Determining the Solubility, Cloud Point, Swelling and Crystallization Properties of Materials in Supercritical Carbon Dioxide
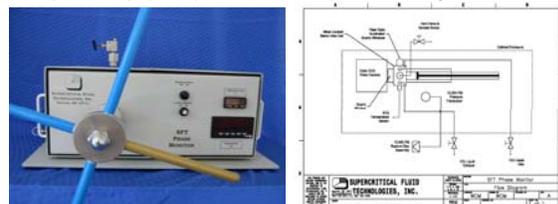
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Introduction

Direct, visual observation of materials under actual supercritical conditions is an important first step in the development and refinement of supercritical fluid extraction, reaction, and chromatographic processes. A specially designed phase equilibrium view cell or "Phase Monitor" is used to observe the dissolution, melting, precipitation, swelling and crystallization of compounds at a wide range of pressures and temperatures. Observations of materials are performed in the supercritical region, under precisely controlled conditions. The Phase Monitor simplifies the determination of critical point for binary, tertiary or complex mixtures. Through a better understanding of phase behavior as a function of temperature, pressure, and sample concentration, a significant time and cost savings for supercritical process development is realized. Examples of the Phase Monitor's utility are presented.

Variable-Volume Equilibrium View Cell Design

Main components include a Variable-Volume Equilibrium View Cell, Pressure Generator, Light Source and Color CCD Video Camera, sample mixing, and optional Video Monitor Display Panel Module, PC Video Capture Software, and Co-Solvent Addition Module. Experiments can be Performed from a Few Hundred psi to 10,000 psi (689 Bar) and from Ambient Temperature to 150° degrees Celsius.

Example #1 Determination of Lower Critical End Point (LCEP) and Depression of Melting Point

Solubility of compounds in SCF-CO_2 is one of the most extensively investigated areas of SCF research as it establishes the technical and economic viability of a particular supercritical process. Over the last few decades, a considerable amount of solubility data has appeared in the literature. However, lack of reliable phase equilibrium data has been one of the major obstacles in the progress of SCF technology.

In the presence of the solute, the vapor pressure curve for pure CO_2 is shifted ending in a critical end point. Solid solutes when in contact with supercritical CO_2 can exhibit complex phase behavior such as depression in melting point resulting in multiple phases. This depression in melting point can considerably influence the determination of solid solubility. In addition, density inversion may occur leading to erroneous solubility data. This emphasizes the need for checking the phase equilibria when measuring solid solubility data. The knowledge of phase behavior of solutes of interest under the SCF conditions is also essential for the development of any SCF process.

In conjunction with research on solubilities of aromatic carboxylic acids and substituted phenols in SCF-CO_2, the phase behavior of single (binary) and multicomponent (ternary and quaternary) systems was studied to ensure that only solid - fluid equilibria existed under the experimental conditions used for the solubility studies.

Experimental Methods

Determination of LCEP: The solute/mixture of solutes were packed in a small glass tube and placed inside the view cell. The system was pressurized and filled with liquid CO2 until the liquid meniscus separating the liquid and gas phases was clearly seen. The LCEP was then determined visually by observing the disappearance and the appearance of the meniscus accompanied by critical opalescence, which is intense at the critical point. The LCEP of the systems presented here have an estimated experimental error of +/- 0.5 K and +/- 0.7 bar respectively. The first critical endpoints for ternary and quaternary systems have also been termed as LCEP in this work for convenience.

Depression in the melting point: Depression in the melting point of the solutes/mixture of solutes at the temperature of interest was checked visually. The solute was placed in a glass tube inside the view cell and filled with CO_2. The system was then pressurized slowly from 101 bar to 240/280 bar over a period of several hours and was then held under static conditions for at least 2 hours.

Validation

The accuracy of the experimental method was validated by comparing the experimentally determined critical point for pure CO_2 with the literature values. The gradual phase transition of carbon dioxide from a single phase supercritical state through the critical point to a two phase subcritical state is pictured below. (The view cell shown here has a glass tube inserted in the cell).

Supercritical state   Critical Point   Subcritical state

Critical point of CO_2	T_c /K	P_c /bar
Literature	304.2	73.8
This work	304.1	73.6

Results

Lower Critical End Point (LCEP)

Stage 1   Stage 2   Stage 3

Stage 1. represents S2-S3-V equilibrium conditions, where the two solid solutes are in equilibrium with the supercritical fluid phase. Stage 2. is at the LCEP, where the contents of the cell become cloudy caused by scattering of light due to the large density fluctuations (critical opalescence). Stage 3. represents S2-S3-L-V equilibrium, where the two solid solutes are in equilibrium with L-V of CO_2.

Depression in melting point under high pressure CO_2

Before melting   After melting   Before melting   After melting

Depression in melting point of 2,5-dimethyl phenol + 4-tert-butyl phenol solute mixture in a glass tube inside the view cell. (Ternary system).

Depression in melting point of 2,3-dimethyl phenol binary system. Solute packed in a glass tube placed horizontally in the view cell.

LCEP and S-V equilibrium of binary, ternary and quaternary systems

Table 1. LCEP data of binary, ternary and quaternary systems

System	LCEP T (K)	LCEP P (bar)
Binary		
Benzoic acid + CO_2	303.8	73.6
Salicylic acid + CO_2	303.8	73.8
Acetylsalicylic acid + CO_2	303.9	74.0
2,3-dimethyl phenol + CO_2	305.5	74.4
2,4,6-trimethyl phenol + CO_2	305.6	74.5
4-tert-butyl phenol + CO_2	304.8	74.4
Ternary		
Salicylic acid + Benzoic acid + CO_2	303.8	75.0
Acetylsalicylic acid + Benzoic acid + CO_2	304.5	74.0
2,5-dimethyl phenol + 4-tert-butyl phenol + CO_2		
2,3,5-trimethyl phenol + 4-phenyl phenol + CO_2	304.7	74.0
2,4,6-trimethyl phenol + 4-phenyl phenol + CO_2	304.6	74.5
Quaternary		
Acetylsalicylic acid + Salicylic acid + Benzoic acid + CO_2	304.1	74.2

Table 2. S-V equilibrium of binary, ternary and quaternary systems.

System	S-V Equilibrium (Under Conditions Studied)
Binary	
Benzoic acid + CO_2	S-V equilibrium; 101-280 bar at 308 K, 318 K and 328 K
Salicylic acid + CO_2	S-V equilibrium; 101-240 bar at 308 K and 318 K
2,3-dimethyl phenol + CO_2	Depression in melting point. Evidence of liquid phase –150 bar at 328 K
2,5-dimethyl phenol + CO_2	S-V equilibrium; 101-280 bar At 308 K and 318 K
4-tert-butyl phenol + CO_2	
2,3,5-trimethyl phenol + CO_2	S-V equilibrium; 101-280 bar At 308 K
2,4,6-trimethyl phenol + CO_2	
Ternary (1:1 Wt%)	
Salicylic acid + Benzoic acid + CO_2	S-V equilibrium; 101-280 bar at 308 K, 318 K and 328 K
Acetylsalicylic acid + Salicylic acid + CO_2	
2,5-dimethyl phenol + 4-tert-butyl phenol + CO_2	Depression in melting point. Evidence of liquid phase under subcritical conditions
2,3,5-trimethyl phenol + 4-phenyl phenol + CO_2	S-V equilibrium; 101-280 bar at 308 K
2,4,6-trimethyl phenol + 4-phenyl phenol + CO_2	
Quaternary (1:1:1 Wt%)	
Acetylsalicylic acid + Salicylic acid + Benzoic acid + CO_2	S-V equilibrium; 101-280 bar at 308 K, 318 K and 328 K

Conclusions

The experimental LCEP data for single and multicomponent systems of aromatic benzoic acids and substituted phenols are presented in Table1. The LCEP determined in this work are close to the critical point of pure CO_2.
Under the conditions investigated the majority of the systems exhibited solid- fluid equilibrium with no liquid phase present (Table 2.). Thus solubility determinations under these conditions represent true solid solubility.

The solid solutes used in this study are nonvolatile. For solutes of low vapor pressure solubility in supercritical fluid CO_2 is relatively low, hence the LCEP lies close to the critical point of pure CO_2 and the depression in melting point is low.

In the case of 2,3-dimethyl phenol (normal melting point- 348 K), liquid phase was observed at 328 K. However, S-V equilibrium conditions existed at 308 K and 318 K in the pressure range studied (101-240 bar).

In the case of 2,5-dimethyl phenol + 4-tert- butyl phenol (normal eutectic melting ~ 331 K), the depression in melting point was significant. Liquid phase was observed under subcritical conditions. The LCEP for this system could not be determined because of the complex phase behavior. There was no evidence of liquid phase in either 2,5-dimethyl phenol (melting point 347 K) or 4-tert butyl phenol (normal melting point-374 K) binary systems under the conditions studied. The melting of the two systems under the conditions studied was also confirmed by solubility studies, which gave unusually high solubility data.

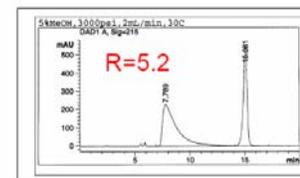## Example #2 Polymer Swelling Experiment

An SFE application of removal of residual monomer and oilgomer from polymer sheet lost efficiency as the process was scaled-up. It was suspected that the polymer sheets were placed to close together in the mounting fixture for extraction and they were swelling, effectively closing spaces in between the sheets dropping the efficiency of the process. An experiment was carried out with the SFT-Phase Monitor II proving out this hypothesis.

Pressure (psi)	Temperature (C)	Physical Dimension (in)	Specimen Size (%)
0	25	0.0205	100%
875	25.3	0.0211	103%
1714	27.2	0.0213	104%
1815	28.5	0.0213	104%
1722	33.7	0.0214	105%
5200	34.8	0.0225	110%
7500	34.9	0.0237	115%

Polymer Swelling in Neat Supercritical Carbon Dioxide

Pressure (psi)	Temperature (C)	Physical Dimension (in)	Specimen Size (%)
0	25	0.0205	100%
845	31.3	0.0214	104%
1647	32.1	0.0215	105%
1850	33.5	0.0218	107%
1860	34.3	0.0221	108%

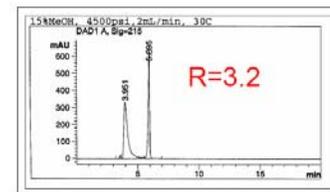Polymer Swelling in a mixture of Supercritical Carbon Dioxide and 5% Methanol

Example #3 Solubility Studies-Prep SF Chromatography

Information pertaining to solubility has been utilized to establish technical and economic feasibility, especially within the realm of SFE and SFR. However, solubility still remains a formidable hurdle in the realm of preparative chromatography. Most scaled-up techniques of chromatography are contingent upon analyte solubility.

Because of the high pressures and temperatures employed with SCF's, it is difficult for preparative scale SFC scientists to predict solubility of an analyte.
One "rule of thumb" stated by SFC manufacturers is: "any solute soluble in methanol or a less polar organic solvent will elute in SFC."

This rule certainly holds true for analytical SFC, however, some classes of compounds have limited solubility in carbon dioxide and modifier. This reality is, at times, not easily detectable on an analytical scale.
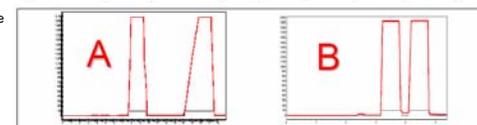
Utilization of a bench-top phase monitor, designed and commercially available from Supercritical Fluid Technologies' Inc. can serve the preparative-scale SFC chromatographer as a useful tool for determining optimum concentrations for preparative SFC scale-up.

Experimental Method

Utilizing commercially available, "pharmaceutical-like" compounds (below), we wish to measure solubility under a variety of temperatures, pressures, modifiers (I.e. IPA, MeOH, EtOH) and modifier concentrations. The data will assist an analyst to determine method parameters that are optimized for analyte solubility. The results optimized for solubility will be compared to resolution optimized chromatographic parameters to determine most efficient method to utilize for preparative chromatography.

The column utilized for this experiment is inconsequential due to the fact that the purpose of the study is to determine optimal mobile phase solubility for enhanced loadability for preparative scale SFC.

Naproxen   Warfarin
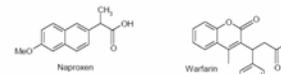
Results

The first stage of our experiment was to determine the analyte's solubility in three different organic phases (Table Below). The solvent that yielded the best solubility for each analyte was utilized as the strong solvent or modifier in the analytical SFC method development.

Sample	MeOH	IPA	EtOH
Naproxen	60.8 mg/mL	37.4 mg/mL	46.7 mg/mL
Warfarin	23.5 mg/mL	12.8 mg/mL	16.3 mg/mL
1:1 Mixture	33.3 mg/mL	14.3 mg/mL	20.0 mg/mL

Table 1: Solubility of selected analytes in three organic phases at atmospheric temperature (30 degrees C) and pressure (Bench-top Technique).

Analytical SFC chromatogram with optimized resolution at 30 degrees Celsius. 16.9 µg injection. Using Berger SFC Instrument

Based upon optimal solvent (determined in Table 1), we determined the solubility of the components at several solvent strengths and pressures via the Phase Monitor (Below) Solubility of this particular analyte, in the phase monitor, appeared to correlate to the solubility in the present volume of organic solvent. Resultant solubility optimized conditions were run on an analytical scale Berger SFC to measure the resolution of the components

Plot of solubility of analyte (1:1 mixture). Optimized point of solubility will be utilized for comparative chromatography.

Analytical SFC Chromatogram of conditions that are optimized, at 30 degrees Celsius, for solubility. 16.9 µg injection.

The two optimized methods (for resolution and solubility) were run on a Berger Mini-Gram system on a 10x 250 mm, 60A, 6µ Silica column, with a 200 µL loop Alcott auto sampler, and Varian Pro-Star detector (λ=250 nm) (Table Below) for comparison.

Chromatography Optimized for	Total Purified	Conc. Injection	# Inj (clean-up)	Run Time (min)	Vol. of Organic solvent	Purity/ Recovery Peak 1	Purity/ Recovery Peak 2
Resolution	275 mg	55mg/200µL in DMSO*	5 (2)	119	59.5 mL	96.8%/ 86.3%	100%/ 69.2%
Solubility	275 mg	40mg/200µL in DMSO*	8 (0)	25	35.6 mL	98.9%/ 96.9%	99.7%/ 95.1%

A   B

Note the poor peak shape in chromatogram A. Also the quantity injected with the resolution-optimized method was limited to solubility of analyte in DMSO and injection loop size.

An advantage demonstrated by the method optimized for solubility was the reproducibility of chromatography. Such reproducibility facilitates a sequence of stacked injections, thereby reducing purification time and solvent consumption.

Conclusion

It been demonstrated that when preparing to scale-up SFC chromatography, solubility studies via commercially supplied SFT-Phase Monitor II supplied by Supercritical Fluid Technologies, Inc. are critical in optimizing the efficiency of the purification. Further studies will need to include the effect of temperature in the optimization process.

Overall Conclusions

Direct, visual observation of materials under actual supercritical conditions to gauge solubility is an important first step in the development and refinement of supercritical fluid extraction, reaction and chromatographic processes. The utility of a Phase Equilibrium View cell for this purpose has been demonstrated.