Solubility of Anti-Inflammatory, Anti-Cancer, and Anti-HIV Drugs in Supercritical Carbon Dioxide

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This paper focuses on the collection of solubility data for pharmaceutical drugs in supercritical carbon dioxide. The experimental techniques used to obtain the data include a supercritical fluid chromatographic technique and a conventional dynamic solubility apparatus. The chromatographic method provided the retention times of the solutes of interest and those of an un-retained substance, which were used to obtain equilibrium partition coefficients. The partition coefficients were subsequently used to obtain solubilities at various temperatures and pressures. The conventional dynamic solubility apparatus was used to provide a calibration parameter for the chromatographic method. The coupling of these two techniques allowed for the fast and accurate determination of the solubility data. Both techniques were validated by measuring the solubility of naphthalene and phenanthrene in carbon dioxide at temperatures between (35 and 55) °C and pressures between (100 and 300) bar. The results agreed within ±10 %, a reasonable experimental uncertainty, to those of other investigators, thus confirming the reliability of the techniques. Additionally, the solubility of anti-inflammatory drugs (naproxen, ibuprofen, and acetaminophen), anti-cancer drugs (paclitaxel, 5-fluorouracil, and thymidine), and anti-HIV drugs (azodicarbonamide and 2-phenyl-4*H*-1,3-benzoxazin-4-one) were measured in supercritical carbon dioxide for the same range of temperatures and pressures. The results are explained in terms of solute volatility and specific interactions as the most significant factors influencing solubility of pharmaceutical drugs in pure carbon dioxide.

Introduction

The search for more effective and environmentally benign separation processes is always of great interest for any chemical application. In the pharmaceutical industry, the use of supercritical CO_2 is a promising alternative to replace sequential processes such as extraction, drying, and crystallization, while more effectively controlling particle size and crystal morphology. Carbon dioxide can replace environmentally toxic and undesirable solvents such as acetone, carbon tetrachloride, methylene chloride, toluene, dimethyl sulfoxide, dimethylformamide, and tetrahydrofuran, which either require extensive solvent recovery units or remain in the final product in small but dangerous concentrations (e.g., ppm). Carbon dioxide has numerous additional attractive features: it has an easily accessible critical point (31.1 °C and 73.8 bar), low cost, abundance, nonflammable, nontoxic, and environmentally benign nature.

To ponder the feasibility of this approach, the phase-equilibrium behavior of pharmaceutical drugs in supercritical CO_2 has to be investigated. Unfortunately, this has not been extensively done due to the experimental limitations of conventional static and dynamic solubility methods. These methods typically require a long time for equilibration, particularly for low-solubility substances, and they also require large amounts of pure solute, which are often unavailable and quite expensive. In addition, melting point depressions may complicate the experimental procedure due to the need of further sampling in the liquid phase.

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This paper describes the combination of two experimental techniques for the rapid and accurate determination of solubility data for pharmacological drugs in supercritical fluids (SCFs). This combination uses a high-pressure chromatographic system equipped with a high-pressure online UV detector and a conventional dynamic solubility apparatus. The approach is therefore to obtain at least one solubility datum with the conventional apparatus and then use it to calibrate the chromatographic method.

Chromatographic Method's Theory

In chromatography, the degree of retention of a solute depends on its equilibrium distribution between the mobile and stationary phases. This distribution is characterized for a solute i by a dimensionless partition coefficient (k_i) readily determined by

$$k_i = \frac{t_i - t_o}{t_o} \tag{1}$$

where t_i is the retention time of the solute (e.g., pharmaceutical drug), and t_o is the retention time of an un-retained solute (e.g., pentane). Assuming equilibrium, then

$$k_i = \frac{n_i^{stat}}{n_i^{SF}} = \frac{x_i}{y_i}\frac{V^{stat}}{v^{stat}}\frac{v^{SF}}{V^{SF}} \tag{2}$$

where x_i and y_i are the mole fractions of the solute i in the stationary and SCF phase, respectively; and V and v are the physical and molar volume, respectively. Phase equilibrium considerations between the stationary and SCF

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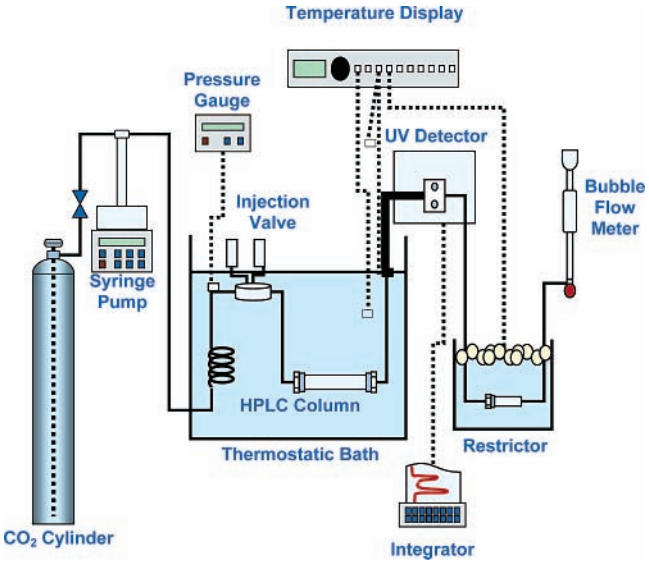

Figure 1. Supercritical fluid chromatographic apparatus.

phases yield the fugacity coefficient of solute i at infinite dilution (ϕ_i^∞):

$$\phi_i^\infty = \frac{k_i}{v^{SF}} \frac{H_i^0}{P} \exp\left\{\frac{v_i}{RT}(P - P^0)\right\}\left[\frac{V^{SF} v^{stat}}{V^{stat}}\right] \quad (3)$$

The solubility of a solid pharmaceutical drug in a SCF is normally low; therefore, its fugacity coefficient in the SCF can be approximated to the fugacity coefficient at infinite dilution. The solubility expression then becomes

$$y_i = \frac{v^{SF}}{k_i}\left[\frac{P_i^{sub}}{H_i^0} \frac{V^{stat}}{v^{stat} V^{SF}} \exp\left\{\frac{v_i(P^0 - P_i^{sub})}{RT}\right\}\right] = \frac{v^{SF}}{k_i}[C_i(T)] \quad (4)$$

The expression in brackets has been previously called the calibration parameter (C_i).[1–6] It does not depend on pressure; however, it depends on the chromatographic column (type and details about the column characteristics) and temperature. C_i could be obtained with detailed knowledge of the chromatographic column (e.g., column i.d., thickness, length, etc.) or with a previously measured experimental solubility datum.[4–7] Once C_i is known, the solubility of the pharmacological drug in the SCF can be easily obtained from the partition coefficients. Note that the density of CO_2 ($1/v^{SF}$) is known with high accuracy.[8,9]

Calculating the constant C_i could be considered a challenge due to the swelling of the stationary phase when in contact with the SCF; however, Johnston and co-workers[10,11] have studied this effect. Their study shows that although swelling can be important in packed columns for the pressure ranges often studied (e.g., (100 to 300) bar), this effect is approximately constant within that pressure range and thus can be included in the constant C_i.

Experimental Section

Chromatographic Method. The high-pressure chromatographic apparatus used for the determination of solubilities is shown in Figure 1. The system consists of a pulse-free delivery system into a chromatographic packed column and then into the UV detector. A syringe pump (ISCO 260D) was used as a pulse-free delivery system. To charge the pump, the fluid (carbon dioxide) was withdrawn as a liquid from a cylinder (equipped with a dip tube) and charged into a cooled high-pressure syringe pump before the experiment. In a typical experiment, the syringe pump delivered the fluid at a constant pressure to the system. The fluid reached thermal equilibrium in the thermostatic bath before entering an injection valve (VALCO 4C16UW1), where small amounts of the pharmaceutical drug dissolved in pentane were injected. The volume injected is 0.1 μL. Pentane was selected as the solvent because it dissolves the pharmaceutical drugs, and it is not retained in the packed column. Its peak was detected each time providing a reference elution time (t_o). The column (100 mm in length and 4.6 mm i.d.) is packed with 5.0-μm particles of Hypersil BDS C_{18}. The small pressure drop through the column and the pressure itself were monitored using a pressure transducer and indicator (HEISE 901B). The effluent then passed to the high-pressure variable-wavelength UV detector (ISCO). The signal out of the detector was stored in the integrator (Hewlett-Packard 3396A). The variable restrictor (Computer Chemical Systems, VR-100) after the detector allowed fluid decompression and flow rate control. The restrictor was heated to overcome the cooling upon expansion of the SCF. This was accomplished using a thermostatic bath (Fisher Polystad Circulator 1252). Air-filled plastic balls were used in this bath as an additional insulating resistance to reduce water evaporation. A soap-film flowmeter (Hewlett-Packard 0100-0113) was used to measure the outlet solvent flow rate. The temperature at various points on the equipment was monitored using RTD elements (Omega Engineering) connected to the proper meter (Omega DP 2000).

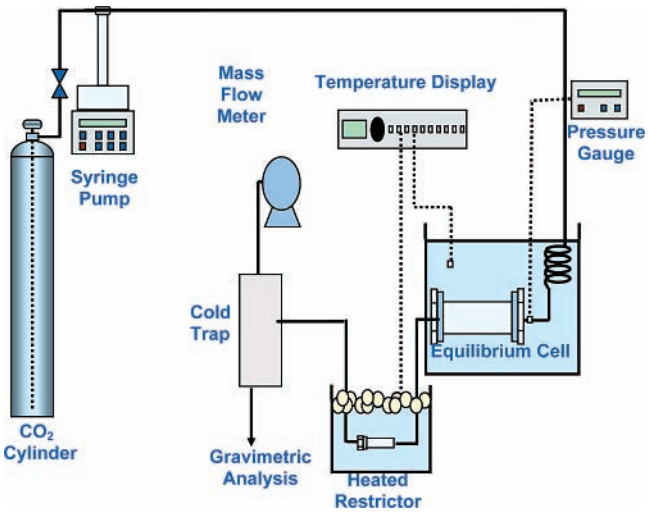

Figure 2. Conventional dynamic high-pressure solubility apparatus.

The retention time for each run corresponds to the maximum for the solute response or peak. The retention times used in the calculation of solubility correspond to an average of at least three measurements. The chromatographic column was kept under pressure at all times to maintain constant its activity and performance.

Dynamic Method. Figure 2 shows the conventional dynamic method used to measure the solubilities in this study. The syringe pump was charged as described before and was used to deliver the fluid to the system in any given run. The fluid entered the constant-temperature bath, where it flowed through a preheater (e.g., section of stainless steel tubing) to ensure that it reached the desired fluid temperature. At this point, the solvent is at supercritical conditions. The SCF then passed to a high-pressure cell filled with the pure solute, where phase equilibrium was attained. After the drug-saturated SCF exits the cell,

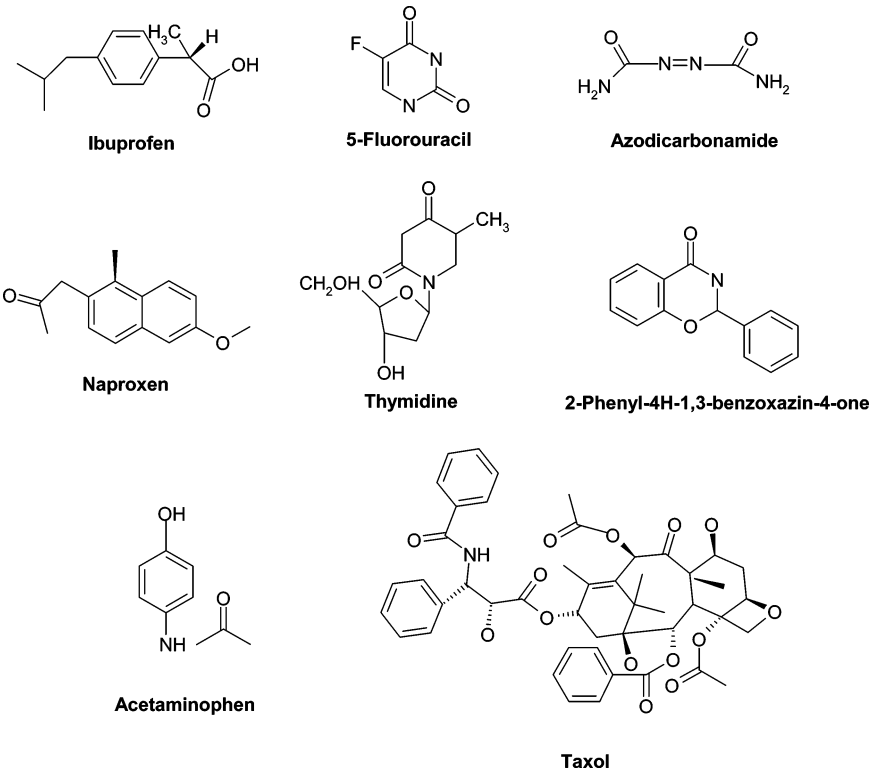

Figure 3. Chemical structure of pharmaceutical drugs studied.

it depressurized in the restrictor. The restrictor was heated to overcome the Joule−Thompson cooling upon expansion of the solvent. The solute dissolved in the SCF precipitated. The solute in the solid state was collected in a cold trap and weighed gravimetrically, providing the moles of solute dissolved in the SCF phase. The total amount of solvent was measured with a mass flowmeter (Omega FMA-A2303), thus giving the number of moles of solvent. The solubility was then readily calculated as the moles of solute over the total number of moles (solute and solvent).

This study used a commercially available, supercritical-fluid extraction unit (ISCO SFX 2-10), as the experimental apparatus to measure solubilities conventionally. This equipment needed to be operated at very low flow rates to ensure equilibrium. Also, the system was equipped with a coaxially heated adjustable flow restrictor (ISCO) to overcome the Joule−Thompson cooling upon expansion and the precipitation problems associated with the decompression.

Chemicals. SFC-grade CO_2 (99.98 % purity) was obtained from Scott Specialty Gases. Pentane [109-66-0] (HPLC grade), acetone [67-64-1] (HPLC grade), naphthalene [91-20-3] (98 % purity), phenanthrene [85-01-8] (98+ % purity), naproxen (*S*)-(+)- or (*S*)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid [22204-53-1] (98 % purity), ibuprofen (*S*)-(+) or α-methyl-4-(isobutyl) phenylacetic acid [15687-27-1] (99 % purity), acetaminophen or 4-acetamidophenol [103-90-2] (99 % purity), paclitaxel [33069-62-4] (95 % purity), 5-fluorouracil or 2,4-dihydroxy-5-fluoropyrimidine [51-21-8] (99 % purity), azodicarbonamide, also called azodicarboxamide or diazenedicarboxamide [123-77-3] (97 % purity), thymidine or 1-(2-deoxy-β-D-ribofuranosyl)-5-methyluracil [50-89-5] (>99 % purity), and 2-phenyl-4*H*-1,3-benzoxazin-4-one [3084-52-4] (98 % purity) were obtained from Sigma-Aldrich Chemical Co. They were used without any further treatment other than the standard safety precautions followed when handling any chemical substance. The chemical structures of the pharmaceutical drugs used in this investigation are presented in Figure 3.

Results and Discussion

The well-studied CO_2−naphthalene system was studied first to confirm the reliability and validity of both techniques. The conventional dynamic solubility method was tested first by measuring the solubility of naphthalene at 35 °C and 200 bar and comparing the results to the published data of Tsekhanskaya et al.[12] and McHugh and Paulaitis.[13] The results agreed within ±10 %, a reasonable experimental uncertainty given the inaccuracies in the weight of the solute collected and possible deposition of the solute in the lines.

To test the validity of the chromatographic method, the value of C_i is needed. The solubility datum from the conventional dynamic solubility apparatus (200 bar and 35 °C) was used to obtain the calibration parameter, C_i (eq 4). Solvent densities were obtained from the *International Thermodynamic Tables of the Fluid State*.[8,9] Once C_i was obtained, the solubilities were calculated from the measured partition coefficients. The solubilities measured in this study are compared to those of other investigators in Figure 4. The results agree within ±10 %. Although the variability between experiments was typically ±10 %, the overall estimated error is approximately 20 %. The largest contributions to the experimental error come from the pressure drop across the column (1 to 3) bar or ∼3 %, the flow variations from the constant pressure control (± 0.2) mL/min or ∼2 %, the maxima of the retention times ± (1 to 3) s or ∼(3 to 5) %, and the error in C_i, which comes from pressure, temperature, and weight loss variations in the dynamic solubility measurement calibration ∼10 %. Additional sources of error include variations in the temperature measurement and control (± 0.2 °C) and the pressure transducer and indicator (± 0.5 bar).

The solubility of phenanthrene in CO_2 was also measured at 45 °C and pressures between (160 and 280) bar to test the reliability of the methods over a different

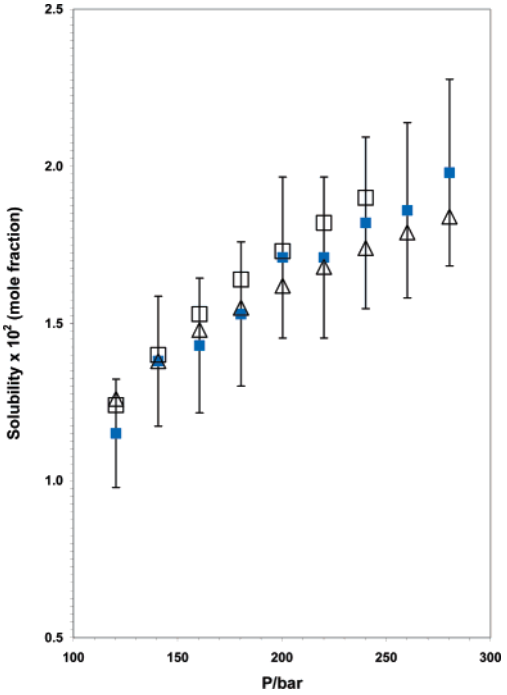

Figure 4. Solubility of naphthalene in supercritical carbon dioxide at 35 °C: ■, this investigation; Δ, Tsekhanskaya et al.;[12] □, McHugh and Paulaitis.[13]

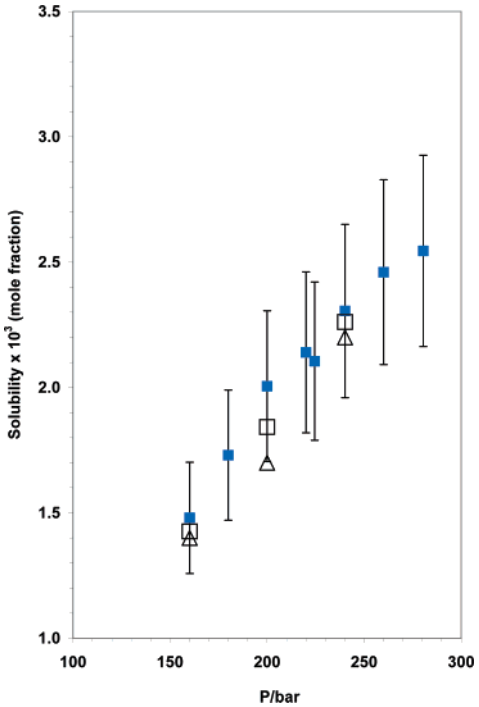

Figure 5. Solubility of phenanthrene in supercritical carbon dioxide at 45 °C: ■, this investigation; Δ, Suleiman et al.;[4] □, Bartle et al.[14]

temperature, solute, and solubility range. Solubilities of phenanthrene are about one order of magnitude lower than those of naphthalene under the conditions studied. These results are shown in Figure 5 and compared with those of other investigators.[4,14] This comparison also confirmed the validity and reliability of the techniques. The value of C_i used for the conversion of the k's to y's came from another datum now for phenanthrene, measured with the conventional dynamic solubility method at 160 bar.

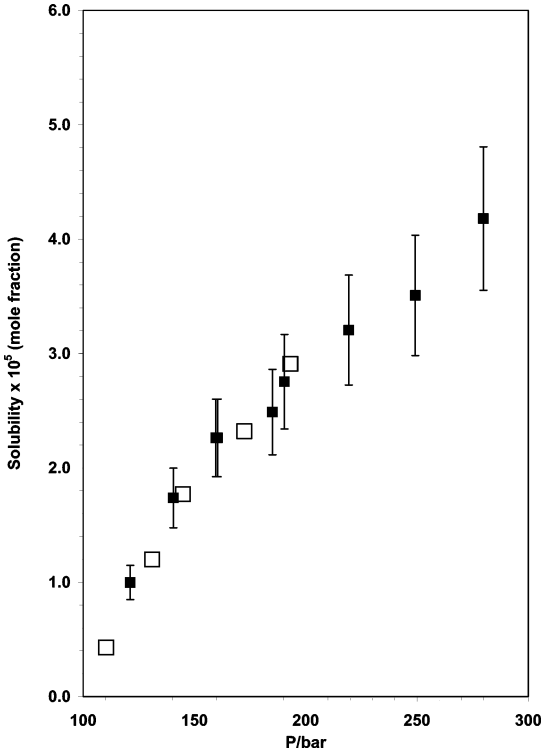

Figure 6. Solubility of (*S*)-(+)-naproxen in supercritical carbon dioxide at 40 °C: ■, this investigation; □, Ting et al.[15]

Once both techniques were validated, three groups of drugs were studied: anti-inflammatory, anti-cancer, and anti-HIV drugs. Corresponding results follow.

Anti-Inflammatory Drugs Group (Naproxen, Ibuprofen, and Acetaminophen). Racemic naproxen was the first pharmaceutical drug studied. The chromatographic method was used to measure the solubility of naproxen in CO_2, and the corresponding calibration parameter was obtained from a solubility datum measured by the conventional method at 200 bar. The solubility of naproxen in supercritical CO_2 at 40 °C and pressures between (140 and 280) bar is presented in Figure 6.

The solubility of racemic ibuprofen was studied next. Again, the calibration parameter was obtained from a solubility datum measured with the conventional apparatus at 200 bar and 40 °C. Figure 7 presents the solubility of ibuprofen at 40 °C and pressures between (100 and 250) bar. For comparison purposes, the solubility of ibuprofen from literature[16] at (35, 40, and 45) °C is also shown. The solubilities of ibuprofen are almost one order of magnitude higher than those of naproxen. Since CO_2 is a nonpolar solvent, this trend could be explained by considering their melting temperatures (Table 1), since the melting point provides an indication of the volatility (sublimation pressure). Lower melting temperatures correspond to higher sublimation pressures at the same temperature and therefore higher ideal solubility. In SCFs, the two major effects influencing solubilities are the solute volatility and the specific interactions contributing to the solvating effects.

Although higher temperatures were also studied with the chromatographic method, Foster and co-workers[16] reveal melting point depression of ibuprofen close to 50 °C. Since the chromatographic method measures retention times regardless of phase changes; those results probably deserve further analysis. Ibuprofen had the lowest melting point of all pharmaceutical drugs studied and was the only

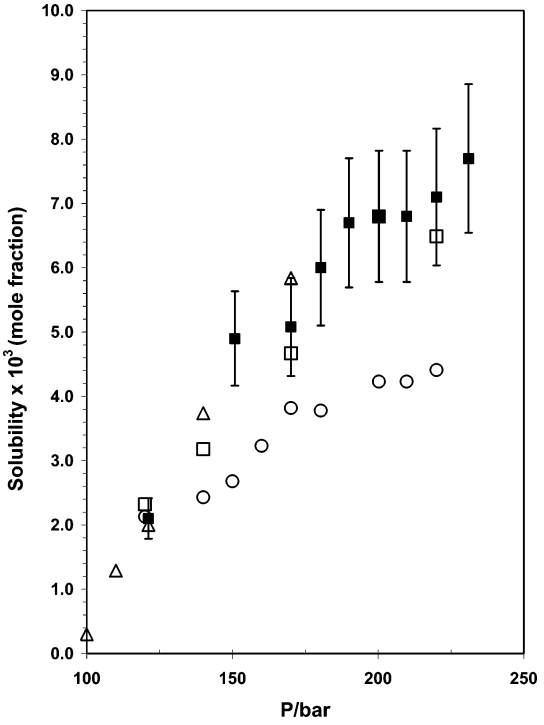

Figure 7. Solubility of (*S*)-(+)-ibuprofen in supercritical carbon dioxide: ■, this investigation, 40 °C; ○, Foster et al.,[16] 35 °C; Δ, Foster et al.,[16] 40 °C ; □, Foster et al.,[16] 45 °C.

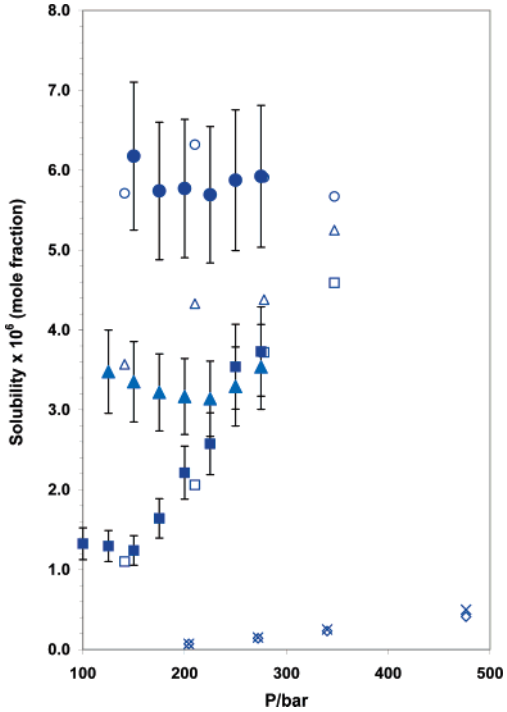

Figure 8. Solubility of paclitaxel in supercritical carbon dioxide: ■, this investigation, 35 °C; ▲, this investigation, 45 °C; ●, this investigation, 55 °C; □, Vandana and Teja,[19] 38.0 °C; Δ, Vandana and Teja,[19] 49.0 °C; ○, Vandana and Teja,[19] 55.75 °C; □, Nalesnik et al.,[20] 35 °C ; ×, Nalesnik et al.,[20] 45 °C.

one that could have melting point depression over the conditions studied.

The third anti-inflammatory drug studied was acetaminophen. The conventional solubility method was used first to measure the solubility of acetaminophen in CO_2. The method was run for over 20 h to collect sufficient sample for an accurate weight measure. The results indicated solubilities in the 7 ± 1 ppm range. This solubility represents an average over three different runs at 200 bar and 50 °C, and the results compared very well with those of other investigators.[17]

Since the solubility of acetaminophen in pure CO_2 was quite low, this was a good example of a system where a SCF reverse separation might be more appropriate. To further assess this approach, a slurry made of acetaminophen and acetone was fed into the precipitation chamber (ISCO SFX-210). The precipitation chamber was modified with a custom-made nozzle to cause supersaturation of the SCF phase and precipitate the acetaminophen. As a result, the recovery of acetaminophen improved to approximately 90 % with this approach.

Anti-Cancer Drugs Group (Paclitaxel, Thymidine, and 5-Fluorouracil). Three chemicals were selected from this group: paclitaxel (also known as Taxol), 5-fluorouracil, and thymidine (Figure 3). Paclitaxel is a commonly used anti-cancer drug for treating breast and ovarian cancer. 5-Fluorouracil is used for the treatment of rectal, colon, breast, stomach, head, and neck cancer. Thymidine, although not an anti-cancer drug, has a chemical structure very similar to the anti-cancer drug 4′-cyanothymidine, which was not available in its active form. They were selected not only for their clinical importance and the need to develop more effective processing methods but also for their chemical nature and size.

Since it was difficult, expensive, and cumbersome to obtain solubility data with the conventional method, it was only used to obtain solubility data at (35 and 55)°C (200 bar) for each solute studied. Each data point was used to obtain the calibration parameter for the chromatographic method (C_i) at each temperature. C_i was linearly interpolated to obtain the value at 45 °C.

Of the three selected compounds, paclitaxel is the only one previously studied by other researchers; thus, the corresponding literature data were used for comparison purposes. The solubility of paclitaxel was extremely low, which may explain the scatter found among literature values.[18,19] Even so, the results obtained in this work are within the range of literature values. Figure 8 shows the results of this work at (35, 45, and 55) °C as well as literature values at similar temperatures. At higher pressures some solvation effect seems to take place with every study.

Table 1. Properties and Solubility Ranges of Solutes Studied

substance	formula	molecular mass	melting temperature/°C	solubility in CO_2 (mole fraction)
ibuprofen (*S*)-(+)	$C_{13}H_{18}O_2$	206	73−76	$(2.1-7.7) \times 10^{-3}$
naproxen (*S*)-(+)	$C_{14}H_{14}O_3$	230	157−158	$(1.0-4.2) \times 10^{-5}$
acetaminophen	$C_8H_9NO_2$	151	168−172	$(2.1-7.7) \times 10^{-6}$
5-fluorouracil	$C_4H_3FN_2O_2$	130	282−286	$(3.6-14.6) \times 10^{-6}$
thymidine	$C_{10}H_{14}N_2O_2$	242	186−188	$(1.2-8.0) \times 10^{-6}$
paclitaxel	$C_{47}H_{51}NO_{14}$	854	213−217	$(1.2-5.9) \times 10^{-6}$
2-phenyl-4*H*-1,3-benzoxazin-4-one	$C_{14}H_9NO_2$	223	123−125	$(0.8-4.5) \times 10^{-4}$
azodicarbonamide	$C_2H_4N_4O_2$	116	224−225	$(0.9-2.6) \times 10^{-5}$

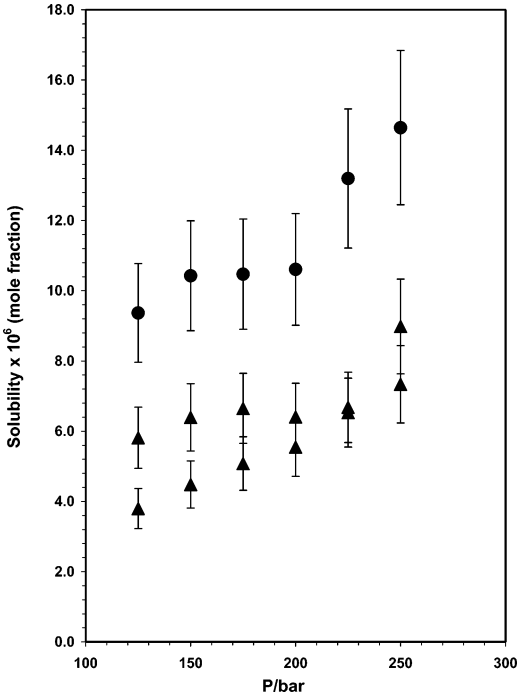

Figure 9. Solubility of 5-fluororacil in supercritical carbon dioxide obtained in this work: ■, 35 °C; ▲, 45 °C; ●, 55 °C.

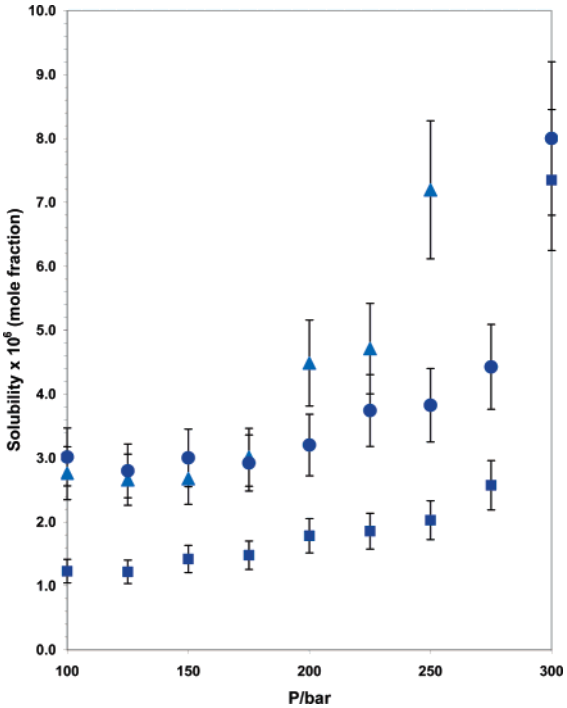

Figure 10. Solubility of thymidine in supercritical carbon dioxide obtained in this work: ■, 35 °C; ▲, 45 °C; ●, 55 °C.

Figure 9 shows the solubility of 5-fluorouracil at (35, 45, and 55)°C for pressure between (100 and 250) bar. These results were only slightly higher than those of paclitaxel at lower pressures. This could be explained by its significantly high melting point; therefore, its sublimation pressure should be lower than any of the other drugs studied. The fluorine in its structure might also produce some solvation in CO_2, despite its low volatility. This effect appears to become more pronounced at higher pressures.

The solubility of thymidine is presented in Figure 10. Again, the low solubility is expected for such a high-melting-point solid; however, the data suggest a crossover

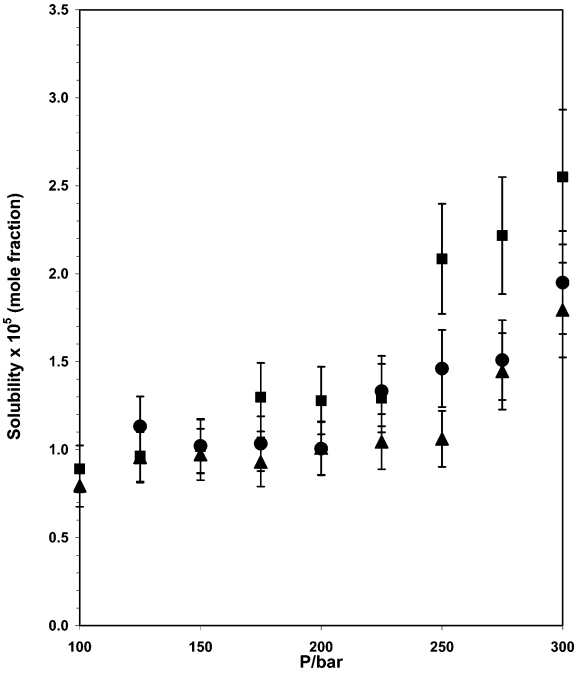

Figure 11. Solubility of azodicarbonamide in supercritical carbon dioxide obtained in this work: ■, 35 °C; ▲, 45 °C; ●, 55 °C.

region and significantly higher solubilities at higher pressures indicating, perhaps, solvating effects at higher densities.

Anti-HIV Drugs Group (Azodicarbonamide and 2-Phenyl-4H-1,3-benzoxazin-4-one). Although anti-HIV drugs are continuously emerging, this investigation selected two substances with some chemical diversity and physical properties. Azodicarbonamide has been shown to inhibit a wide variety of HIV-1 and HIV-2 strains as well as SIV. It is a fairly small molecule containing C−H−O−N but with a significantly high melting temperature (224 to 225) °C. 2-Phenyl-4*H*-1,3-benzoxaxin-4-one, although not an anti-HIV drug, was studied because it has a structure similar to the anti-HIV drug Sustiva, which could not be obtained in its active ingredient form. Although it was a heavy molecule containing C−H−O−N, it had an unusually low melting temperature (123 to 125) °C.

Figures 11 and 12 present the solubility of azodicarbonamide and 2-phenyl-4*H*-1,3-benzoxaxin-4-one, respectively. Azodicarbonamide has a very high melting temperature for its molecular weight. Its solubility is in the same order of magnitude as substances with similar melting points, as shown in Table 1.

To have a basis of comparison among all drugs studied, Table 1 presents the chemical formula, size, melting temperature, and solubility range over the conditions studied. Since all the drugs were studied under similar conditions, their solubilities in SCF CO_2 can be meaningfully compared. Solute volatility (indicated by melting point) seems to affect solubility significantly. Unfortunately, sublimation pressures for the solute studied are so small that cannot be accurately measured. An attempt to estimate sublimation properties[20] disagrees with the calorimetric data measured in our laboratory. Our calorimetric data (Mettler-Toledo DSC 822) suggests that the pharmacological drugs have a higher heat of fusion-to-melting point ratio (75 ± 15) J·mol^{-1}·K^{-1} than estimation methods[20] suggest for organic compounds (40 ± 5) J·mol^{-1}·K^{-1}. Our thermogravimetric data (Mettler Toledo TGA/SDTA 851) also suggests that the drugs decompose before reaching the liquid−gas-phase boundary. These limitations led us to use

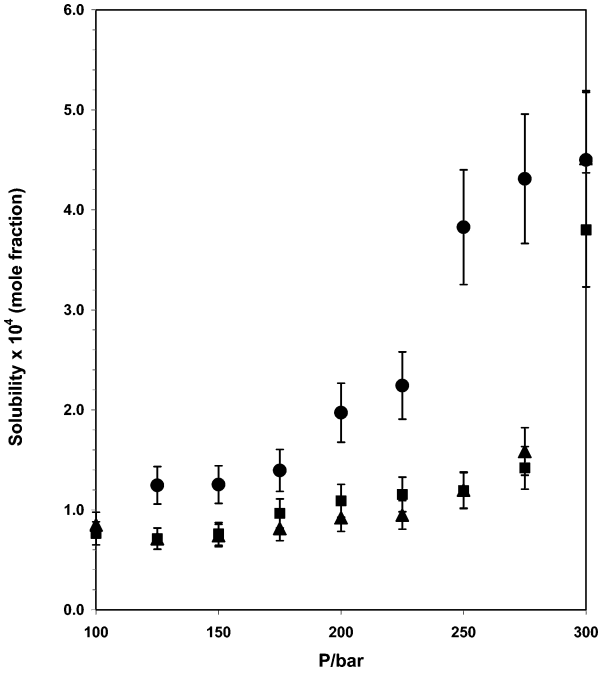

Figure 12. Solubility of 2-phenyl-4*H*-3,1-benzoxazin-4-one in supercritical carbon dioxide obtained in this work: ■, 35 °C; ▲, 45 °C; ●, 55 °C.

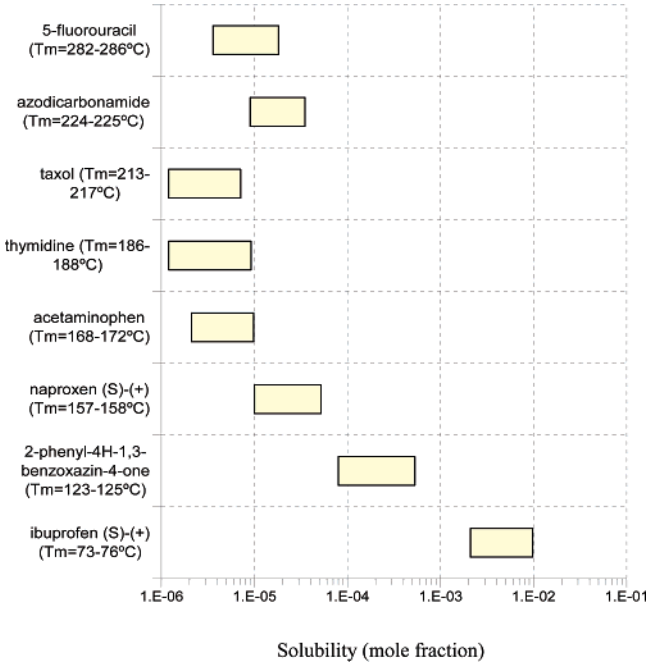

Figure 13. Solubility ranges of pharmaceutical drugs studied for increasing melting temperatures.

the melting temperature as the best indicator of solute volatility. The results in Table 1 and Figure 13 suggest that specific interactions, even in pure CO_2, might be significant, especially for azodicarbonamide and 5-fluorouracil. These interactions are spectroscopically studied in detail, using UV and FT-IR techniques, in extensive communications.[21–23]

Conclusions

Two experimental techniques, a conventional dynamic solubility apparatus and a custom-made chromatographic method were combined for the fast and accurate determination of solubilities of pharmaceutical drugs in SCF CO_2. The methods were tested by measuring naphthalene and phenanthrene solubilities to verify the validity of these techniques. They were further used to measure the solubility of: naproxen, ibuprofen, acetaminophen, paclitaxel, 5-fluorouracil, thymidine, azodicarbonamide, and 2-phenyl-4*H*-3,1-benzoxazin-4-one in supercritical carbon dioxide over a range of temperatures (35 to 55) °C and pressures (100 to 300) bar. The results were explained in terms of solute volatility and solvating effects in SCF CO_2. The proposed coupling of techniques provides a way to obtain a large database of solubilities of solid pharmacological drugs in SCFs. These data, besides their fundamental scientific significance, constitute an important contribution to the knowledge needed to design and operate processes involving new technologies with supercritical fluids.

Supporting Information Available:

Tables providing solubility data for anti-inflammatory, anticancer, and anti-HIV drugs studied and calibration paramters used for calculation of solubilities from chromatogram capacity factors. This material is available free of charge via the Internet at http://pubs.acs.org.

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