phasex

The Supercritical Fluids People

Supercritical Fluids … a primer

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Summary

Industry is faced with increasing demands on products and processes: increasingly stringent regulations on liquid solvent use in the workplace, on residual solvents in products, and on solvent emissions. Consumers and end-users are demanding higher quality, value-added, and safer products. All of these factors have motivated the application of supercritical fluids, especially supercritical carbon dioxide, to the development of processes to satisfy these requirements, especially where traditional solvents and processing methods fall short.

This primer offers an introduction to supercritical fluids, from their early discovery as pressure-dependent solvents to their current state of operation in many diverse and industrially important applications.

Every compound has a critical point: the pressure and temperature at which its liquid and vapor phases become identical, and a gas at pressure and temperature conditions that are above its critical point is termed a supercritical fluid. Supercritical fluids exhibit a pressure-dependent dissolving power, and these solubility properties have been applied to the development of processes to extract, purify, and fractionate a wide variety of materials. Carbon dioxide, one of the most commonly used supercritical fluids, offers numerous industrial advantages: CO2 is GRAS (Generally Recognized as Safe), it is non-toxic, non-hazardous, and leaves no solvent residue, and, with its critical temperature of 31°C, CO2 is used to carry out separations at biologically attractive temperatures (40-50°C).

Although supercritical fluid solubility phenomena were first studied more than 100 years ago, it was not until the 1950s that the use of these gaseous solvents in designing extraction/separation processes was suggested. Today scores of large scale industrial applications have emerged, ranging from coffee decaffeination, to extraction of hops and nutraceuticals, to purification of medical polymers. Whereas supercritical fluid technology was once viewed as a “laboratory curiosity”, it has earned credibility as an industrial unit operation.

Supercritical fluids are used in many industries, and several applications described in the narrative include:

- Purification of temperature-labile, reactive monomers
- Extraction/fractionation of silicone and polyolefin polymers
- Cleaning of medical devices and components
- Concentration of actives in nutraceuticals and natural products
- Recrystallization of pharma compounds to nanosize
- Infiltration of chemicals into microporous substrates

Phasex Corporation, founded in 1981, applies the attributes of supercritical fluids to these and scores of other applications, helping its customers to create value-added products. As product and process requirements continue to evolve, Phasex remains committed to developing new applications for the technology to meet the changing needs of industry.

I. Solubilty In Supercritical Fluids

In 1879 two Scottish researchers reported that supercritical fluids could dissolve selected compounds and that their dissolving power was pressure-dependent, the higher the pressure, the higher the dissolving power. (Hannay, J.B. and J. Hogarth, 1879. On the Solubility of Solids in Gases, Proc. Roy. Soc, London, 29, 324-326.)

Their initial work involved supercritical ethanol and acetone as solvents and a number of inorganic salts as solutes, but their findings were subsequently found to apply to many gases and to organic compounds as well. Excerpting from their 1879 paper

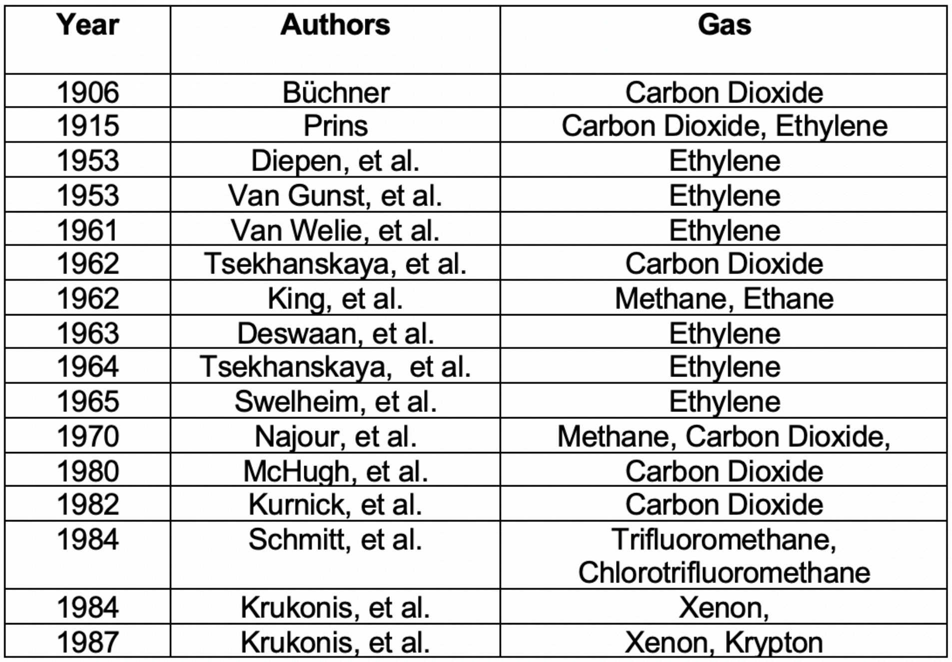
"…we have, then, the phenomenon of a solid…dissolving in a gas…showing it to be a gaseous solution…"

"…when the solid is precipitated by suddenly reducing the pressure, it is brought down at a 'snow', but it is easily re-dissolved by increasing the pressure."

Interestingly this first paper, presented at a monthly meeting of the Royal Society (London), motivated lively discussion among the attendees, some of them opining during the discussion that the authors had found nothing new, merely solubility in "a hot liquid". Subsequent work by the authors substantiated that a supercritical fluid can indeed dissolve many compounds and that a gas above its critical point exhibits a pressure-dependent dissolving power. (This pressure-dependent dissolving power was, 100 years later, to be applied to the design and implementation of new concept gas-based extraction and purification processes.)

Starting in the early 1900s many research groups studied the properties of supercritical fluids, investigating primarily thermodynamic phase behavior, and they extended the list of gases and solutes. One early researcher, E. Büchner (in 1905), reported on the solubility and phase behavior of naphthalene in CO2 over a wide range of pressure-temperature space. (The critical temperature, Tc, of CO2 is 31°C, the critical pressure, Pc, 73atm.) Büchner's paper was followed by many, many others who also studied naphthalene solubility, and for relevance to subsequent discussion Table 1 lists some of the naphthalene solubility and phase behavior studies that have been reported in the literature.

Table 1. Naphthalene Solubility Studies



Year	Authors	Gas
1906	Büchner	Carbon Dioxide
1915	Prins	Carbon Dioxide, Ethylene
1953	Diepen, et al.	Ethylene
1953	Van Gunst, et al.	Ethylene
1961	Van Welie, et al.	Ethylene
1962	Tsekhanskaya, et al.	Carbon Dioxide
1962	King, et al.	Methane, Ethane
1963	Deswaan, et al.	Ethylene
1964	Tsekhanskaya, et al.	Ethylene
1965	Swelheim, et al.	Ethylene
1970	Najour, et al.	Methane, Carbon Dioxide,
1980	McHugh, et al.	Carbon Dioxide
1982	Kurnick, et al.	Carbon Dioxide
1984	Schmitt, et al.	Trifluoromethane, Chlorotrifluoromethane
1984	Krukonis, et al.	Xenon,
1987	Krukonis, et al.	Xenon, Krypton

As is evident from the quite long list of authors and gases, naphthalene has been studied quite extensively, primarily because it has been found to serve as a model compound for many organic solutes that dissolve in CO2 and other gases.

Figure 1 shows the solubility behavior of naphthalene in two gases, ethylene and CO2. Both solubility curves show that naphthalene solubility is essentially nil until the pressure level exceeds the respective critical pressures (50 and 73atm).

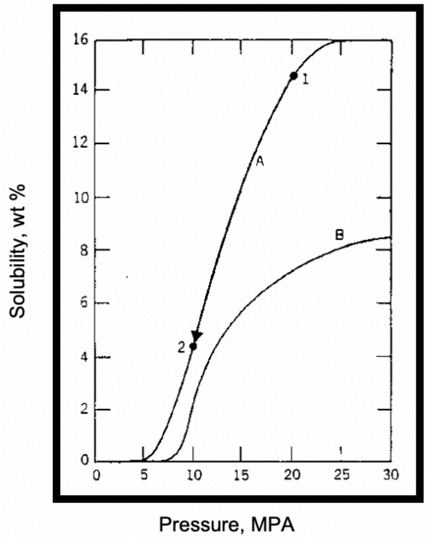


Figure 1. Solubility of Naphthalene in CO2 (45°C) and ethylene (35°C)

At sufficiently high pressure both solubility curves asymptote, to a level of ~ 16% for ethylene, ~ 8% for CO2, and perhaps it is to be anticipated that the solubility level is not the same in each gases, just as the solubility of naphthalene is different in, say, hexane and ethanol.

Naphthalene-in-CO2 solubility data from many researchers can be assembled into a solubility "map" as shown in Figure 2. The abscissa in this figure is temperature, and the curves are constant pressure isobars.

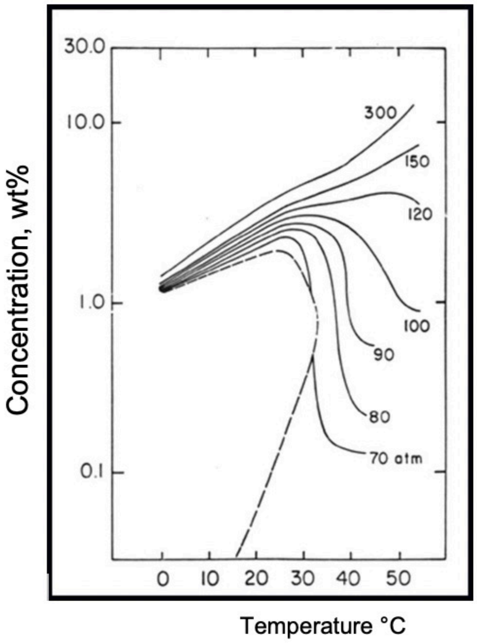


Figure 2. Solubility of Naphthalene in CO2

There are three regimes of solubility: At high pressure supercritical CO2 exhibits liquid-like behavior, i.e., solubility increases with temperature (as it does in liquids); at low pressure, solubility decreases with temperature (because of a steep decrease in density of the gas); and at intermediate pressure levels, e.g., 120atm, both factors are in play. Not developed in this paper, any compound that dissolves in any supercritical fluid exhibits the pressure-temperature solubility profiles seen in Figure 2, not in absolute values of concentration, but the high pressure, low pressure, intermediate pressure trends.

II. Implications Of Solubility In Supercritical Fluid

In early 1950 a study of solubility and phase behavior in supercritical ethylene was undertaken at Princeton University. A paper at the Annual AIChE meeting in San Francisco in 1952 presented solubility and phase equilibria data for many solid and liquid compounds, and a seminal paper appearing in the first issue of the AIChE Journal suggested in closing that supercritical fluids could be used in an extraction process, similar in concept to leaching with a liquid solvent. (Todd, D.B. and J.C. Elgin, 1955. Phase Equilibria in Systems with Ethylene Above its Critical Temperature. A.I.Ch.E. J., 1, 20-27.) (Joseph Elgin was a world renown thermodynamicist, and David Todd was the first of Elgin's many thesis students who studied supercritical fluid phase behavior in the '50s.)

By the ‘60s with the physico-chemical solubility phenomena widely known and understood the process/product implications of supercritical fluid solubility were being examined by many sectors of industry: first in the foods industry, later in polymers, lubricants, pharmaceuticals, and specialty chemicals, among still others. The first description of a supercritical fluid extraction (SFE) process having appeared in a US journal, notwithstanding, Europe, especially Germany, spearheaded industrial process/product development. In addition their solubility properties other attractive attributes of supercritical fluids were exploited in the foods industry: CO2 is non-hazardous, GRAS, and leaves no solvent residues in the product.

By the early ‘70s supercritical CO2 processes for coffee and hops had been developed and scaled up to huge production levels, again, first in Germany, later throughout Europe, US, and Asia. A plant in Bremen decaffeinates coffee at 60,000 MT/yr using supercritical CO2, and several plants throughout Bavaria extract hops flavors, each one at production throughputs of 10-20,000 MT/yr. The “no-solvent-residues” feature of CO2 was the initial motivation for replacing, for example, chlorinated solvents used in coffee decaffeination, but CO2-decaffeinated coffee also possesses a superior flavor profile, so technical and market advantages also accrue to the process.

Coffee decaffeination and hops extraction plants have proliferated: One large (60,000MT/yr) decaffeination plant is located in Houston, TX and another in Venafro, Italy (20,000MT/yr). In addition to the three Bavarian hops plants, many, many other hops extraction plants are operating in the US (three in Washington State), Europe, Asia, and Australia. Most of the world’s coffee is decaffeinated with CO2 and most of the world’s beer is flavored with CO2-extracted hops. Still other SFE plants, not at the level of coffee and hops, but each at “a few” 1000 MT/yr, are being operated in the nutraceuticals industry for producing specialty products, such as lipids, phytosterols, and carotenoids. (A quick examination of nutraceuticals packages on the shelves in nutritional supplement stores will identify the large number of products that are being extracted with supercritical CO2.)

III. Operation of a Supercritical Fluid Extraction Process

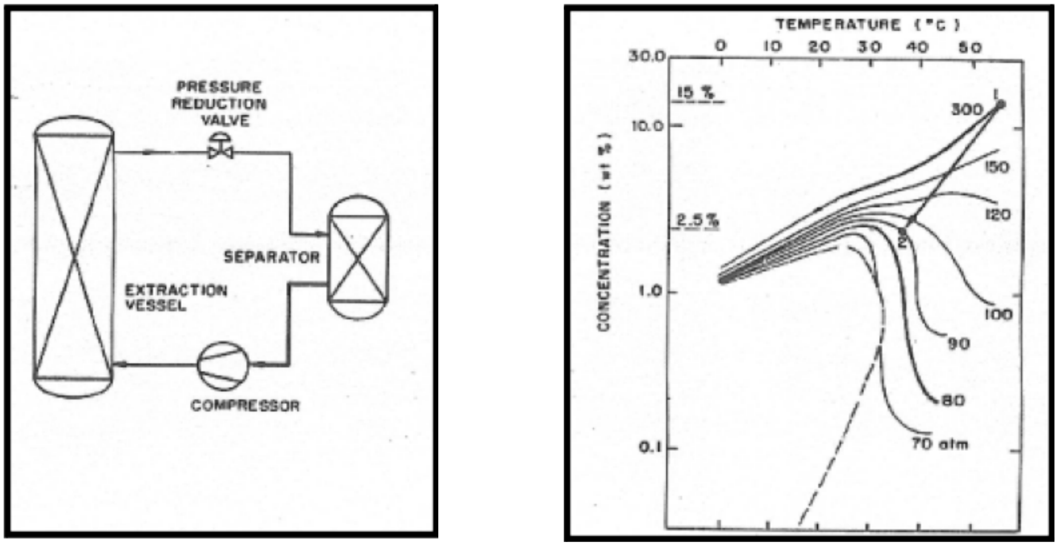
Although the 1955 AIChE Journal paper described primarily physico-chemical phenomena and thermodynamic phase equilibria of many compounds with supercritical ethylene, a new extraction concept was proffered based upon the data developed: excerpting from the paper

“…the principles can be applied in operations wherein the nonideality is intentionally created. The magnitude of solubility of a compound in a gas above its critical temperature is sufficient to consider the gas as an extracting medium”.

This was the first literature reference to a gas extraction process, and the authors went on to describe a specific embodiment of the general principle:

“…compression of a gas over a mixture of compounds could selectively dissolve one compound, permitting it to be removed from the mixture. Partial decompression of the fluid elsewhere would drop out the dissolved compound, and the gas could be used for further extraction”.

With the description that Todd and Elgin proffered an SFE process for extracting a compound from a solid substrate can be devised, and a simplified process schematic indicating how an extraction process with separation and recovery of extract and gas operates is shown in Figure 3a. A quantitative process description is given with the aid of the naphthalene solubility map in Figure 3b.



a. Process Schematic

b. Solubility Map

Figure 3. Supercritical Fluid Extraction

With reference to Figure 3 supercritical CO2 at selected pressure-temperature conditions of 300atm, 55°C (Point 1) is passed through the vessel that has been charged with naphthalene (in admixture with some other solid). As CO2 passes (percolates) through the vessel contents, naphthalene is dissolved, up to its solubility limit of 15 wt%, and it is extracted from the mixture. The gaseous solution (of CO2 and naphthalene) is passed through the pressure reduction valve and dropped in pressure to 90atm (the temperature drops to 35°C). At 90atm, 35°C the solubility of naphthalene is only ~ 2%; more than 90% "drops out like a snow" in the separator and is separated from the gas stream; the gas is then "re-used" (recompressed) for further extraction, the cycle continuing until all the naphthalene is extracted from the vessel and precipitated in the separator.

Based on the successful and widely-known applications in coffee, tea, and hops processing supercritical fluid extraction has been applied in other industrial sectors starting in the '90s. SFE is being used to extract essential oils and nutraceuticals from botanical substrates, remove solvent residues and unreacted raw materials from medical polymers and monomers, extract machining and lubricating oils from intricate electronic and porous medical devices. In the latter instance supercritical CO2 easily penetrates small pores to dissolve oils present there. To illustrate the wide applicability of SFE many diverse examples

IV. Industrial Applications of Supercritical Fluid Extraction

Selected examples of SFE operations with polymers, monomers, botanical substrates and specialty surfactants are presented in this section. To conserve narrative chromatograms of starting materials and purified products are used liberally to illustrate the purification or fractionation achieved.

A. Purification of Reactive Monomers

Macromonomers with acrylate and methacrylate functionality usually contain residual acrylic acid and small molecule byproducts, which are difficult to remove from the monomer via the traditional methods of wiped film evaporation or short path distillation. Free-radical inhibitors such as MEHQ are normally present in the material to prevent polymerization during storage, but at the temperature and vacuum levels required to remove (volatilize) acrylic acid, for example, the free-radical inhibitor will simultaneously be removed, thus increasing the propensity of the macromonomer to gel.

Supercritical fluid extraction, especially because it can be carried out at a low temperature, say, 35° or 40°C, can remove residual acrylic acid at an operating pressure level of only 1200psi; at that low extraction pressure the MEHQ remains with the macromonomer, thus performing its intended function, viz., preventing gelation of the monomer.

Figure 4 is a HPLC chromatogram of a silicone soft lens monomer, mono end-capped with methacryloxy functionality.

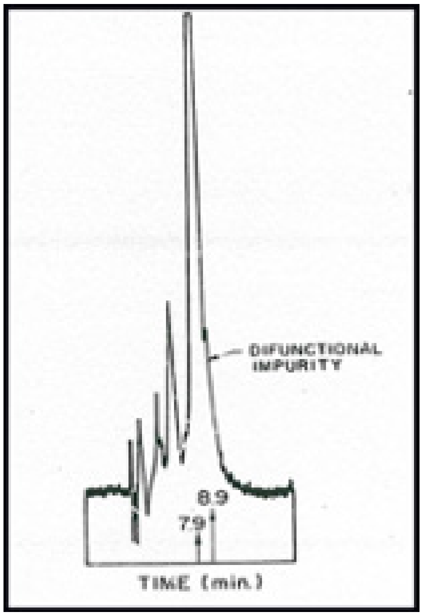


Figure 4. HPLC of Silicone Lens Monomer

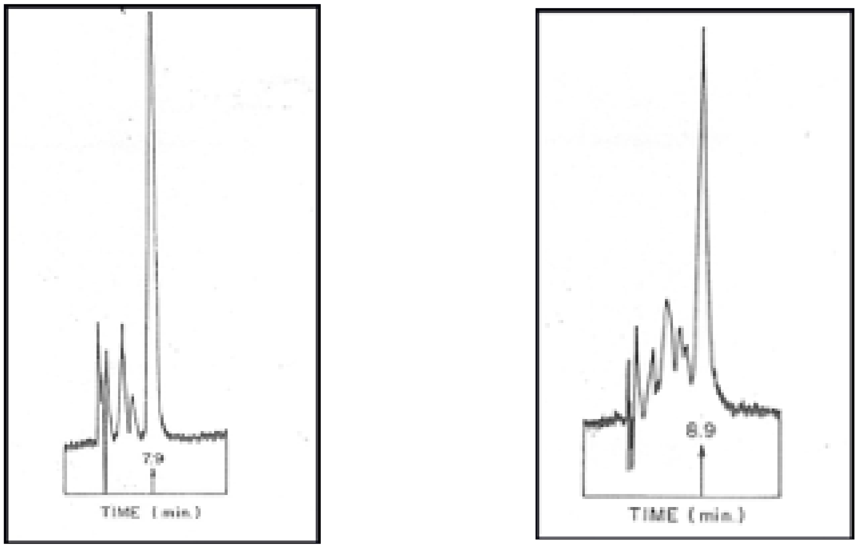
During synthesis about 5% of an α, ω end-capped by product is formed, and its presence can cause undesired cross-linking reactions certainly not conducive to “softness”. From the figure it is seen that the monomer elutes at 7.9min, the impurity at 8.9min.

As related earlier certain reactive low vapor pressure monomers requiring high purity are virtually impossible to purify via WFE or short path distillation because of their propensity to gel when the free radical inhibitor is simultaneously volatilized. Separation of the undesired byproduct as well as residual methacrylic acid is readily achieved by supercritical CO2 extraction. CO2 selectively extracts the monofunctional silicone monomer, and HPLCs illustrating the separation into two fractions are given in Figure 5a and 5b.

Single peaks at 7.9 and 8.9min, respectively, show the level of purification achieved.

B. Extraction/Fractionation of Polymers

A wide molecular weight range polymer cannot be readily fractionated with a liquid solvent into a large number of low polydispersity index (PDI) fractions merely by changing the temperature of the liquid. To be sure the solvent power of a liquid can be modified with temperature, but it cannot be fine-tuned sufficiently to discriminate by polymer chain length to produce low PDI fractions. Although at a specified temperature the high molecular weight chains of a polymer dissolve in a liquid solvent to a lesser extent than low molecular weight chains, the particular fractions obtained at a given temperature will still exhibit a wide PDI because in practice liquid solvents are “too good”: A liquid solvent cannot discriminate sufficiently to achieve narrow molecular weight distribution.



a. Purified Monomer

b. Impurity

Figure 5. HPLCs of Purified Monomer and Impurity

Supercritical fluid fractionation exploits the pressure-dependent dissolving power of gases above critical conditions, not just for a neat compound but for different chain lengths of a polymer as well. At some low pressure (but sufficiently high to dissolve some of the polymer) the polymer “lows” can be extracted, but at that condition the solubility of the “highs” is virtually nil. Thus, sequential increasing-pressure levels can be selected so as to extract only a narrow range of chain length at each pressure. For practical application any polymer that dissolves in any supercritical fluid can be fractionated; as examples, siloxanes with CO2, polyolefins with propane, polymethylmethacrylate (PMMA) with chlorodifluoromethane (F-22); many other polymer/solvent pairs have been studied at Phasex (and elsewhere), and several selected examples are described.

1. Silicone Polymers

Silicon-containing polymers (e.g., siloxanes, silanes, carbosilanes) are used in many industry applications: hydraulic fluids, adhesives, surgically implanted medical devices, ceramic precursors. Most applications do not require further fractionation of as-produced polymers, but several require further purification or fractionation to produce a satisfactory product, and when the requisite specifications and performance cannot be achieved with either organic liquid extraction or wiped film evaporation, supercritical fluid extraction is usually effective in achieving the goals.

Polydimethylsiloxanes are used in many medical applications: surgically-implanted devices, temporary catheters, and external medical devices and tubing in contact with blood. All as-produced silicone raw materials and all lightly cross-linked silicone devices contain residual cyclic siloxanes that cannot be removed completely by wiped film evaporation. Cyclics exhibit the propensity to diffuse from a cross-linked structure; if diffusion is deleterious in the application, the cyclics can be removed by SFE.

Figure 6 is a GPC of an exemplary as-produced polydimethylsiloxane (Mn= 42,500 daltons). The small peak is composed of cyclic siloxanes comprised of from three to fifty (or more) siloxy segments.

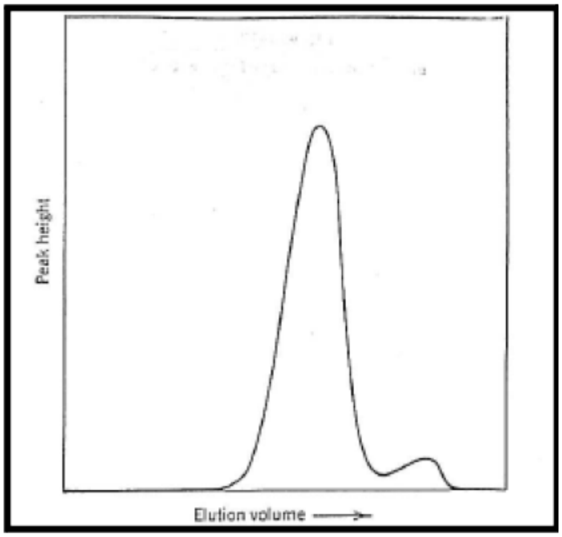
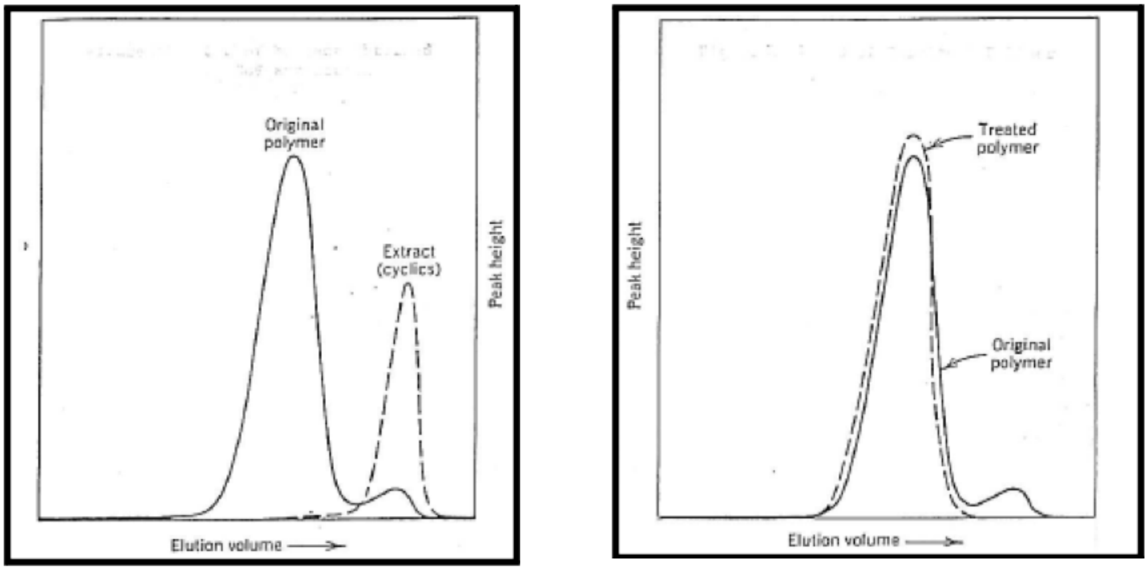


Figure 6. GPC of As-Produced Polydimethylsiloxane

Supercritical CO2 can be tailored (by pressure level) to selectively remove the cyclics. The GPC of the extracted cyclics is shown in Figure 7a, superposed on the Parent GPC; 7b is a GPC of the purified, cyclics-free polymer.



a. Cyclics b. Cyclics-free polydimethylsiloxane

Figure 7. GPC of Purified Silicone Polymer

As implied earlier, cyclic siloxanes can be extracted from parts that have been formed from cross-linkable silicone polymers. Lightly cross-linked silicone parts are expanded in volume when contacted with supercritical CO2; thus, the internal volume can be penetrated easily by CO2, thus allowing cyclics to be readily extracted. At the end of the extraction process when the pressure is reduced to ambient, the CO2 diffuses from the parts, and they return to their starting dimensions.

Figure 8 shows an array of catheters, hydrocephalus shunts, and defibrillator leads that have been purified by supercritical CO2. (The hydrocephalus shunt is positioned at the bottom left of the photograph.)

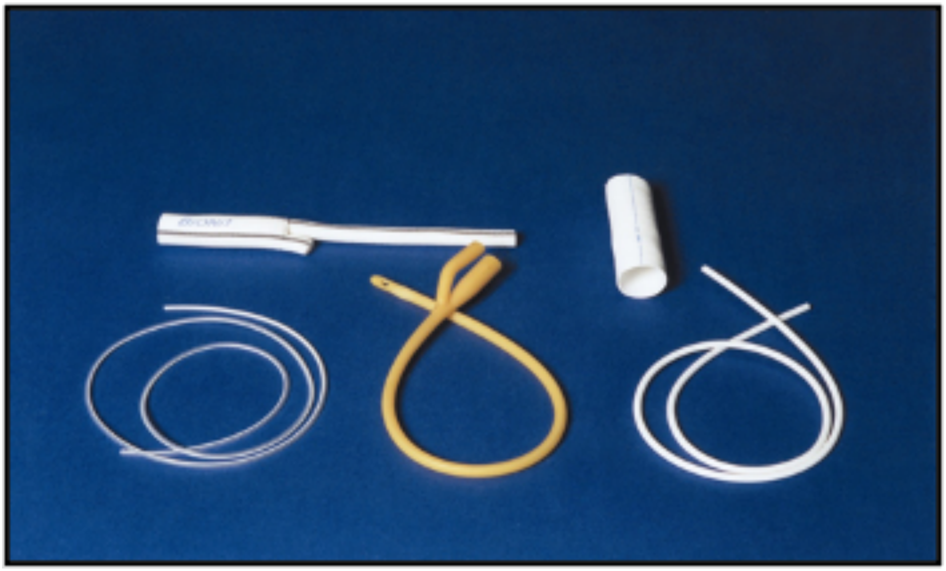


Figure 8. Various medical tubes

Other medical devices both polymeric and metal based, e.g., porous titanium hip sockets and knee joints, wound dressings, tissue scaffolds, etc., are advantageously cleaned of lubricants, processing oils, or oligomeric species using supercritical technology while leaving no solvent residues.

2. Polyolefins

New catalysts and new processes for producing olefin polymers and copolymers are continually in development, and information about catalyst productivity, kinetic mechanisms, and reactor(s) performance is important for continually improving products/processes; this information can be obtained from analysis of narrow molecular weight fractions of the polyolofins. Additionally, the narrow molecular weight fractions can themselves serve as polymer-specific GPC standards for their analysis.

Figure 9 shows GPCs of fractions obtained from a copolymer of ethylene and butene. The parent polymer was fractionated into 18 fractions by the process called Increasing Pressure Profiling: The charge of copolymer was extracted with supercritical fluids at 18 increasing pressure levels, the material extracted at each pressure level comprising a fraction.

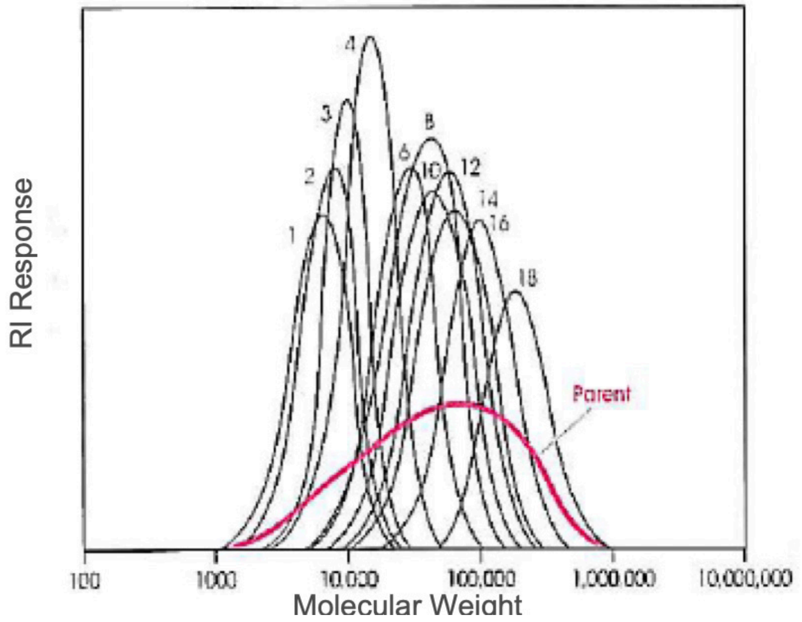


Figure 9. GPCs, Parent and Fractions

The seemingly low PDIs are evident from the narrow breadth of the fractions, and the data in Table 1 confirm the narrow molecular weight and PDI for the fractions deduced visually.

Table 1. Molecular Weight of Poly (ethylene co-butene) Fractions

Fraction	Mn	Mw	Mn/Mw	Cum. % Mass
Parent	**13,700**	**63,800**	**4.7**	—
1	6,300	8,300	1.3	2.5
2	8,100	9,400	1.2	3.1
3	9,200	10,800	1.2	7.8
4	13,900	16,800	1.2	15.9
5	17,400	23,900	1.4	17.5
6	21,200	28,200	1.3	20.9
7	24,800	33,600	1.4	29.7
8	29,200	37,400	1.3	33.7
9	30,400	44,200	1.5	39.9
10	31,600	46,400	1.5	46.4
11	37,400	58,200	1.6	50.9
12	39,200	58,400	1.5	56.1
13	40,900	60,600	1.5	56.1
14	43,200	69,800	1.6	68.8
15	52,000	82,400	1.6	81.1
16	60,500	94,000	1.6	91.2
17	92,000	152,000	1.6	98.1
18	113,000	239,000	2.1	100

Many, many other polymers have been fractionated with supercritical fluids for the purpose of increasing performance or for providing information about their synthesis. (A quite large number of examples are given in Chapter 9 of the text Supercritical Fluid Extraction: Principles and Practice, McHugh, M.A. and V. Krukonis, Butterworth-Heinemann, Boston, 1994.)

C. Extraction of Active Components from Botanical Substrates

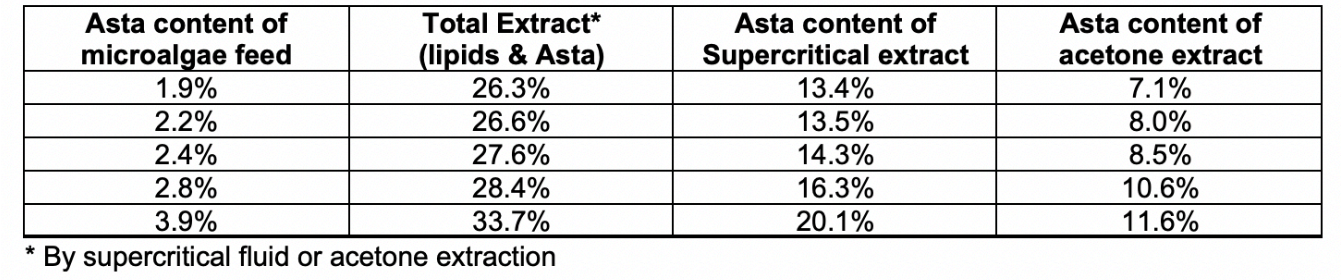
Based on the information about large scale coffee, tea, and hops processing that became widely known during the '80s, literally scores of other supercritical CO2 plants have been constructed throughout the US, Europe, and Asia to extract nutraceutical products from botanical and biological substrates. Two examples that are described below exemplify extractions and separations that are being carried out in the nutra industry.

1. Carotenoids (astaxanthin, lutein, lycopene)

Natural carotenoids (as contrasted with synthetic carotenoids) such as ß-carotene, lutein, and astaxanthin have been extracted from botanical sources such as marigolds, algae, and other substrates at large scale with liquid organic solvents, most notably hexane, but with the proliferation of supercritical CO2 plants, again, first in Germany, then in the rest of the world, supercritical CO2 extracts have become the standard and accepted product form for human use. (In an aside, some huge, 1000s ton/day, plants throughout the world still use hexane to extract lutein from marigolds, for example, but these extracts are used for poultry or fish feed.)

Supercritical CO2 extraction and hexane extraction are equally efficient for extracting the actives from botanical substrates, but the pressure-dependent dissolving power of CO2 makes possible the production of extracts with enhanced concentration: CO2 can be tailored to separate the triglycerides from the carotenoid. Table 2 lists various products that are obtained from one algae source, Haematococcus pluvialis.

Table 2. Astaxanthin Concentration



Asta content of microalgae feed	Total Extract* (lipids & Asta)	Asta content of Supercritical extract	Asta content of acetone extract
1.9%	26.3%	13.4%	7.1%
2.2%	26.6%	13.5%	8.0%
2.4%	27.6%	14.3%	8.5%
2.8%	28.4%	16.3%	10.6%
3.9%	33.7%	20.1%	11.6%

* By supercritical fluid or acetone extraction

2. Paclitaxel

Yew needles and roots represent a renewable source for the important cancer-treatment drug, paclitaxel. (One product is trade named Taxol® .) Paclitaxel is present in yew trees at almost vanishingly small concentration, about 0.02% (such a low content can be recovered economically because purified paclitaxel sells for $2-400,000/kg). When the yew substrate is extracted, with methanol, for example, many, many unwanted compounds are co-extracted, which makes subsequent work up, concentration, and purification complex and costly.

Supercritical fluids are effective in extracting paclitaxel but importantly, many of the very polar interfering compounds are not co-extracted with the paclitaxel, leading to much simpler work up and purification steps. With a methanol process 40% of the yew substrate is extracted, and the concentration of paclitaxel in the methanol free solid is about 0.05%.

Figure 10 is a photograph of the supercritical extract from yew needles. The paclitaxel is extracted with only 7% of other materials, and the paclitaxel concentration is about 0.30%. The factor of 6 concentration relative to methanol extraction represents a huge advantage in subsequent work up and purification.

Figure 10. Photograph of Paclitaxel Extract

D. Supercritical Fluids in Non-Extractive Operations

The pressure-dependent dissolving power of supercritical fluids has also been successfully applied to operations that are, strictly speaking, not extraction processes. For example, recrystallization of solids, infiltration of materials into microporous substrates, and some others, do involve first, the dissolution of a substance, but only in prelude to the specific non-extractive operation that is carried out with the supercritical solution.

1. Recrystallization of Pharmaceuticals

The 1879 statement of Hannay and Hogarth, viz., "drops out like a snow" when the pressure of a supercritical fluid solution is reduced, presaged the application of supercritical fluids to the development of a new process to recrystallize solid materials, especially pharmaceutical compounds: The process was named Rapid Expansion of Supercritical Solution (acronym, RESS). Extending the applications for supercritical fluids, when RESS cannot be applied to the specific compound, another process, Gas Anti-Solvent Recrystallization (acronym, GAS), was developed.

a. RESS (Rapid Expansion of Supercritical Solution)

The pressure-dependent dissolving power of supercritical fluids provides the means of producing virtually monodisperse submicron particles: At high pressure a pharma compound is dissolved and the pressure then lowered virtually instantaneously (through a pressure reduction valve, for example), the rapid expansion and concomitant very high supersaturation ratio that is achieved during expansion results in the formation of almost monodisperse nanoparticles. If supercritical CO2 is used for RESS, the advantageous regulatory and safety attributes are self-evident: It is non-toxic, environmentally conscious, GRAS.

Unfortunately, very few pharma compounds are soluble in CO2. To be sure, other gases such as the light hydrocarbons can dissolve a wider variety of pharma compounds, and patents and publications describe many applications; flammability considerations often limit their wide acceptability, however. Because CO2 is the gas of choice in the pharma industry, but because supercritical CO2 can dissolve so few compounds, RESS has only limited applicability in the pharmaceuticals industry.

Another supercritical fluid-based process invented by Phasex overcomes the solubility limitations of CO2. It is termed Gas Anti-Solvent (GAS) Recrystallization and in abbreviated form simply as GAS.

b. GAS (Gas Anti-Solvent Recrystallization)

Liquid organic solvents are ubiquitous in the pharmaceuticals industry. They are used for carrying out synthesis reactions and for recrystallizing compounds (although primarily for purification rather than for particle size control). Wide classes of solvents include chlorinated hydrocarbons (e.g., chloroform and methylene chloride), polar solvents (e.g., NMP, DMF, DMSO), alcohols, esters, ketones, and (of course) water. Pharma compounds are purified/recrystallized from liquid solution via a process referred to as Anti-Solvent (sometimes, Non-Solvent) Recrystallization. Anti-Solvent Recrystallization from liquid solution requires that the two liquids (the solvent and the anti-solvent) be miscible and that the pharma compound be soluble in one (the solvent) and insoluble in the other (the anti-solvent). Addition of a liquid anti-solvent to a pharmaceutical dissolving in a solvent causes recrystallization to occur when sufficient anti-solvent has been added to the solution to lower the solubility of the pharma compound.

CO2 is soluble in virtually all organic solvents, and this virtually universal solubility property is exploited in the GAS Recrystallization process: CO2 is added to a solution of a pharma compound and when sufficient CO2 is admixed, recrystallization from solution occurs. The ability to admix the pharma solution with CO2 virtually instantaneously results in very high supersaturation, providing enhanced physico-chemical driving forces that can form particles of smaller size than any liquid/liquid recrystallization process can; it is this feature/benefit that has motivated the use of the GAS process in the pharma industry. (When the advantages of RAS Recrystallization were recognized in the academic and industrial communities, other names and acronyms for the process entered the lexicon: SAS, Supercritical Anti-Solvent; PCA, Precipitation Compressed Anti-Solvent; ASES, Aerosol Solvent Extraction System; SEDS, Solution Enhanced Dispersion by Supercritical Fluid. All the acronymed processes exploit CO2-organic solvent miscibility.)

As an example of CO2 miscibility characteristics that are exploited for recrystallization in the GAS process, Figure 11 shows the pressure-driven absorption/expansion behavior of CO2 and one liquid solvent, acetone, at several temperature levels. As the % expansion curves show, at a certain pressure for each temperature CO2 becomes completely miscible (the vertical asymptote) with acetone. Note that at 27°C and 800psi, CO2 is liquid, and at 40°C and 50°C, it is supercritical.

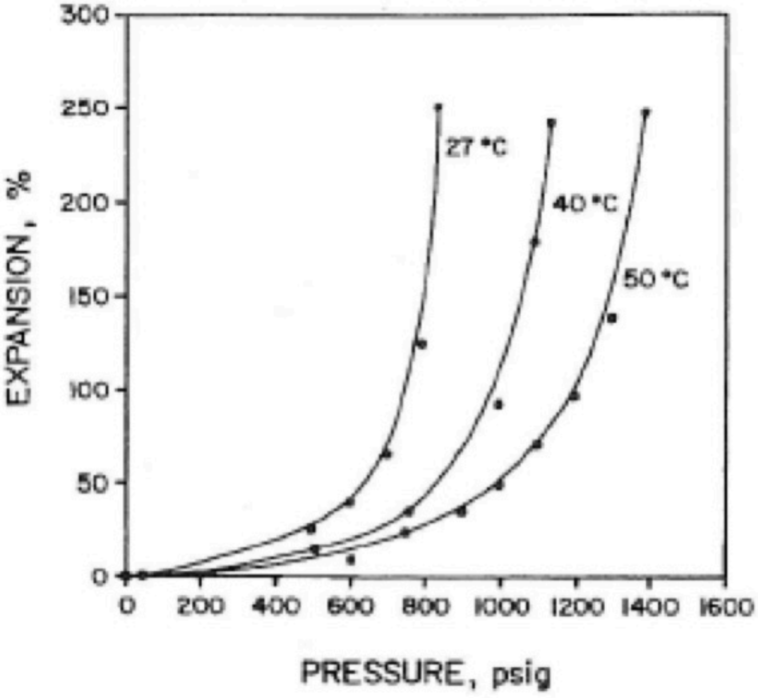
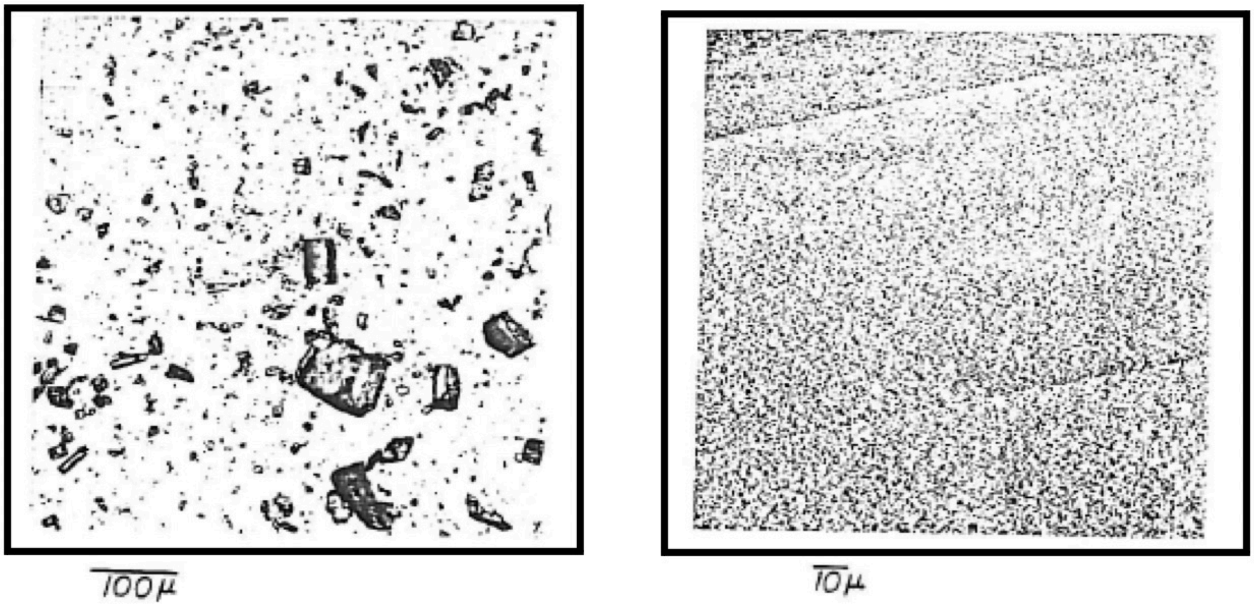


Figure 11. Absorption of Carbon Dioxide by Acetone

Two illustrative examples of supercritical fluid recrystallization by RESS and GAS are presented. For ease of presentation and conservation of narrative, examples are described pictorially using photomicrographs that give comparison of Parent materials with the recrystallized forms.

One example of RESS with ß-estradiol is presented to illustrate the conversion of “big” particles into “small” ones by expanding a supercritical CO2 solution of the compound, for example from 4000psi, 60°C to ambient through a 60μ orifice.

Figure 12a is a photomicrograph of the Parent ß-estradiol, Figure 12b, the particles formed by RESS.



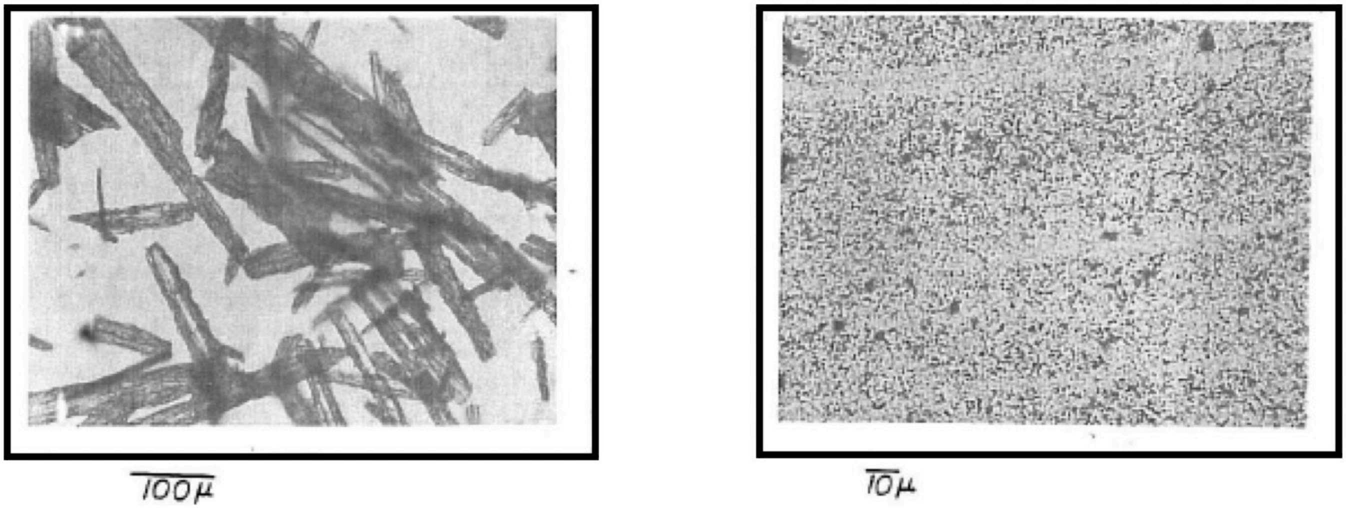
a. Parent

b. Particles by RESS

Figure 12. ß-estradiol Particles

Parent particles range from ~ 1μ to 100μ, and the ultra-fine ß-estradial is quite monodisperse at < 1μ. (Note the difference in scale markers. The very small particles in Figure 12b are difficult to measure quantitatively by optical microscopy.) As related earlier the supersaturation ratio that is reached during pressure reduction through a valve or orifice is so high that a virtually monodisperse particle size distribution results.

GAS Recystallization is more widely applicable: Essentially all compounds are soluble in some solvent and therefore can be recrystallized to small size by CO2. One example of GAS Recrystallization is given in Figure 13; Figure 13a is a photomicrograph of Parent prednisolone acetate, Figure 13b of prednisolone acetate processed by GAS.



a. Parent

b. Particles by GAS

Figure 13. Prednisolone Acetate

Prednisolone acetate dissolves in acetone (and acetone is used during its manufacture). A solution of 0.6% in acetone was injected via a 60μ orifice into CO2 at 1400psi, 40°C, and the particles formed by GAS are <1μ and again essentially monodisperse. Note again the change in scale; it is difficult to resolve the <1μ particles (and the large dark spots are clumps of small particles, not individual large particles).

2. Infiltration of Materials into Microporous Substrates

Gases do not suffer from adverse surface tension limitations. They can travel into and through pores of literally any diameter, free of the LaPlace "gate",

$$\Delta P = 2\gamma/r$$

that limits a liquid's ability to penetrate small pores. A gas (supercritical fluid) can be used therefore to convey soluble materials into the micropores of virtually any size present in a substrate.

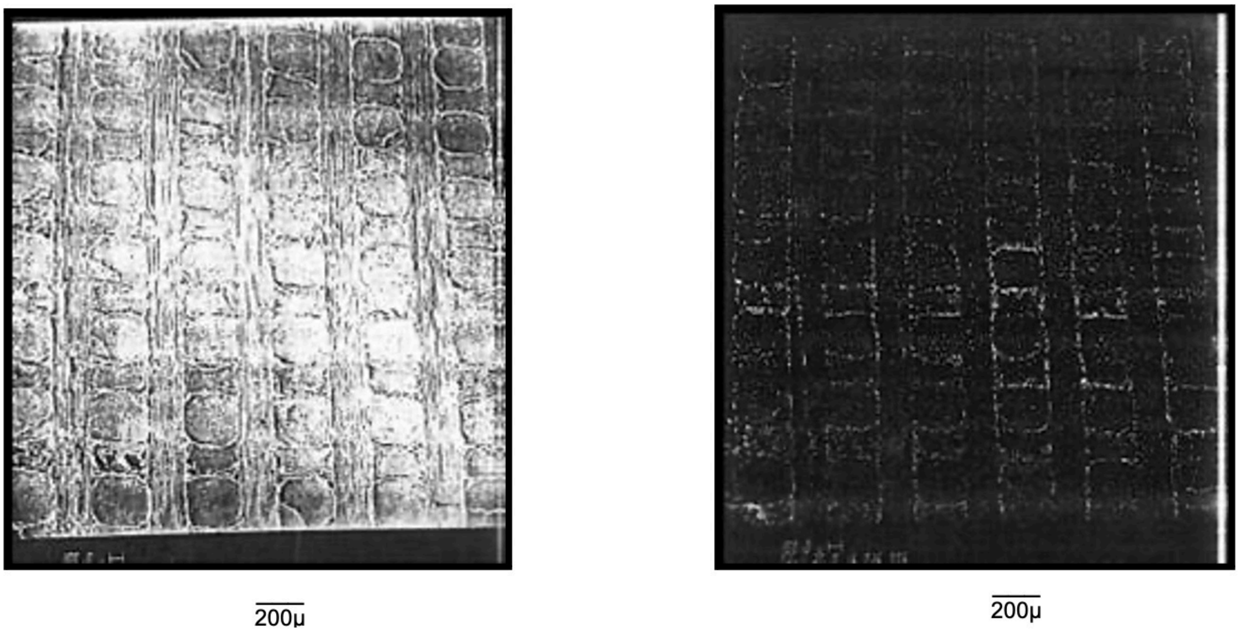
Exemplary of the concept of supercritical fluid infiltration is the work carried out for DARPA (Defense Advanced Research Projects Agency): Improvement of Oxidation, Resistance of Carbon/Carbon Components. Carbon/carbon (C/C) composites (carbon fibers arrayed in a carbon matrix) possess very high temperature strength and stability and are used in specialized high performance applications such as military and commercial aircraft brakes, rocket nozzles, and missile heat shields.

C/C composites are produced industrially by a process called Pressure-Infiltration Carbonization (acronym, PIC): Arrayed carbon fibers (e.g., knitted mats or woven structures) are placed in an autoclave, a carbon precursor such as pitch (heated to above its melting temperature) is charged to the vessel, the vessel sealed, and high hydrostatic pressure applied to push (infiltrate) the pitch into the fiber structure. The infiltrated assembly is next removed from the autoclave, placed in a furnace, and heated to 2000°C in an inert atmosphere to carbonize the pitch. During carbonization some of the pitch gasifies resulting in a porous structure.

The PIC procedure is repeated three more times (i.e., the part pressurized with hot pitch then carbonized) to fill in pores, and the final product after four infiltrations is called ACC4 (advanced CC composite-infiltrated four times), but even this high-performance material possesses a few percent voids which negatively impacts its performance in a high-oxidizing environment such as a rocket nozzle. (Today rockets continue to be launched carrying both military and non-military satellite payloads.)

On the DARPA-funded program 2-dimensional carbon fiber preforms (structures formed by weaving bundles or tows of carbon fibers) were infiltrated with a silicon carbide precursor polymer (a polycarbosilane) dissolved in supercritical propane. The resultant structure was removed from the autoclave, heated to 1000°C in an inert atmosphere to pyrolyze the polymer to SiC. Because of the absence of surface tension limitations the gaseous solution penetrated the micropores and the precursor polymer was deposited in 1μ voids that the PIC process could not fill.

Pictorial presentation will again be explanatory of the concept and results with minimum narrative. Silicon carbide can be identified visually by back scatter electron imaging (BSE) and chemically by energy dispersive spectroscopy (EDS), and Figure 14 shows cross sections of a C/C sample whose micropores have been infiltrated with SiC precursor polymer, the polymer pyrolyzed to SiC, and the silicon identified by EDS.



a. BSE Image

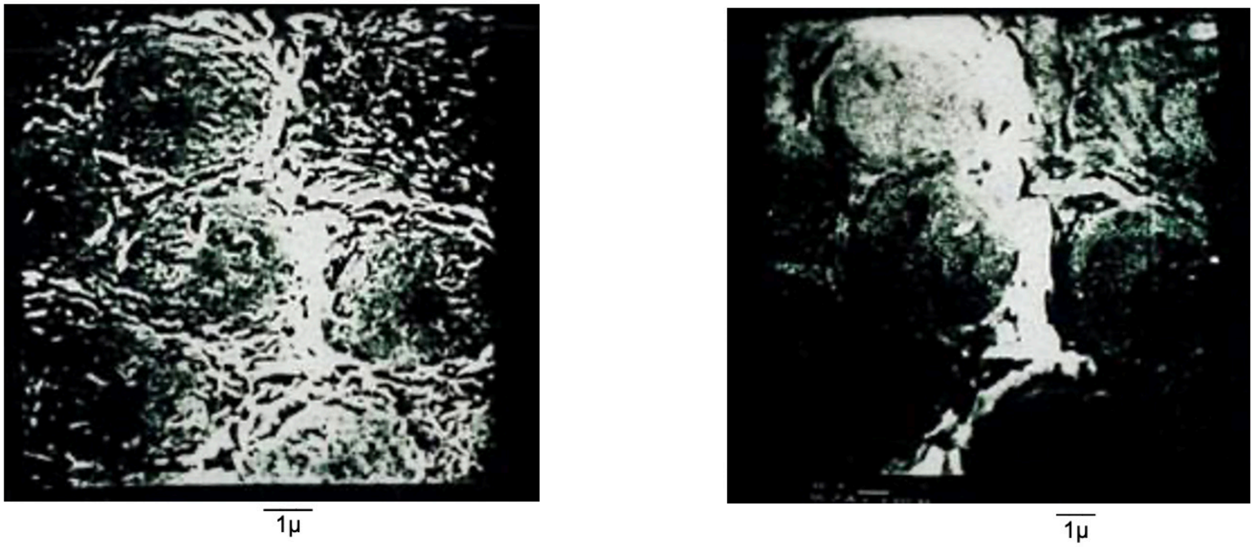
b. EDS Image

Figure 14. Micrographs of Deposited SiC

A scale marker of 200μ is indicated on both micrographs. The orthogonal (90° orientation) tows of carbon fiber are seen in Figure 14a and the SiC deposited in the voids located around the tows is viewed as bright dots in Figure 14b. Voids were present in the spaces surrounding the bundles.

Were there any voids surrounding the individual (8μ) carbon fibers, and was SiC deposited in the voids?

Figure 15 at much higher magnification (and the scale marker of 1μ is shown in the figures), and the SiC that has been deposited in voids of a micron or less is apparent in the interstitial space between the individual 8μ diameter carbon fibers.



a. BSE Image

b. EDS Image

Figure 15. SiC Deposited in Micropores

The concept of supercritical fluid infiltration has been presented in its capacity for carrying a high performance material to still greater performance, but infiltration of any compound soluble in a supercritical fluid can be carried out with porous materials of virtually any pore size, and microporous substrates such as high specific area catalyst carriers and chromatography substrates are currently being studied.

V. About Phasex Corporation

Phasex Corporation, founded in 1981, is internationally recognized for its development of improved products and superior separations processes using supercritical fluid technology. The company is staffed with a team of problem-solving chemical engineers, chemists, and manufacturing specialists. Phasex offers laboratory feasibility testing and process optimization, product development, toll processing, and licensing for all sectors of industry.

Phasex directs the attributes of supercritical fluids to the solution of difficult processing problems for the pharmaceuticals, polymers, natural products, and fine chemicals industries, especially in those problems that cannot be carried out by industry's traditional processes. For example, supercritical fluids are currently used at Toll Processing scale for extracting residual raw materials and solvents from medical polymers, volatile materials from high vacuum adhesives, low molecular weight oligomers from synthetic lubricants, and non-functionalized species from very reactive macromonomers. It is the unique combination of physical properties of supercritical fluids, viz., low viscosity, high diffusivity, liquid-like density, and the absence of surface tension limitations that afford these fluids unique capabilities compared to traditional liquid solvents, and the complete absence of solvent residues in products is becoming an increasingly important attribute of supercritical fluids.

Phasex has state-of-the-art facilities for developing supercritical fluid processes starting at the laboratory scale through pilot plant and extending to manufacturing. The company's equipment includes bench scale extraction systems for processing materials from the grams to kilograms level, and a Class 1, Division 2 production plant capable of processing liquid and solid feedstocks in multi-ton campaigns. In addition to the processing of lubricants, specialty polymers, and nutraceuticals in the Toll Plant, currently several surgically implanted products are being processed under GMP guidelines in product-dedicated equipment in a Class 10,000 clean room.

VI. Closing Remarks

A short description of some subject, like this one on supercritical fluids, cannot possibly cover all aspects of the subject completely. The information in this primer, although abbreviated, is nevertheless quite complete in its development of the progression of solubility in supercritical fluids from the first report of solubility experiments in 1879 to the enunciation of the extraction process concept in 1955 to today's scores of supercritical fluid extraction plants that are in operation throughout the world.

It has been lamented by some that processing with supercritical fluids is not economical, and, unfortunately, the general impression still exists among chemists and chemical engineers that supercritical fluid processing is associated with high costs. However, CO2-decaffeinated coffee and tea and CO2-extracted hops are being sold at prices competitive with their organic solvent extracted counterparts, and this fact should certainly contradict the high cost association.

The erroneous association of high cost with supercritical fluid processes undoubtedly derived from the fate of several widely publicized (but ill-advised) studies in the late 1970s, early 1980s, when their lack of industrial viability was attributed solely to a "high processing cost". In actuality, there were technical limitations to the applications, (and for their potential pedagogical value these limitations, unfortunately, were not described in the articles). Supercritical fluids are frequently excellent solvents with far ranging applications to many purification problems. But as attractive as they may appear a priori they may not be economically viable in each case, and applied industrial research should be carefully examined, and justifiably motivated, especially in today's' economic climate.

As the primer has pointed out, supercritical fluids offer technical advantages for products in many industries: polymers, monomers, lubricants, nutraceuticals, processing medical devices, and medical and biopolymers. In the latter applications interfering components are extracted with a gas, thus leaving no solvent residues in the parts. Additionally, supercritical CO2 possesses attractive health, environmental, and work place characteristics. It is non-toxic, non-hazardous, Generally Recognized as Safe (GRAS), and Organic. Because of its ability to penetrate porous structures, supercritical CO2 provides a superior means of cleaning machining oils from porous titanium components implanted in the body. Finally, (but not covered in the paper) supercritical CO2 can swell polymers, and thus, it can infuse and deposit antimicrobial compounds in polymeric components such as catheters. There are still myriad other applications not covered herein.

Increasing performance demands and increasingly stringent consumer and regulatory constraints being placed on many products are being satisfied with supercritical fluid based processes.

phasex

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