Precipitation of Microsize Organic Particles from Supercritical Fluids

The precipitation of organic particles from supercritical fluids (SF) by expansion (SFX) has become an interesting alternative to milling without thermal decomposition. Through the rapid expansion process, a dramatic change of the solute supersaturation ratio is created causing subsequent precipitation with a narrow particle-size distribution. It was found that β-carotene precipitates from SF ethylene and ethane have the feed material crystallinity. However, SF CO_2 reacted with β-carotene and did not give characteristic β-carotene X-ray spectra. The mean particle sizes of these precipitates were in the submicron range (*ca* 0.3 μm). Increased solubility was obtained by addition of toluene as cosolvent in SF ethylene. It was found that the mean size of β-carotene particles, generally remained unchanged if the toluene concentration was less than 1½ mol %. The SFX process appears to be in a single fluid phase when up to 1½ mol % toluene cosolvent is used.

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Introduction

Most SF extraction studies of organic solids have concentrated on solubility measurements and thermodynamic correlations of solubility data with the SF mixture properties (Johnston and Eckert, 1981; Kurnik et al., 1981, Schmitt and Reid, 1986; Tsekhanskaya et al., 1964; Kaul and Prausnitz, 1978; Wong and Johnston, 1986; Dobbs and Johnston, 1987; Dobbs et al., 1987; Tan and Weng, 1987; Schaeffer et al., 1988). BASF Company (1979, 1982), Krukonis (1984), Larson et al. (1986), Pacific Northwest Laboratories (Petersen et al., 1986; Smith et al., 1986; Matson et al., 1986a, b, 1987a, b) and Mohamed et al. (1989) studied crystallization (or precipitation) of organic solids using supercritical fluids.

Supercritical fluids have higher thermal diffusivities than liquids and higher densities than gases, and are sensitive to changes in density. Solvent power changes due to density changes can be obtained by depressurization. SF precipitation processes, unlike conventional crystallization processes (which give a wide distribution of sizes due to continued nucleation), can generate a uniform density gradient upon rapid expansion of the solute-loaded solution and subsequently produce a narrow particle-size distribution. Solute/SF solubility data are a necessary starting point in the analysis of any SF precipitation process. Kaul and Prausnitz (1978) used a flow system to obtain such solubility data. In their experiments, solids were collected in a cold trap after expansion of the compressed gas through a needle valve. A similar gravimetric technique was also used by Johnston and Eckert (1981), Kurnik et al. (1981), and Schmitt and Reid (1986) to obtain solubility data. In order to achieve solid-fluid equilibrium in continuous operation, the SF flow rate and the length of the packed extractor need to be properly adjusted (Tan and Weng, 1987).

Larson and King (1986) concluded that various steroids precipitate from SF CO_2 as small particles, but still retain their crystallinity. Because the intensity of the diffraction patterns varied somewhat, the presence of some degraded or amorphous material is possible. When a cosolvent (5.0 mol % methanol) was used, the precipitated particles were significantly larger, possibly due to a fluid phase in the expansion valve resulting in solute reprecipitation from liquid methanol.

A more fundamental study of precipitation from various supercritical fluids was undertaken by Petersen et al. (1986) and Smith et al. (1986) at Battelle Pacific Northwest Laboratories. They investigated the rapid expansion of supercritical fluid solution (RESS) through a fused coated capillary restrictor (i.e., isenthalpic expansion through a nozzle). They evaluated the range of precipitates that can be produced by the rapid loss of solvating power. Precipitates included films, fine powders having narrow size distributions, and amorphous mixtures, all produced by the expansion process. With different experimental conditions, silica may form uniform films (amorphous silica) or discrete particles with a relatively narrow size distribution. They concluded that solute concentration, controlled by manipulating temperature in the dissolution region, greatly affects particle size. Silica particles ranging from <0.01 μm to 0.5 μm in diameter were obtained by expansion of silica solutions over an estimated concentration range of <10 ppm to 500 ppm.

Fundamental studies reported in their latest work (Matson et al., 1986a, b, 1987a, b) consisted of investigating precipitate morphologies from a variety of organic polymers and inorganic ceramics, and phase characteristics of depressurization around the nozzle. These were explained using an enthalpy-entropy-pressure diagram for the RESS process. They found that, at certain initial fluid conditions, the fluid would remain in a single phase when it was isenthalpically expanded to low pressures, assuming the outlet temperature is high enough. They pointed out that operation of the RESS process in a single-phase solvent expansion mode allows collecting solute products in the dry state, with no liquid solvent condensed in the product structure. This work finally concluded that the rate of nuclei formation, developed according to classical nucleation theory, could be qualitatively interpreted by several independent variables such as the degree of solute supersaturation and the temperature at which nucleation occurs. They concluded that particle size is most readily controlled by variation of the solute concentration, although the nozzle design, substrate conditions, the expansion background conditions, and the preexpansion temperature and pressure of the SF may also influence RESS product morphologies.

The increase in solubility when a cosolvent is used has been noted elsewhere (Dobbs and Johnston, 1987; Dobbs et al., 1987; Schmitt and Reid, 1986). The effect of a cosolvent on the solubility has been discussed by Walsh et al. (1987). A systematic method for selecting cosolvents for supercritical fluids solubilization of organics has been developed using a simple gas chromatography affinity (residence time) measurement of the cosolvent, which is reversibly adsorbed on the organic solids (Tavana et al., 1989). A potentially useful cosolvent might be found by this method. Potential increases of solubility with the addition of cosolvents in a SFX process, operated in a single-phase precipitation region, are possible. A SF mixture phase equilibrium diagram is required for detailed analysis of such a process. For low volatility compounds, a solid, solvent and cosolvent ternary system would condense to a solvent and cosolvent binary system (Brady et al., 1987; Dooley et al., 1987).

The goal of this work was to investigate possible ways to operate the precipitation process in a single-phase condition while dispersing the precipitate into a suitable suspending medium. We also wished to observe if one-phase expansion conditions predicted from a P-X-Y phase diagram corresponded to apparent one-phase expansion/precipitation conditions in the suspending medium while observing particle size and morphology at these conditions.

Experimental Studies

Reagents and materials

The solids investigated in this study were trans-beta-carotene (Hoffmann-LaRoche, Nutley, NJ). Anaerobic grade CO_2(99.99%, $O_2 < 10$ ppm), chemical-purified-grade C_2H_6(99%), and chemical-purified-grade C_2H_4(99.8%, $O_2 < 10$ ppm) from Alphagaz Co. were used as received for SF solvents. AR-grade liquid solvents were used for chemical analyses and cosolvents without further purification.

Chromosorb T (Supelco, Inc.) was used as the packing material in a general-purpose GC column in a study to scan potentially attractive cosolvents in the β-carotene-SF ethylene system. This cosolvent scan is reported elsewhere (Tavana et al., 1989). Toluene was found to be the most suitable cosolvent of those scanned. Formvar on 200 mesh grids (Ted Pella, Inc.), MF-Millipore 0.1-mm filters (Millipore Corp.), and aluminum stubs (Ted Pella, Inc.) were used as sampling supports in SEM analyses. Tween 80 and Tween 40 (Aldrich) were used a surfactants. Silica Gel-GF TLC plates (Analtech) were used for TLC analysis. Commerical gelatine, sugar, and distilled water were used for aqueous colloidal solution.

Equipment and procedures

A flow diagram of the system is shown in Figure 1. In the solubilization section, the first vessel acts as a premixer and preheater to mix cosolvent with solvent and to heat the solvents to the desired temperature. When the desired temperature and pressure in the premixer were attained, the supercritical mixture was then brought in contact with the solute in a packed saturator already heated to the desired temperature. (This desired temperature should vaporize all incoming co-solvent to form a single phase in the saturator.) Two grams of solute were packed with 50-100-μm glass beads into the 10.0-cm-long by 2.54-cm-OD teflon tube, which was airtight with the inner wall of the 316 SS cylinder (by three buna N O-rings) to avoid side flow between the teflon tube and the SS cylinder. In the precipitation section, the equilibrium mixture (extract) was rapidly depressurized through a heated fine metering valve with 0.157-cm orifice and 0.873-cm length of pass. The solute was collected in a heated glass U-tube packed with glass wool. The cosolvent (in cosolvent runs) was collected in a flask immersed in liquid N_2. The depressurized gas passed through a wet test meter (Precision Instrument Company) for determination of the total flow. The mass of precipitate solid was found after each experiment by weight gain of the U-tube plus the solute removed manually from the metering valve. Total solute weight was determined with a Mettler analytical balance (model B6) accurate to ±0.1

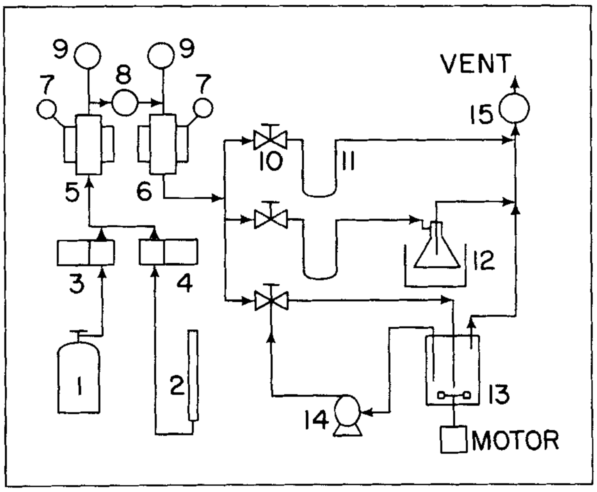

Figure 1. Flow diagram of SFX apparatus.

1. Pressurized Cylinder
2. Graduated Burette
3, 4. Duplex Metering Pump
5. Preheater
6. Saturator
7. Temperature Controller
8. Pressure Regulator
9. Pressure Indicator
10. Micrometering Valve
11. Glass U-Tube
12. Liquid N_2 Trap
13. Homogenizer
14. Circulating Pump
15. Wet Test Flow Meter

mg. With this value and total flow, the concentration of the organic compound in pure solvent (or solvent mixture) can readily be calculated.

The system was calibrated for solubility measurements, using SF ethylene-naphthalene at 25°C and 45°C at a series of pressures in the range 68–136 atm. Naphthalene solubilities were found to match the data of Tsekhanskaya et al. (1964) within ±10% (Figure 2).

For dispersive precipitation, the system was designed to include closed-loop circulation of an aqueous colloidal gelatine solution around the fine metering valve. In this way the solute nucleation rate, occurring in the orifice of the metering valve, could be obtained at a given temperature. The precipitate was evenly dispersed in the aqueous gelatine solution. In later experiments the SF was expanded directly in a blender through a 15-μm laser-drilled orifice similar to the one used by Mohamed et al. (1989). In all experiments the SF was heated so that the expanded fluid had a temperature close to the saturator temperature.

Results

Structure analysis of precipitates

Several β-carotene precipitates from SF anaerobic CO_2, SF ethylene, and SF ethane were analyzed by powder X-ray diffraction (GE, model XRD-5), SEM (ISI, model super IIIA; JEOL, model JSM-840A), infrared radiation (IR) (BECKMAN, model IR-33), Fourier transformation proton nuclear magnetic resonance (FTNMR) (JEOL, model FX-90Q), BET surface area measurement (QUANTASORB, model QS-10) to examine their physical structure, degree of crystallinity, morphology, chemical structure, and surface area. Some results are briefly summarized as follows:

- X-ray diffraction patterns (Figure 3) showed that precipitates from SF ethylene and SF ethane have the same degree of crystallinity as the feed material. This, however, is not the case for the precipitate from SF anaerobic CO_2.

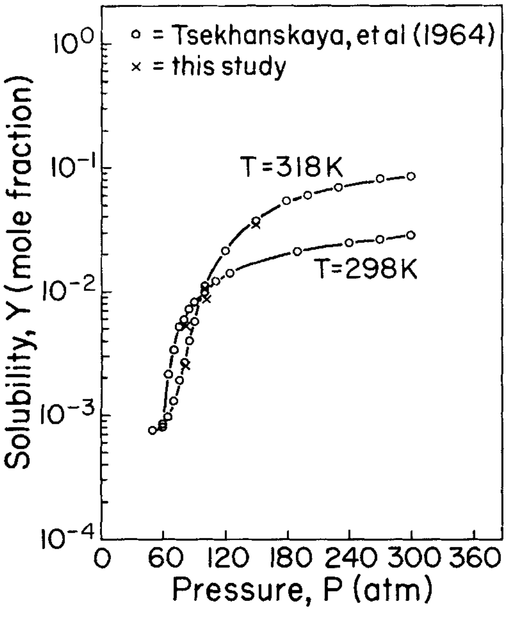

Figure 2. Experimental solubilities for pure naphthalene in SF C_2H_4 at 298 and 318 K.

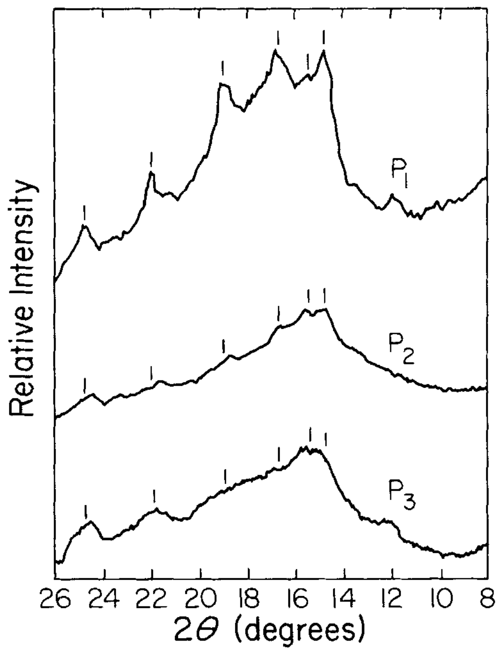

Figure 3. X-ray diffraction patterns of (P_1) feed material, (P_2) precipitated from SF C_2H_4, and (P_3) precipitated from SF C_2H_6.

- SEM photomicrographs (Figure 4a) show that the feed β-carotene had platelet morphology (monoclinic structure) and formed aggregates. These particles were produced by conventional crystallization followed by grinding. The precipitates obtained via rapid expansion of SF C_2H_4 (or SF C_2H_6) are also platelet particles, but of 1–2-μm size, Most of the particles are aggregated, as shown in Figure 4b. They could be dispersed in an aqueous solution with a few drops of Tween 40 biosurfactant.
- BET surface area of the feed β-carotene was 0.6 m^2/g. The BET surface area of precipitates from SF C_2H_4 (or SF C_2H_6) were not measured because of limited sample volume. However, the extreme size reduction achieved by SFX is shown in Figure 5, which shows a typical 0.3-μm particle (in this case having spherical morphology).
- IR and FTNMR spectra (Figures 6a and b) show that the precipitate from CO_2 had different oleic bonds which appeared between 900 to 1,600 wave numbers in IR spectra and had some epoxide bonds which appeared between 3 to 5 ppm in NMR spectra. It is evident that the CO_2 reacted with β-carotene at supercritical conditions to produce some β-carotene-related epoxide compound.

Solubility study

A flow study was done at 306.1 atm and 70°C to show that at the maximum flow rate (up to 0.045 m^3/h, STP) the β-carotene saturator was still in equilibrium. Additionally, to avoid a decrease of active surface area due to an aggregating effect on the solute, the same amount of fresh β-carotene and the same packing conditions were used for each run.

The solubility of pure β-carotene in ethylene was measured as a function of pressure along two isotherms, 50°C and 70°C. Pressure ranged from 102.0 atm to 374.2 atm, the latter corresponding to the upper pressure limit of the apparatus. Solubili-

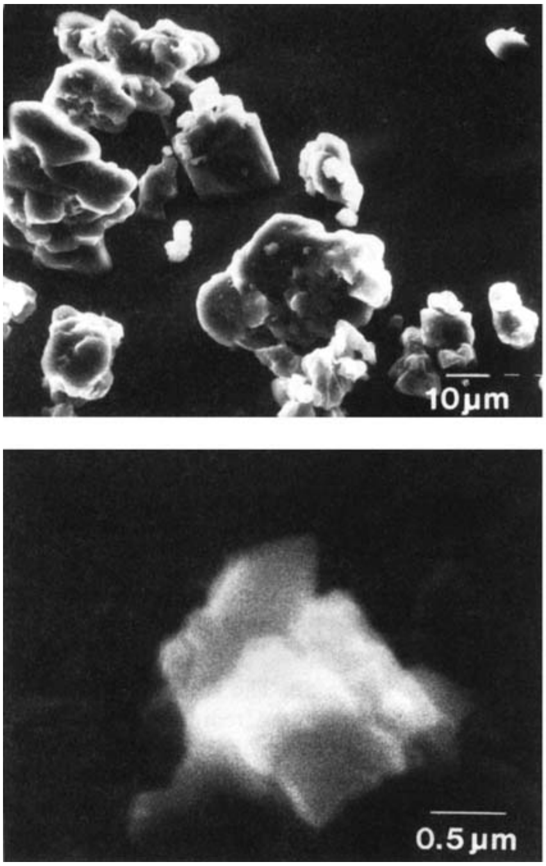

Figure 4. SEM photomicrographs of (a) feed β-carotene and (b) precipitated particles from SF C_2H_4 at 306.1 atm and 343 K.

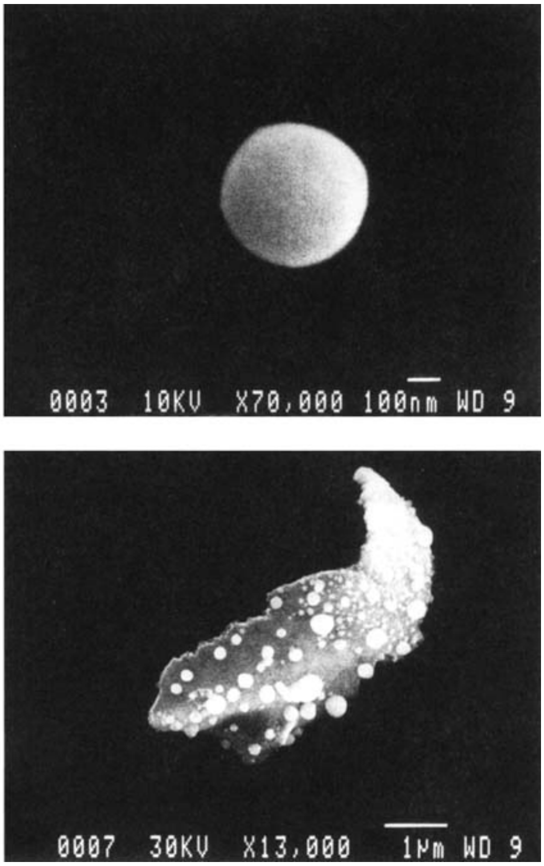

Figure 5. Precipitated β-carotene particles from SF C_2H_4 in 10 wt. % gelatine solution (a) individual particle and (b) particles nucleated on a surface.

ties are presented in Table 1. The experimental and correlated solubilities using the modified Peng-Robinson Equation of State (PREOS) (Schmitt and Reid, 1986) are shown in Figure 7. They were found to range from 0.72×10^{-5} to 12.15×10^{-5} mol fraction. Reproducibility was ±7.0%. The solubility of β-carotene in ethylene/toluene mixtures was measured as a function of the mole fraction of toluene at 306.1 atm/70°C and 374.2 atm/70°C, respectively, as shown in Figure 8. These solubilities were as high as 11.68×10^{-4} mol fraction at 2.36% toluene concentration, 374.2 atm, and 70°C. The maximum increase in solubility due to the addition of toluene was ninefold at these conditions.

In order to estimate the maximum toluene addition while still having single-phase expansion, a P-X-Y phase diagram of an ethylene-toluene binary system (Figure 9) was made using the Soave-Redlich-Kwong EOS (SRKEOS). To compare with King et al. date (1983) the SRKEOS was used here. This shows that the critical pressure along a 73.5°C isotherm is 110 atm. The maximum toluene addition without two-phase formation, during depressurization in a SF C_2H_4 mixture, should be less than 1.5 mol %.

SF dispersive precipitation study

Figure 5a shows a single rounded β-carotene particle produced from rapid expansion of SF C_2H_4 in 10 wt. % gelatine solution, having a particle size of 0.3 µm. The expansion conditions were 306.1 atm and 70°C. Figure 5b shows that many sub-

Table 1a. Solubility of Beta-Carotene in SF Ethylene

Pressure atm	Solubility, 10^5 mol fraction 323 K	343 K
102.0	0.95	0.72
170.1	5.42	4.10
238.1	6.02	6.62
306.1	7.33	10.50
374.2	8.82	12.15

Table 1b. Solubility of Beta-Carotene in SF Ethylene/Toluene Mixture

Toluene mol %	Solubility, 10^4 mol fraction at 343 K 306.1 atm	374.2 atm
0.70	1.51	
1.07	1.66	
1.85	3.59	
2.07	3.75	
2.18	3.65	
0.80		02.86
1.22		4.55
1.51		5.59
1.54		7.58
1.88		8.37
2.36		11.68

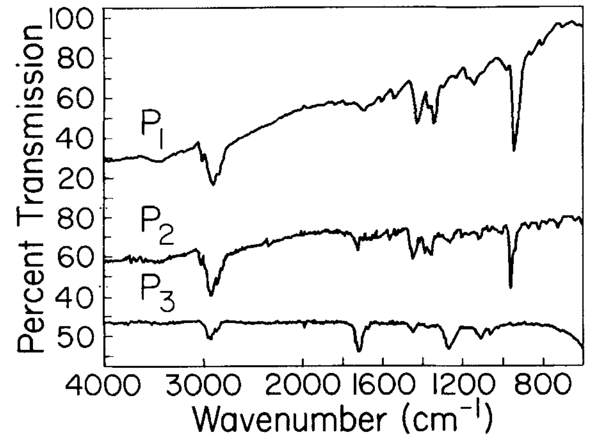

Figure 6a. IR spectra of (P_1) feed material, (P_2) precipitated from SF C_2H_4, and (P_3) precipitated from SF CO_2.

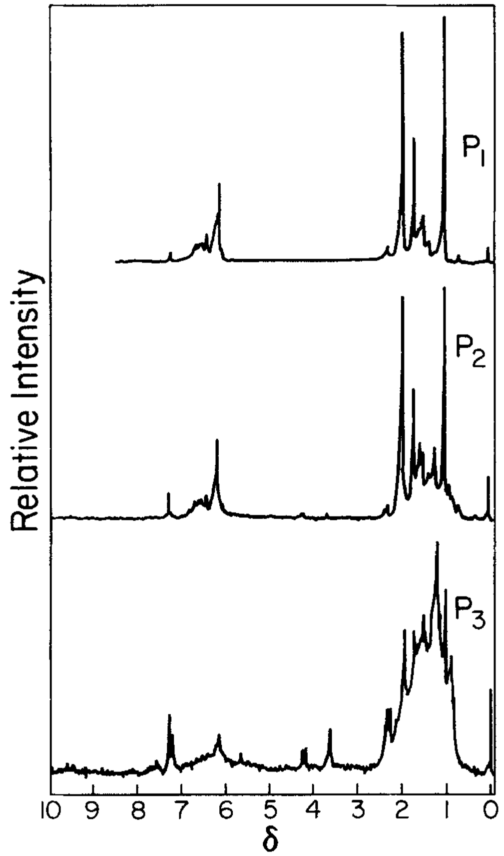

Figure 6b. NMR spectra of (P_1) feed material, (P_2) precipitated from SF C_2H_4, and (P_3) precipitated from SF CO_2.

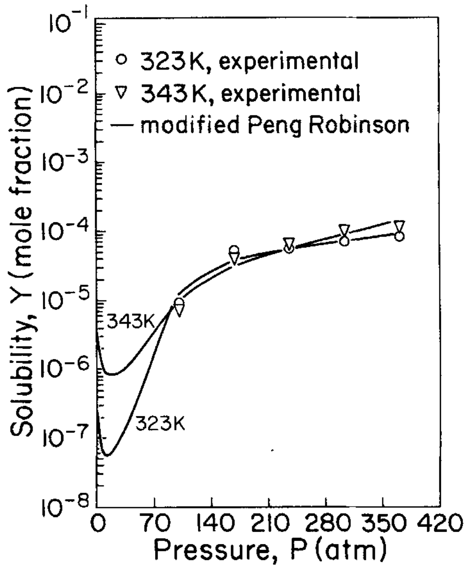

Figure 7. Correlation of β-carotene solubiliites in SF C_2H_4 with modified PR equation of state.

micron particles nucleated on a piece of impurity. Particle-size analyses were performed using a PDI counter (model 80xy) and COULTER counter (model N4) for feed material and precipitates from SF C_2H_4, respectively. The mean particle sizes of feed β-carotene and precipitates from SF C_2H_4 expanded to atmosphere, and SF C_2H_4 expanded in gelatine solution are 20.0, 1.0, and 0.3 μm, respectively. Particle-size distributions of these particles, which were sonicated before measuring, are shown as a differential plot in Figure 10. The coefficients of variance of feed β-carotene and precipitates from SF C_2H_4, and SF C_2H_4 expanded in gelatine solution are 52, 36, and 34%, respectively.

In the cosolvent precipitation study at 306.1 atm and 70°C when β-carotene particles were precipitated in gelatine solution at one-phase conditions ($\leq$1.5 mol % of toluene), the particles were still in the submicron size range of 0.5 μm. With two-phase conditions the mean size of β-carotene precipitate was increased to 5 μm (Figure 11).

Discussion of Results

β-carotene is a long chain material, has weak Van-Der-Waals molecular forces, and is a strong reducer. Thus β-carotene reacted with SF CO_2, an oxidizer. The geometric surface area of the β-carotene feed material, estimated from the particle-size

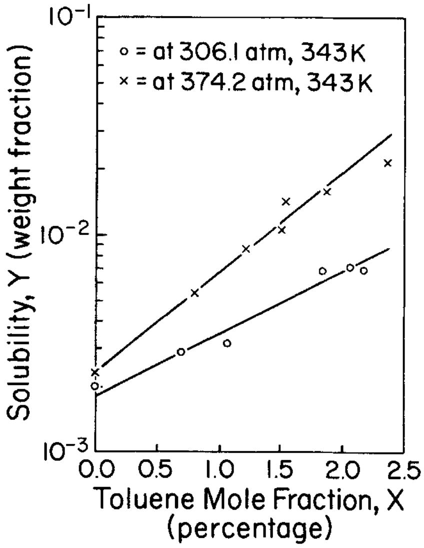

Figure 8. Solubilities of β-carotene in SF C_2H_4/toluene mixture at 306.1 atm/343 K and 374.2 atm/343 K.

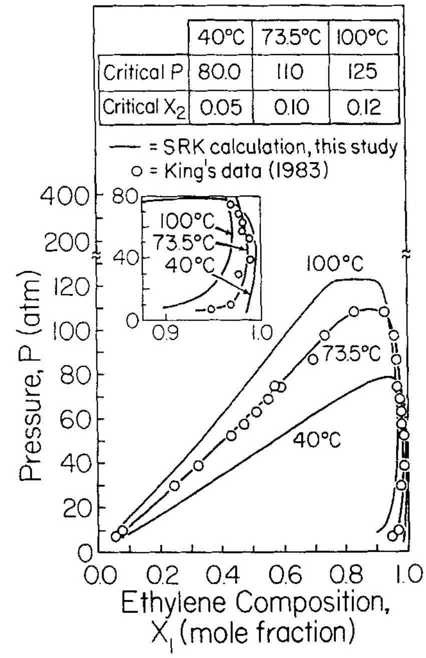

Figure 9. P-X-Y phase diagram of C_2H_4/toluene binary system.

distribution, is in good agreement with the BET surface area, which was measured by a single point flow method.

Beta-carotene is a relatively nonvolatile compound. Thus, weight corrections were not necessary for β-carotene escaping with the flow of expanded exit gases. A solid-SF equilibrium condition was achieved by adjusting the flow rate and the active surface area of the packed material. The mole fraction toluene addition to the SF mixture was accounted for by a simple mass balance calculation around the liquid N_2 cold trap.

The solubility of β-carotene in SF C_2H_4 is a weak function of temperature, increasing slowly with temperature at high pressure. A temperature-solubility upper crossover point $[dy/dT]_p = 0$ was clearly observed around 204 atm. At concentrations above this point, a crystalline product was obtained upon expansion. According to classical primary nucleation mechanisms, a possible reason for the observed crystallinity may be the high nucleation rate (for depressurization from 306.1 atm to 1 atm the calculated nucleation rate is 2.4×10^{16} #/cm^3 · s at a supersaturation ratio of 5.3×10^5 and temperature of 343 K). Concentration, rather than temperature, dominated the nucleation process. A large β-carotene solubility enhancement factor (see Figure 8) was observed when toluene was used as cosolvent, as predicted from a GC affinity scan.

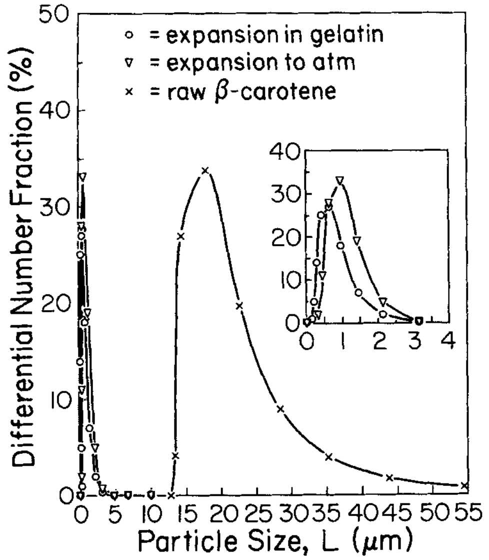

Figure 10. Differential particle-size distributions for raw β-carotene and SF (C_2H_4).

Product obtained by rapid expansion.

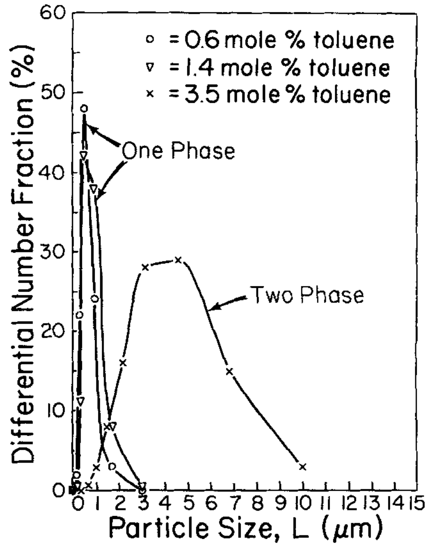

Figure 11. Differential particle-size distributions of β-carotene precipitated in gelatine solutions.

Theoretical toluene addition giving a single supercritical phase agreed well with experimental observations if the expansion valve was kept isothermal during depressurization. In order to enhance solubility by toluene addition with the process still in a desirable region of operation, a mixture phase diagram at various termperature isotherms is necessary to delineate single-phase regions.

SF dispersive precipitation might be a practical continuous process to obtain dispersed particles in a suitable medium. The degree of aggregation decreased in an intensely-agitated dispersive medium, i.e., with gel/H_2O in a blender. Precipitation with cosolvent in a gelatine solution (68°C) with calculated one-phase conditions gave submicron particles with narrow particle-size distribution. The heated gelatine solution, a colloidal dispersion medium, prevents submicron precipitates from aggregating and contamination by cosolvent vapor. When calculated two-phase precipitation occurred, the particle size and distribution narrowness were altered by cosolvent condensation, presumably in the expansion orifice. Two liquid phases were not observed in the gelatin suspension. Liquid toluene in the gel suspension would totally destroy the particle distribution.

Conclusions

We have studied the dissolution of β-carotene (a food additive and prospective cancer-inhibiting material) in SF carbon dioxide, SF ethylene, and SF ethane. Data show that CO_2 acted as an oxidizer and reacted with β-carotene at supercritical conditions to produce a β-carotene-related epoxide compound. Precipitates nucleated by rapid expansion of different SF solutions are not likely to have different crystalline structures, as shown by the X-ray diffraction analyses of our study. A phase equilibrium diagram is necessary to estimate the maximum cosolvent addition to the SF solvent to still maintain a single-phase precipitation process in the expansion orifice. For low volatility compounds (such as β-carotene), the modified PR EOS gave a reasonable fit to experimental data with only two solute-related parameters.

SF dispersive precipitation generates a narrow particle-size distribution of micron-sized particles if expansion occurs as a single vapor phase. The controlling factor determining crystallinity of a precipitate is probably the nucleation rate, which in turn is controlled by solute concentration in the SF. SF dispersive precipitation in a gel/H_2O solution using a cosolvent might be a feasible way to obtain micron-size particles with high production rates, provided the cosolvent concentration and expansion temperature provide single-phase expansion through the expansion orifice. Two-phase expansion would provide higher productivities (up to ninefold), but at the price of a larger wider-particle-size distribution.

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