (0.01) \times 10^{-5}$	9.71×10^{-7}
249	17.90	$3.00\ (0.45) \times 10^{-5}$	1.68×10^{-6}
290	18.70	$5.06\ (1.13) \times 10^{-5}$	2.71×10^{-6}
321	19.20	$6.33\ (0.78) \times 10^{-5}$	3.30×10^{-6}
345	19.55	$7.17\ (0.46) \times 10^{-5}$	3.67×10^{-6}
384	20.05	$8.22\ (0.08) \times 10^{-5}$	4.10×10^{-6}
420	20.45	$9.12\ (1.07) \times 10^{-5}$	4.46×10^{-6}
472	21.00	$10.14\ (1.02) \times 10^{-5}$	4.83×10^{-6}

[a] The standard deviation is given in parentheses.

Solubility data in SC-CO_2 were obtained at two temperatures (40 and 60 °C) and at pressures up to 488 bar, which is the pressure limit of the modified SFE apparatus (Maxwell et al., 1991). Solubility data are listed in Tables 2−4 and shown in Figures 2−4. Each data point with standard deviation represents at least three determinations made on separate days. Comparing Tables 2−4 shows that SME, with a maximum solubility of 10.14×10^{-5} mol·L^{-1},

Table 3. Solubility *S* of Sulfamethazine (SMZ) in Supercritical Carbon Dioxide at 40 °C and 60 °C

P/bar	$\rho(CO_2)$/(mol·L^{-1})	*S*[a]/(mol·L^{-1})	*y*
		$t = 40$ °C	
181	18.70	1.65×10^{-5}	8.82×10^{-7}
211	19.30	$2.32\ (1.29) \times 10^{-5}$	1.20×10^{-6}
254	20.05	$3.30\ (0.61) \times 10^{-5}$	1.65×10^{-6}
281	20.45	$3.81\ (0.81) \times 10^{-5}$	1.86×10^{-6}
316	20.90	$4.18\ (1.05) \times 10^{-5}$	2.00×10^{-6}
360	21.40	$4.30\ (0.80) \times 10^{-5}$	2.01×10^{-6}
398	21.70	$4.51\ (0.74) \times 10^{-5}$	2.08×10^{-6}
414	21.85	$4.72\ (0.89) \times 10^{-5}$	2.16×10^{-6}
459	22.25	$4.91\ (0.23) \times 10^{-5}$	2.21×10^{-6}
		$t = 60$ °C	
136	12.30	$1.62\ (0.46) \times 10^{-5}$	1.32×10^{-6}
175	15.40	$2.37\ (0.30) \times 10^{-5}$	1.54×10^{-6}
215	16.95	$2.86\ (0.23) \times 10^{-5}$	1.69×10^{-6}
251	17.90	$3.29\ (0.13) \times 10^{-5}$	1.84×10^{-6}
259	18.10	$3.52\ (0.30) \times 10^{-5}$	1.94×10^{-6}
288	18.65	$3.86\ (0.23) \times 10^{-5}$	2.07×10^{-6}
326	19.30	$4.46\ (0.30) \times 10^{-5}$	2.31×10^{-6}
356	19.70	$4.65\ (0.03) \times 10^{-5}$	2.36×10^{-6}
396	20.20	$5.25\ (0.11) \times 10^{-5}$	2.60×10^{-6}
436	20.65	$5.62\ (0.13) \times 10^{-5}$	2.72×10^{-6}
476	21.00	$6.59\ (0.43) \times 10^{-5}$	3.14×10^{-6}

[a] The standard deviation is given in parentheses.

Table 4. Solubility *S* of Sulfadimethoxine (SDM) in Supercritical Carbon Dioxide at 40 °C and 60 °C

P/bar	$\rho(CO_2)$/(mol·L^{-1})	*S*[a]/(mol·L^{-1})	*y*
		$t = 40$ °C	
131	16.95	2.06×10^{-5}	1.22×10^{-6}
166	18.30	$3.06\ (0.09) \times 10^{-5}$	1.67×10^{-6}
196	19.00	$3.74\ (0.63) \times 10^{-5}$	1.97×10^{-6}
235	19.70	$4.36\ (0.35) \times 10^{-5}$	2.21×10^{-6}
275	20.35	$5.45\ (0.64) \times 10^{-5}$	2.68×10^{-6}
320	20.95	$5.58\ (0.92) \times 10^{-5}$	2.66×10^{-6}
358	21.35	$5.69\ (0.80) \times 10^{-5}$	2.67×10^{-6}
391	21.65	$5.59\ (0.81) \times 10^{-5}$	2.58×10^{-6}
437	22.05	$5.94\ (0.70) \times 10^{-5}$	2.69×10^{-6}
466	22.30	$6.09\ (0.50) \times 10^{-5}$	2.73×10^{-6}
		$t = 60$ °C	
202	16.50	4.25×10^{-6}	2.58×10^{-7}
237	17.30	$1.70\ (0.30) \times 10^{-5}$	9.82×10^{-7}
270	18.30	$3.85\ (2.26) \times 10^{-5}$	2.10×10^{-6}
306	19.00	$4.47\ (1.94) \times 10^{-5}$	2.35×10^{-6}
342	19.50	$4.78\ (1.20) \times 10^{-5}$	2.45×10^{-6}
377	20.00	$5.33\ (0.85) \times 10^{-5}$	2.67×10^{-6}
414	20.40	$5.81\ (0.93) \times 10^{-5}$	2.85×10^{-6}
449	20.78	$6.21\ (1.17) \times 10^{-5}$	2.99×10^{-6}
488	21.13	$6.50\ (1.17) \times 10^{-5}$	3.08×10^{-6}

[a] The standard deviation is given in parentheses.

had limited solubility in SC-CO_2 but displayed the highest solubility of the three sulfonamides studied. This result was unexpected because, as shown in Table 1, SME has a melting point which is considerably higher than those of SMZ and SDM. Since the crystal structure of SME breaks down at the highest temperature of the three sulfonamides studied, it was expected to have the lowest sublimation pressure. However, the calculated sublimation pressure, although a rough approximation, indicated that, relative to SMZ and SDM, SME has the higher sublimation pressure. This could explain SME's slightly higher solubility.

As expected, the solubility of the sulfonamides in SC-CO_2 increased with increasing pressure and therefore density, although the effect was not that pronounced for SMZ. The sulfonamides as a group had greater solubility

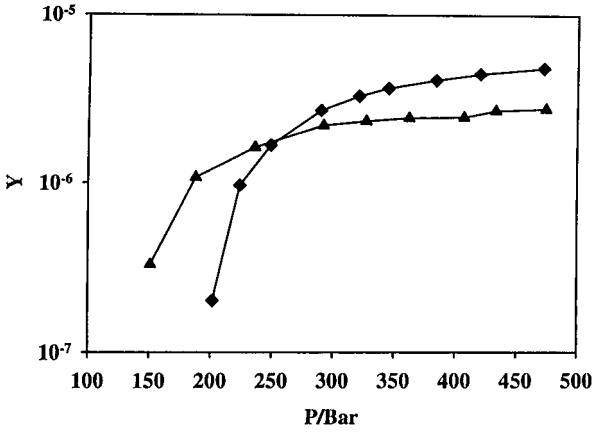

Figure 2. Sulfamerazine solubility in supercritical CO_2 at 40 (▲) and 60 °C (◆).

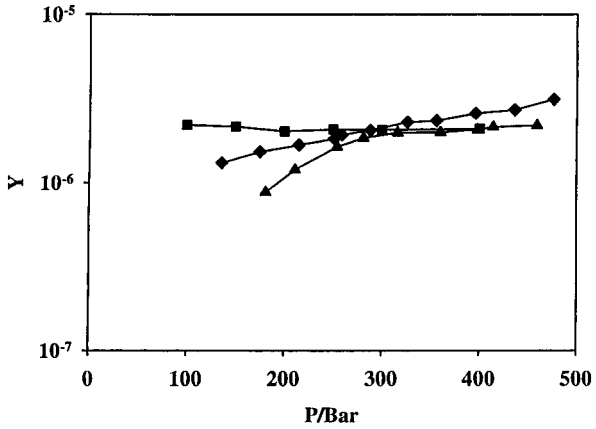

Figure 3. Sulfamethazine solubility in supercritical CO_2 at 40 (▲) and 60 °C (◆) from literature at 40 °C (■) (Ashraf-Khorassani et al., 1997).

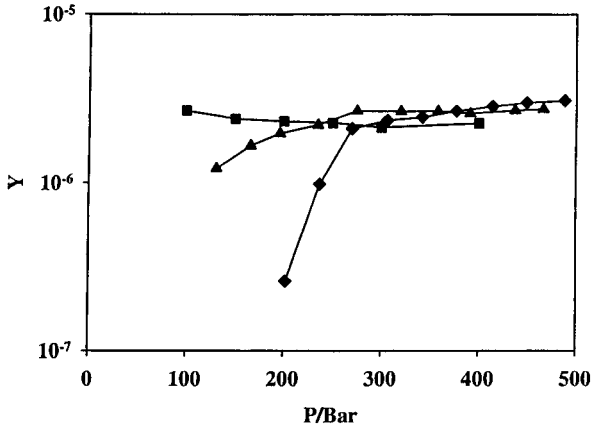

Figure 4. Sulfadimethoxine solubility in supercritical CO_2 at 40 (▲) and 60 °C (◆) from literature at 40 °C (■) (Ashraf-Khorassani et al., 1997).

at 60 than at 40 °C. In his review on SFE, Rizvi et al. (1986) reported that amides are not likely to be very soluble in SC-CO_2 because amides are not very soluble in liquid carbon dioxide. We did a preliminary examination of some nitrobenzamide solubilities and confirmed that these amides are not very soluble in SC-CO_2. The most soluble nitrobenzamide, aklomid (2-chloro-4-nitrobenzamide), had a maximum solubility of 0.6 g·L^{-1} (60 °C, 450 bar). That solubility, however, is about 20 times greater than that of the most soluble sulfonamide (SME). Thus, in general, it may be that

sulfonamides are significantly less soluble than other amides in SC-CO_2 due to aspects of their chemical structure, for example, a substituted pyrimidine ring.

The effect of temperature (60 °C versus 40 °C) on the solubility of the sulfonamides showed that as the temperature increased, the solubility of the three sulfonamides increased 13−74% at the higher temperature but identical pressure. As indicated in the previous report (Hampson, 1996), the increases in solubility at 60 °C must be due to the increased vapor pressure of the sulfonamides because at this higher temperature CO_2 is less dense. Two sulfonamides, SME and SDM (Figures 2 and 4), showed a crossover point where the solubility increased with pressure, but solubility was greater at the higher temperature, which is the less dense condition of CO_2. SMZ did not show a crossover point but did have a higher solubility at 60 °C compared to 40 °C. Ideally, pressure data at a minimum of three temperatures are required to determine the crossover point, which is a good indication of data reliability (Foster et al., 1991). Our data, however, were limited to two temperatures, 40 and 60 °C, to coincide with SFE studies of drug residues in animal tissue.

Only solubility data for SMZ and SDM in SC-CO_2 at 40 °C have been reported previously (Ashraf-Khorassani et al., 1997). In that report they used a similar recirculating fluid apparatus. Unfortunately, their data were obtained at only one temperature and thus no crossover point could have been observed (Figures 3 and 4). There is a reasonable agreement of our data with theirs at high pressure (300−500 bar) but substantial differences at lower pressures (100−300 bar). For example, at 40 °C we find a mole fraction solubility for SMZ of 2.08×10^{-6} at 398 bar, whereas they reported a value of 2.11×10^{-6} at 400 bar. For SDM we find a mole fraction solubility of 2.58×10^{-6} at 391 bar compared to 2.26×10^{-6} at 400 bar. We plotted their data for these two compounds together with our results, which are displayed in Figures 3 and 4. Our mole fraction solubility data in Tables 2−4 all increase with increasing pressure, which is in contrast to the literature data cited. The literature cited shows very little difference in mole fraction solubility as the pressure increases. Indeed, the literature cited shows a slightly higher mole fraction solubility at the lower pressure (where density is also lower), which is counter to expected behavior, especially at pressures >100 bar. This is particularly unexpected due to the estimated low sublimation pressure of SMZ and SDM (Table 1).

The solubility data obtained in this work indicate that the three sulfonamides studied are soluble in the ppm range in SC-CO_2 and that substitution of methyl, dimethyl, or dimethyoxy groups in the pyrimidine ring made very little difference in their overall solubility in SC-CO_2. There is sufficient solubility, however, to develop a multiresidue SFE method to extract these drugs from animal tissue where they are present in trace amounts. Since it was shown that sulfonamides had some limited solubility in SC-CO_2, supercritical fluid extraction (SFE) methods, both in-line and off-line, have been and are being developed to extract these and other sulfonamide residues from biological samples. Also, in preliminary SC-CO_2 solubility studies with other sulfonamides (sulfadiazine, sulfapyridine, sulfachloropyridazine, sulfaquinoxaline, and sulfathiazole), only sulfathiazole had no detectable solubility.

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Nomenclature

P = pressure
S = solubility
t = temperature
y = mole fraction
ρ = molar density

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