phasex

The Supercritical Fluids People

Formation of Submicron and NanoParticles with Supercritical Fluids

1. Supercritical Fluid Extraction – Current Status

Supercritical fluid extraction, especially with supercritical CO_2, has progressed from its position as solely a laboratory curiosity of the 1960s to today's very large scale commercial operation in the foods and beverages industry. Coffee and tea are being decaffeinated at more than 150,000 T/yr in plants in the US, and in Europe, and hops (for flavoring beer) are being extracted at levels of more than 50,000 T/yr. On a smaller scale, supercritical fluid extraction is used to concentrate fractions of spices, essential oils, and nutraceuticals.

Other industries such as pharmaceuticals, specialty chemicals, lubricants, and polymers, are also applying the properties of supercritical fluids to improve products faced with increasing performance demands, to modify processes under increasing scrutiny because of regulatory constraints, and to develop entirely new products that offer advantages for unmet needs. These industries exploit the pressure-tunable dissolving properties of supercritical fluids, especially CO_2, to selectively remove objectionable or interfering components from substrates, e.g., low molecular, migrateable species from a medical polymer, volatile materials from a high vacuum oil, low molecular weight oligomers from synthetic lubricants.

Starting in the early 1980s supercritical fluids were applied to the recrystallization of pharmaceuticals, and today supercritical fluid processes for forming nanoparticles are in active development or in production operation at many pharma companies. Several drug formulations are currently produced in GMP manufacturing processes in the US and Europe. In these recrystallization processes supercritical CO_2, is used either as a solvent or (borrowing terminology from the pharma industry) as an anti-solvent.

2. Supercritical Fluid Recrystallization Principles

Two supercritical fluid-based processes have been developed to recrystallize pharma compounds: Rapid Expansion of Supercritical Solutions, acronym, RESS; and Gas Anti-Solvent Recrystallization, acronym, GAS.

A. RESS (Rapid Expansion of Supercritical Solution)

Supercritical fluids exhibit a pressure dependent dissolving power, which offers the means of producing virtually monodisperse submicron particles: At high pressure a pharma compound is dissolved and the pressure subsequently lowered virtually instantaneously (through a pressure reduction valve, for example). The rapid expansion and concomitant solubility decrease results in the nucleation and formation of almost monodisperse nanoparticles because of the very high supersaturation ratios that are achieved during expansion. If supercritical CO_2 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 CO_2. 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 CO_2 is the gas of choice but because supercritical CO_2 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 CO_2. It is termed Gas Anti-Solvent (GAS), Recrystallization.

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 (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 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). In concept, then, addition of a liquid anti-solvent to a solution of a pharmaceutical causes recrystallization to occur when sufficient anti-solvent has been added to the solution to lower the solubility of the pharma compound. As is well known within (and outside of) the pharma industry, substantial art, as well as science, is associated with liquid solvent/anti-solvent recrystallization; for example, the direction of addition (liquid A into B or vice versa), the rapidity of addition and stirring, compound concentration, solution temperature, etc., all influence particle size and the separability of interfering impurities.

A landmark paper in 1954 (Francis, A.W. 1954. Ternary Systems of Liquid Carbon Dioxide, J. Phys.Chem. 58, 1099-1114) showed that liquid CO_2 is miscible with virtually all organic solvents, and this property has been exploited by Phasex Corporation in the development of the GAS process to recrystallize pharma compounds to submicron or nanosize size. GAS is similar in concept and operation to liquid anti-solvent recrystallization except a gas is used as the anti-solvent. (Water, a commonly-used solvent, is not miscible with CO_2, but Phasex has developed a GAS Recrystallization variant for water solutions of proteins and other biomolecules.) Some of the same "art and science" factors described above also influence recrystallization and particle size in the GAS process. However, the ability to admix the pharma solution with CO_2 virtually instantaneously provides enhanced physico-chemical driving forces that can form particles of smaller size than any liquid/liquid recrystallization process can, and it is this feature/benefit that has motivated the developments in the pharma industry.

As an example of CO_2 miscibility characteristics that are responsible for recrystallization in GAS, Figure 1 shows the pressure driven absorption/expansion behavior of CO_2 and one liquid solvent, acetone, at several temperature levels. As the % expansion curves show, at a certain pressure for each temperature CO_2 becomes completely miscible (the vertical asymptote) with acetone. Note that at 27°C and 800psi, CO_2 is liquid, and at 40°C and 50°C, it is supercritical.

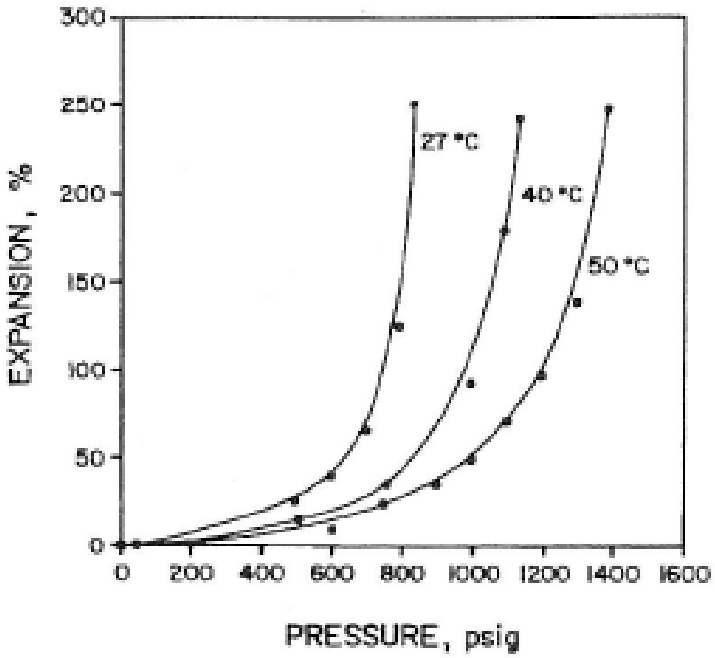


Figure 1. Absorption of Carbon Dioxide

Some illustrative examples of supercritical fluid recrystallization by RESS and GAS are presented in the next selection.

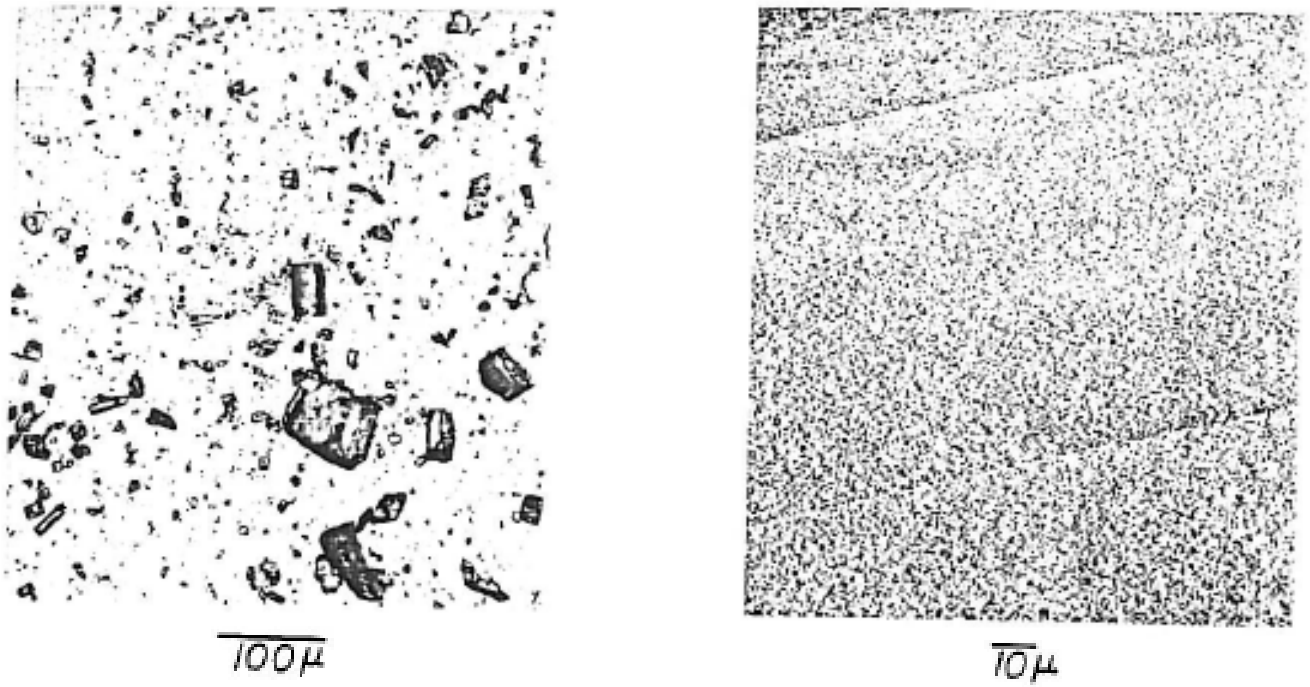
3. Selected Examples Of Materials Recrystallized By Ress And Gas

For ease of presentation and conservation of narrative, examples are described pictorially using photomicrographs that give comparison of Parent materials with the recrystallized forms.

A.Pharma Compounds Processed by RESS

As related above not many pharma compounds are soluble in supercritical CO_2, and thus, RESS is not broadly applicable in the pharmaceuticals industry. One example, ß-estradiol, is presented to illustrate the conversion of "big" particles into "small" ones by expanding a supercritical CO_2 solution of the compound, for example from 4000psi, 60°C to ambient through a 60µ orifice.

Figure 2a is a photomicrograph of the Parent, Figure 2b, particles formed by RESS.



a. Parent

b. Particles by RESS

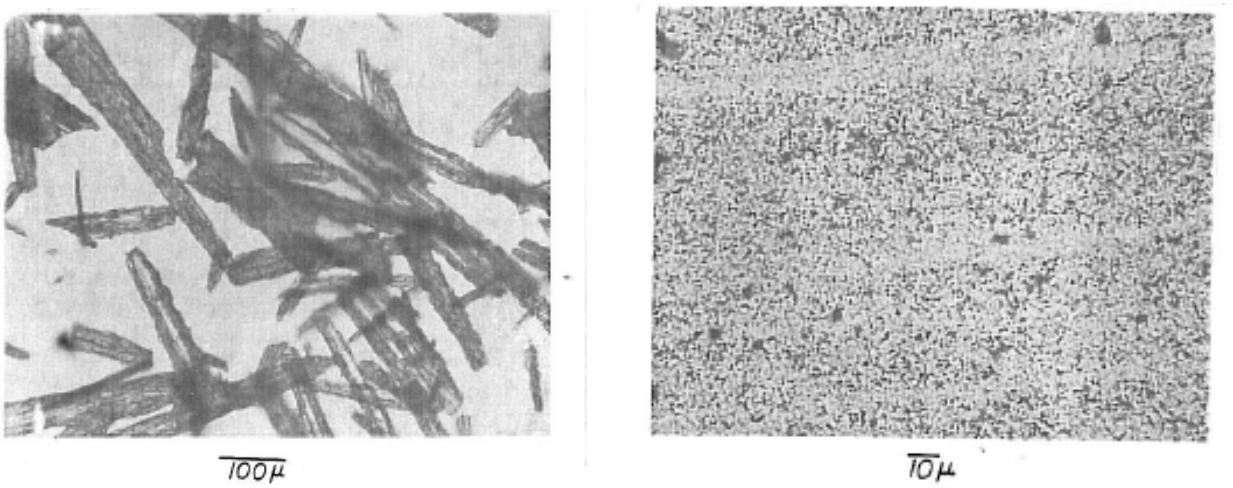
Figure 2. ß-estradiol Particles

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 2b 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.

B. Pharma Compounds by GAS

The GAS process is widely applicable in the pharmaceuticals industry because again, virtually every pharma compound dissolves in some organic solvent, and because CO_2 is miscible with all organic solvents, it serves as a virtually universal anti-solvent to produce nanoparticles of pharmaceuticals. (As related earlier, CO_2 and water are not miscible, and compounds that are soluble only in water are discussed subsequently.)

Figure 3a is a photomicrograph of Parent prednisolone acetate, Figure 3b of prednisolone acetate processed by GAS.



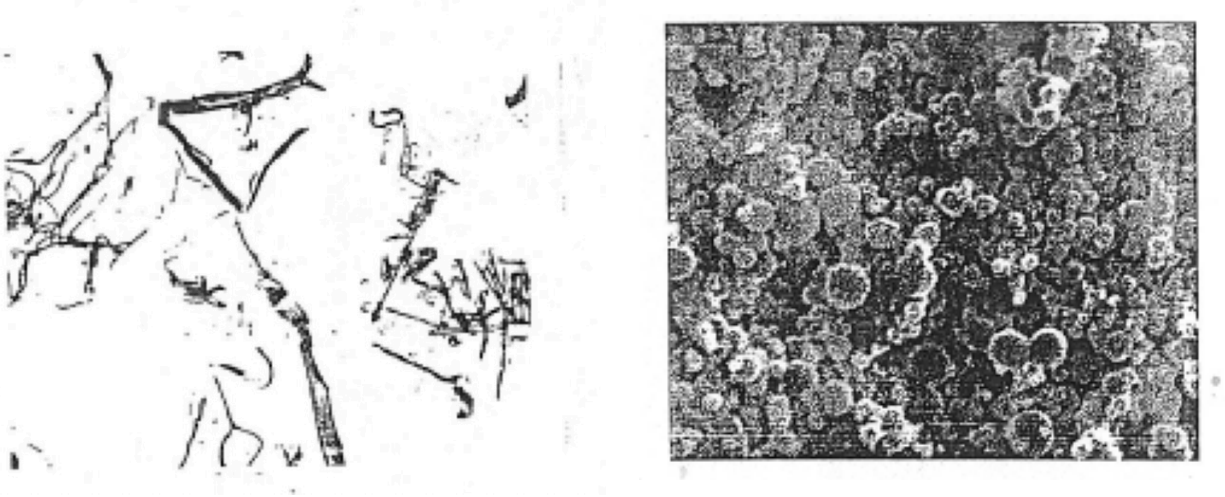
a. Parent b. Particles by GAS

Figure 3. 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 CO_2 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).

A GAS variant for pharma compounds soluble only in water, compounds such as proteins and enzymes has been developed by Phasex, and one illustrative example is an enzyme, chymotrypsin, which has been recrystallized via GAS.

Figure 4a shows thin flakes of the Parent enzyme; Figure 4b, which is a scanning electron micrograph shows in detail the 0.2-0.4μ particles produced.



a. Parent b. Particles by GAS

Figure 4. Chymotrypsin Particles

C. Explosives by RESS

With no levity intended, explosives are difficult to grind to small size, and the usual mechanical processes of crushing, grinding, and jet milling are not applicable processes to convert as-produced explosives to fine powders. (One comminution process, "pump-grinding", viz., recycling a water slurry of an explosive through a centrifugal pump, can be practiced safely and is used in the explosives industry to reduce particle size.)

As with pharma compounds, not very many explosives are soluble in CO_2. One explosive, pentaerythitol tetranitrate, PETN, is, and it exemplifies an extremely sensitive explosive, simultaneously, one that merits examination for nanosizing because of potential (military) applications where flexibility of the impregnated substrate is important: If extremely small particles were available, higher loading of explosive in the device could be achieved. In response to a government solicitation Phasex carried out a program to produce submicron PETN via RESS with supercritical CO_2.

For the photographs shown below PETN was dissolved in supercritical CO_2 (at 8500psi, 45°C) and expanded through a 60μ orifice to a pressure of 1000psi.

Figure 5a is the parent PETN, and Figure 5b, 0.2μ PETN with narrow size distribution produced by RESS.

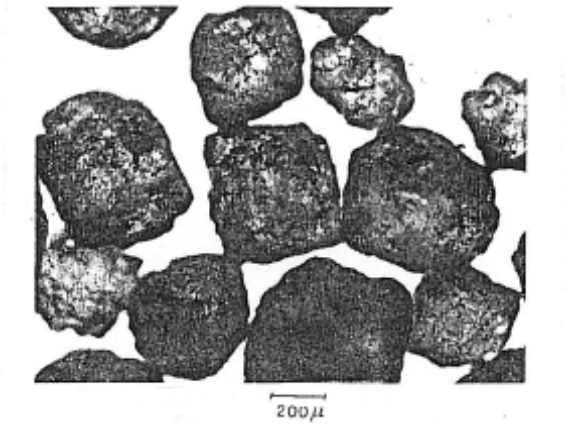


Figure 5a. Parent PETN

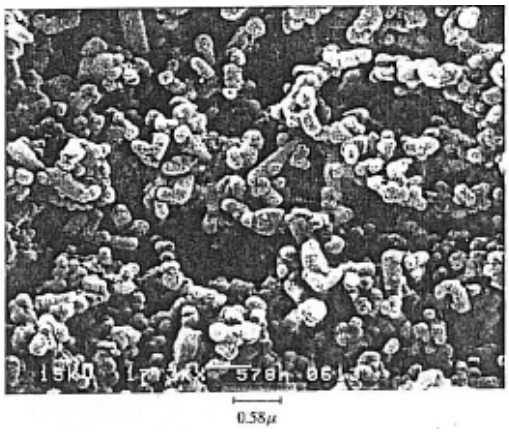


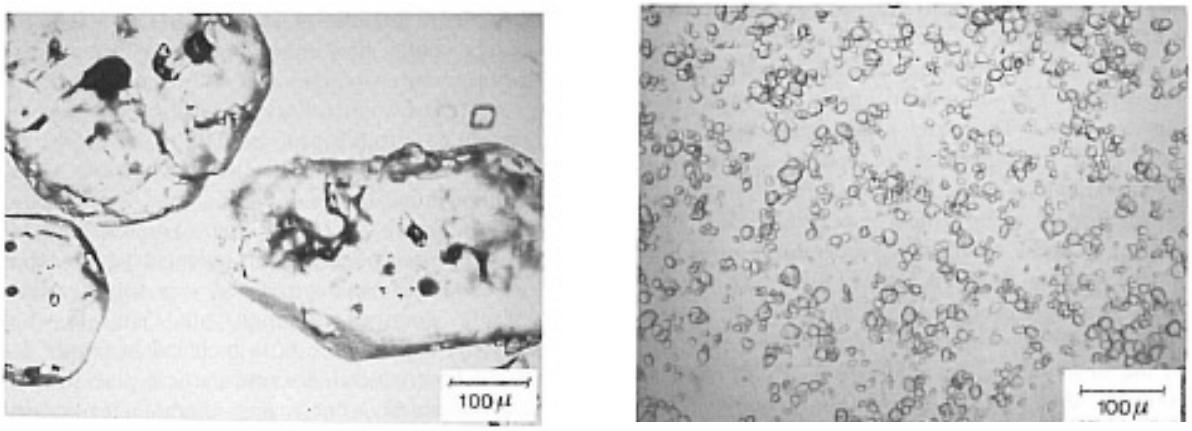
Figure 5b. Particles by RESS

Figure 5. PETN Particles

D. Explosives by GAS

As was the case for pharmaceuticals most explosives dissolve in liquid organic solvents, and, thus, GAS is generally applicable to the recrystallization of explosives. Again, in response to government solicitations Phasex has carried out extensive programs to recrystallize several explosives via GAS. The objective of the program to recrystallize cyclotrimethylenetrinitramine, RDX, was the elimination of intragranular voids of as-produced RDX. RDX is synthesized in cyclohexanone solution and, as has become well known to the reader, because CO_2 is miscible with organic solvents, cyclohexanone among them, it serves as an anti-solvent for RDX from cyclohexanone solution.

Figure 6a shows as-produced parent RDX; large intragranular cavities (the black spots) in the 600µ particles are evident. Figure 6b shows recrystallized, cavity-free 10µ particles formed by GAS.



a. As Produced b. Particles by GAS

Figure 6. RDX Particles

Many other industries and products take advantage of nanoparticles, for example, solid agricultural chemicals such as insecticides and herbicides that are applied as dispersions. Dispersions of large particles are often not optimally effective in amount of active per unit of field area, and nanoparticle formulations extend the field area of application with no decrease in efficacy.

4. 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 to those materials and compounds that cannot be processed by industry's traditional methods. 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. (Very reactive, low vapor pressure monomers are uniquely purified of raw materials by supercritical fluids; impurities can be extracted at near-ambient temperature and free radical inhibitors can preferentially be not extracted.)

It is the unique combination of physical properties, viz., low viscosity, high diffusivity, liquid-like density, and the absence of surface tension limitations that provide the unique capabilities of supercritical fluids to produce ultrafine particles of a wide range of compounds. The complete absence of solvent residues in products is becoming an increasingly important attribute of supercritical fluids, especially for extraction of phytosterols, anti-oxidants, and specialty lipids from botanical and algal substrates. Processing with supercritical CO_2 is currently recognized as a technically superior environmentally conscious alternative to organic solvent processing.

Phasex has state-of-the-art facilities for developing supercritical fluid processes from laboratory scale to manufacturing. The company's equipment includes bench scale extraction systems for processing materials from the grams to kilograms level, and two Class 1, Division 2 production plants capable of processing liquid and solid feedstocks in multi-ton campaigns. Several products are currently processed under GMP guidelines in the Toll Processing plant or in product-dedicated equipment in a Class 10,000 clean room.

5. Closing Remarks

For its relevance to the supercritical fluid particle formation processes previously described, Phasex invented both the RESS (1981) and GAS (1988) recrystallization processes. (Phasex had named its CO_2 recrystallization process, Supercritical Fluid Nucleation, SFN. Another group of researchers subsequently named it RESS. RESS was a much more user-friendly acronym, and it entered the lexicon of the supercritical fluid community.)

After GAS was described in the literature by Phasex, its quite general applicability was immediately recognized by many researchers, both academic and industrial in the supercritical fluid community: Almost every compound dissolves in some organic solvent, and because CO_2 is miscible with all organic solvents, almost every compound can be recrystallized via GAS processing. GAS was widely studied, at first, primarily in the pharmaceutical sector. Other supercritical fluid researchers ascribed other names and acronyms to the process that Phasex named GAS, e.g., SAS (Supercritical Anti-Solvent Precipitation), PCA (Precipitation by Compressed Anti Solvent), ASES (Aerosol Solvent Extraction System), and most recently SEDS (Solution Enhanced Dispersion by Supercritical Fluid). All the processes are virtually identical: They exploit the miscibility characteristics of CO_2 and organic liquids, and the acronym GAS is the most broadly encompassing in description; CO_2 is a gas (for the G in GAS). It not need be supercritical (above1087psi, 31°C) to be effective as an anti-solvent; it is an anti-solvent in many regimes of phase space: as a vapor just below its vapor pressure, as a liquid, and as a supercritical fluid.

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