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SUPERCRITICAL FLUID CRYSTALLIZATION

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Introduction

Supercritical crystallization processes use the special properties of supercritical fluids that make these fluids particularly suitable as solvents or antisolvents. In both cases, an expansion of a solution is used to create supersaturation, which is the driving force for nucleation and growth of the solute.

A supercritical fluid (SCF) is a fluid above its critical temperature and pressure. It is characterized by physical properties (such as viscosity and diffusivity) that can be continuously varied between those of liquids and gases. The liquid-like density of a SCF is associated with its ability to dissolve solutes, and hence its solvent power. Since this density can be changed significantly by changing the pressure and temperature in the critical region, the solvent properties of a supercritical fluid can be tailored for specific applications. **Figure 1** shows the relationship between pressure and density of carbon dioxide. The region above the critical pressure and temperature (7.38 MPa, 302.3 K) is commonly referred to as the supercritical region of carbon dioxide. It is important to note that the largest changes in the fluid density with changes in temperature and/or pressure in the single-phase region occur near the critical point. Therefore, large changes of solvent power can be achieved with small changes in pressure or temperature in the critical region. It should be added here that a supercritical crystallization process involves mixtures of solute and solvent; however, these mixtures are generally dilute so that their critical points are close to the critical point of the solvent. The behaviour depicted in Figure 1 may therefore be considered to be representative of the behaviour of dilute mixtures of constant composition.

If a supercritical fluid loaded with solute is expanded, then the resulting change in density may lead to precipitation of the solute. If these changes in density are made to occur rapidly, then the process is known as the rapid expansion of supercritical solutions, or RESS. Very high supersaturations may be achieved in RESS processes over a very short period of time. This generally favours the deposition of small crystals and narrow size distributions. Also, the crys-

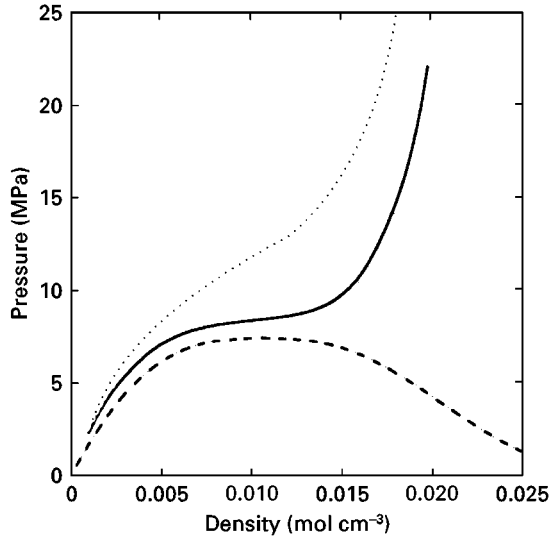

Figure 1 Pressure–density behaviour of CO_2. ⋯, 330 K; ———, 310 K; – – – –, phase boundary.

tals are generally free of solvent inclusions because the solvent is likely to be in the gaseous state at the end of the expansion.

Introduction of a supercritical fluid into an organic solvent can also result in expansion of the liquid phase, and hence, in large changes in density. If a solution containing a desired solute is expanded sufficiently by the supercritical fluid, then the liquid phase will no longer be a good solvent for the solute and nucleation will occur. In this case, the supercritical fluid acts as an antisolvent, and the crystallization process is known as the supercritical antisolvent (SAS) process, or by a variety of other names that are discussed below. Changes in the pressure, temperature, or rate of supercritical fluid addition provide an opportunity for tailoring the SAS crystallization process for specific applications.

Crystallization by the Rapid Expansion of a Supercritical Solution (RESS)

The rapid expansion of a supercritical solution (RESS) by decompression can lead to very large changes in density and, hence, in the solubility of a solute in the supercritical solvent. This can result in very high supersaturation when supercritical solutions are depressurized, leading to the formation of a large number of nuclei. A typical RESS apparatus is shown in **Figure 2**. Solvent is pressurized in a pump until a pressure above its critical pressure is attained. The supercritical state is achieved by passing the pressurized solvent through a heat exchanger maintained at a temperature above the critical temperature of the solvent in a constant-temperature bath. The supercritical fluid is then passed through a bed of solute where it becomes saturated with the solute. The loaded solution is then heated to a designed pre-expansion temperature, and finally expanded quickly through an expansion device, such as a nozzle or a capillary, into a collection vessel. The expansion device is generally heated to prevent resublimation or solvent condensation. The collection vessel is maintained at a constant temperature and pressure or vacuum, and the products are collected on a suitable substrate placed in the path of the expansion jet. The pressure in the collection vessel is ambient, but may sometimes be higher in order to control the particle size; or it may be below atmospheric to prevent condensation of any solvent that is a liquid at ambient conditions. Variations of this equipment are possible, particularly if the solvent is to be recycled. Also, a dual RESS or DURESS process has been proposed whereby two RESS expansions are carried out in a concentric expansion device and yield, for example, a solid solute coated with a polymer.

The RESS process is applicable to any material that can be dissolved in a supercritical solvent and is particularly useful for materials of low volatility. A few examples of crystallized materials using the RESS process are shown in **Table 1**. Scanning electron microscopy (SEM) micrographs of crystals obtained by RESS processes are shown in **Figure 3**. RESS expansions result in essentially homogeneous nucleation of the solute. The morphology of the product is determined by a number of factors, including the solute and its concentration, the device used for the expansion, the pre-expansion temperature, the flow rate, and the pressure drop on expansion. High concentrations of solute tend to produce powders, whereas low concentrations generally produce thin layers or films. The particle size has been found to increase with solute concentration prior to expansion. Also, processing conditions may be chosen such that the solvent is a gas at exit conditions and can be easily separated from the deposited solute. If conditions are chosen so that a two-phase mixture is

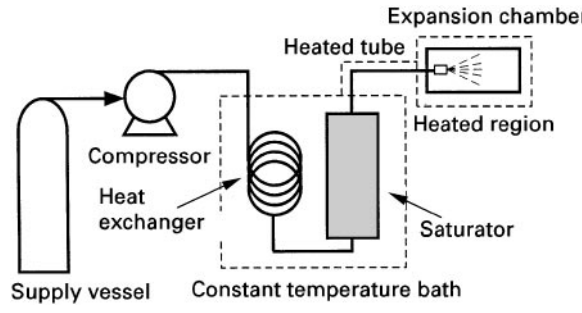

Figure 2 Experimental apparatus for a RESS process.

Table 1 Substances processed using RESS

Materials	*Supercritical fluid*	*Morphologies, particle size (μm)*
Inorganics		
α-Al_2O_3	Water	Films, ~ 0.08 thickness
SiO_2	Water	Spheres, 0.1–0.5
		Films, > 1.0 thickness
GeO_2	Water	Spheres, 0.5–1.3
$ZrO(NO_3)_2$	Ethanol	Particles, ~0.1
Polycarbosilane	Pentane	Fibres, 1 diameter
		Particles, < 0.1
Organics		
Benzoic acid	CO_2	Particles, 3–8
β-Carotene	Ethylene	Particles, 1–2
Cellulose acetate	Pentane	Fibres, 0.8 diameter
Naphthalene	CO_2	Particles, 2–50
n-Octacosane	CO_2	Particles, 2–6
Phenacetin	CO_2	Particles, ~ 10
Phenanthrene	Trifluoromethane	Particles, ~ 3
	CO_2	Particles,1.6–6.6
Stigmasterol	CO_2	Fibres, ~ 0.2 diameter
Polymers		
Poly-1-butene	CO_2	Spheres, < 5
Poly(carbosilane)	Pentane	Particles, < 0.1
		Fibres, 1 diameter
Polycaprolactone	CO_2	Spheres, < 5
	CDFM[a]	Spheres, 1–5
		Fibres, 2–7
Polyethylene succinate	CO_2	Spheres, < 5
Polyethylene methacrylate	CDFM	Particle/fibre blend
Poly(glycolic acid)	CO_2	Particles, 10–20
Poly(L+)-lactic acid	CO_2	Particles, 10–120
	CDFM	Particles, 0.2–0.6
Poly(DL)-lactic acid	CO_2	Particles, 10–20
Polymethyl methacrylate	Propane	Particles, 0.5–1.0
		Fibres, 1 diameter
	CDFM	Particles/fibres
Polyphenylsulfone	Propane	Spheres, ~ 0.5
Polypropylene	Propylene	Fibres, ~ 2.5 diameter
	Pentane	Fibres, 1 diameter
Polystyrene	Pentane	Spheres, 20
		Fibres, 0.8–2.5 diameter

[a]CDFM, chlorodifluormethane.

formed during the expansion, solid may condense to yield a thin solid film.

There is a possibility of fibre formation from supercritical solutions when an organic polymer is the solute. The polymer may form either a liquid or solid after decompression, depending on the polymer melting temperature relative to the post-expansion temperature. Fibres are generally formed when the expansion is carried out in a capillary nozzle and the post-expansion temperature is close to the melting temperature of the polymer so that the polymer deposits as a liquid on the nozzle walls. RESS expansion of polymers yields powders when the temperature is not close to the melting temperature of the polymer. The extremely short times of product formation in the expansion of supercritical solutions also makes it possible to produce multicomponent mixtures of powders with uniform distribution of the components. Such powders have tremendous commercial potential in the ceramic industry.

The pressure, temperature, and supersaturation profiles in and outside the expansion device determine the size of the crystals produced in the RESS process and the crystal size distribution. The pressure and temperature profiles in the expansion device can be modelled by solving the mass, energy, and momentum conservation equations for the adiabatic expansion of the supercritical fluid. Typical profiles for a capillary nozzle are shown in **Figure 4**. The free-jet expansion after the fluid exits

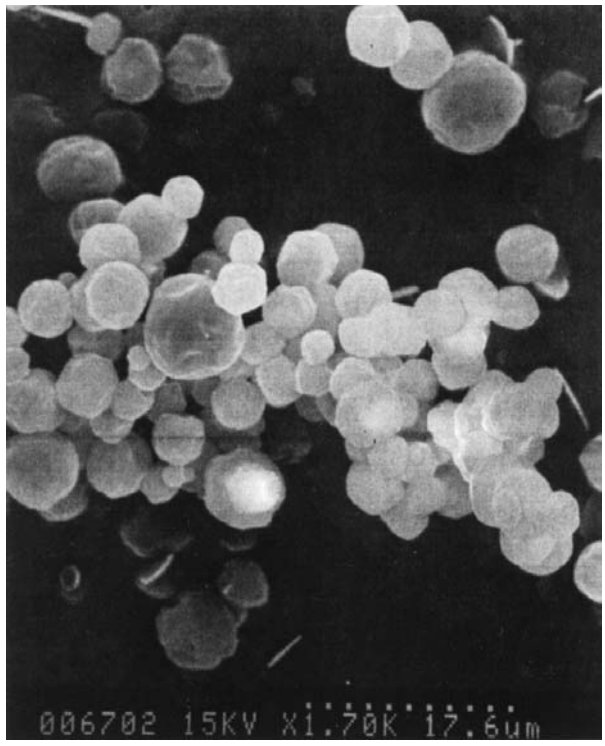

Figure 3 SEM micrographs of *n*-octacosane crystals obtained in RESS expansion of a CO_2 solution.

the device can also be modelled and is shown schematically in **Figure 5**. Calculations have shown that a Mach disc is formed a few nozzle diameters downstream from the nozzle exit and that the pressure and temperature are very low in the region between the exit and the Mach disc. High supersaturations may therefore be obtained before, in, or after the fluid exits the nozzle and the exact profile must be known

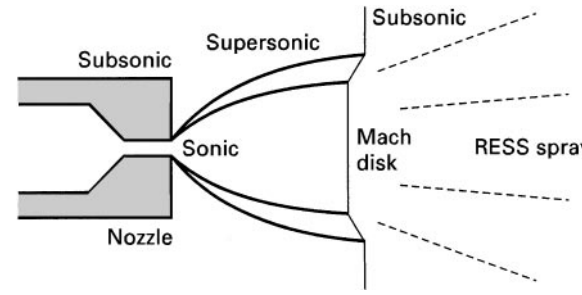

Figure 5 Free jet expansion of a supercritical fluid solution from a capillary.

if control of the crystal size and crystal size distribution is desired.

Crystallization by the Addition of a Supercritical Antisolvent (SAS)

In the supercritical antisolvent (SAS) process, a pressurized fluid is used as an antisolvent for precipitating a solid that is dissolved in a liquid solvent. The supersaturation of the solid is created by the volumetric expansion of the liquid solution. After crystallization of the solute, it is possible to remove the antisolvent completely by pressure reduction. Control of the particle size distribution is also possible by manipulation of the process variables.

Many organic solvents show at least partial miscibility with gases and supercritical fluids at moderate to high pressures. Introduction of the SCF antisolvent into such organic solvents will result in dissolution of the antisolvent and an expansion of the liquid phase. This expansion can be quite significant, as shown for ethyl acetate–carbon dioxide mixtures in **Figure 6**. In

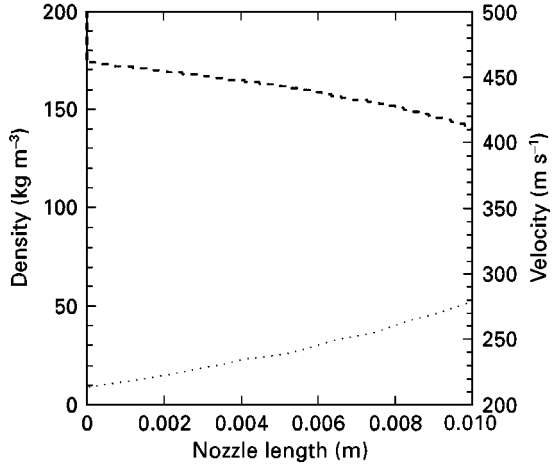

Figure 4 Density and velocity profiles in a RESS expansion of CO_2 through a capillary nozzle at 443 K and 17.39 MPa. ···, Velocity; – – – –, density.

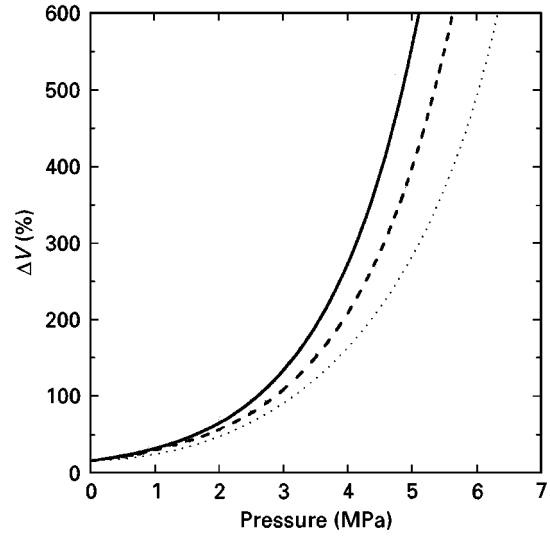

Figure 6 Volumetric expansion of a ethyl acetate with CO_2. ———, 25°C; – – – –, 30°C; ···, 40°C.

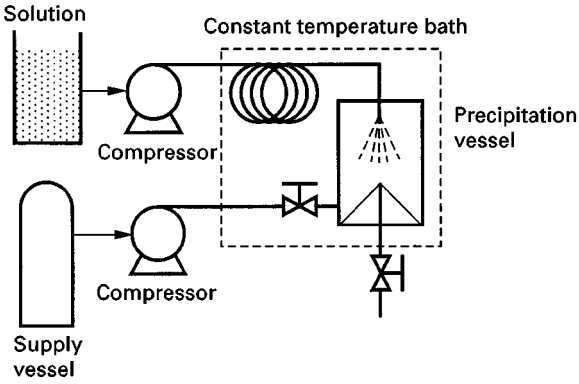

Figure 7 Experimental apparatus for a batch SAS process.

this figure, $\Delta V(\%)$ is defined as follows:

$$\Delta V(\%) = 100\{V(p, T) - V_0\}/V_0 \qquad [1]$$

where $V(p, T)$ is the volume of the liquid phase when loaded with antisolvent, and V_0 is the volume of the pure liquid phase at atmospheric conditions. This expansion is large near the critical temperature of the antisolvent.

The following requirements must be satisfied for a successful SAS process: the solute must be soluble in the organic solvent at ambient temperatures and insoluble (or sparingly soluble) in the SCF antisolvent. The organic solvent must be at least partially miscible with the SCF antisolvent as described above. Many organic solids satisfy these requirements, although this is not true of inorganic compounds. Inorganic compounds are generally soluble in water or acids such as sulfuric acid, but these solvents do not expand appreciably when contacted with simple gases such as CO_2 or light hydrocarbons. However, many cobalt, nickel iron and chromium salts are soluble in acetone, cyclohexane or *N*-methylpyrrolidone, and these solvents have been used to develop SAS recrystallization processes.

The SAS process may involve antisolvent injection into a liquid phase (gas injection) or liquid solution injection into a SCF antisolvent (liquid injection) operation. Both these processes can be operated continuously or in batch mode.

A typical experimental apparatus for batch operations is shown in **Figure 7**. In the case of gas injection, a vessel is loaded with a known quantity of liquid solution containing the dissolved solute, and then the SCF antisolvent is added to the solution from the top or bottom of the vessel. This causes the liquid phase to expand and the solute to precipitate. The rate of antisolvent addition is an important parameter for the control of morphology and size of the solid particles obtained in this process. Rapid addition of the antisolvent generally leads to smaller and more uniform particles. Slower addition of the SCF can result in a range of particle sizes. The morphology of the particles can also be controlled by the rate of antisolvent addition, and by the organic solvent used to dissolve the solute. Examples of particles precipitated in gas injection operations are summarized in **Table 2**.

In the case of liquid injection, the precipitation vessel is pressurized by the addition of the SCF and then the liquid solution is injected into the vessel. The injected liquid solution is expanded by the dissolving SCF causing the solids to precipitate. In one variation of this type of operation, the liquid solution and the SCF antisolvent are continuously delivered to a

Table 2 Substances processed using SAS with gas injection

Compounds	*Solvent*[a]	*Antisolvent*	*Morphologies, particle size (μm)*
Explosives and propellants			
Nitroguanidine	DMF, cyclohexane	CO_2	Crystals: spheres, snow-balls, starbursts, 1–100
Cyclonite, homocyclonite	Acetone, γ-butyrolactone	CO_2	Crystals, > 200
Cyclonite	Acetone, cyclohexanone	CO_2	Crystals, < 5
Homocyclonite	Acetone	CO_2	Crystals, 2–5
Polymers			
Aramids	DMF	CO_2	Crystalline spherulites, 1–10 long fibres
Polyhyaluronic acid methyl ester	DMSO	CO_2	Spheres, 0.3
Pharmaceuticals			
Abecarnil	Isopropyl acetate	CO_2	Crystals, 10–50
Inorganics			
Cobalt chloride	Acetone	CO_2	Crystals

[a] DMF, Dimethylformamide; DMSO, Dimethyl sulfoxide.

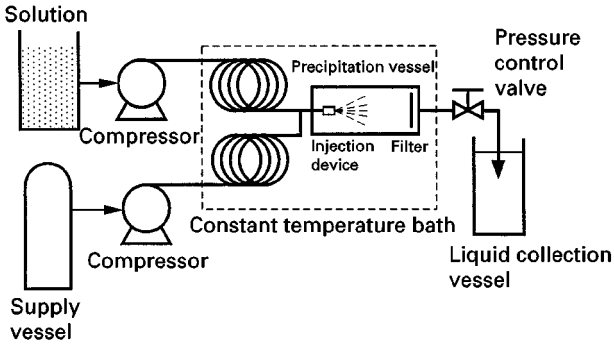

Figure 8 Experimental apparatus for a continuous liquid injection SAS process.

precipitation vessel in an apparatus similar to that shown in **Figure 8**. In this operation, solids precipitate continuously in the vessel, as the gas phase (SCF) leaves through a pressure-control valve. The valve also maintains the pressure inside the vessel constant. The ratio of the two flow rates (flow rate of the liquid solution and that of the SCF antisolvent), and the type of contact (co-current or countercurrent) can be important in the evolution of the precipitation process. Continuous precipitation using liquid injection has been given various acronyms such as precipitation by compressed antisolvent (PCA), aerosol solvent extraction system (ASES) and solution enhanced dispersion by supercritical (SEDS) fluid process. These processes have been carried out using slightly different precipitation procedures and in slightly different apparatus. At the end of the precipitation procedure, the vessel is washed with antisolvent to remove the liquid. This washing procedure is necessary because any liquid solvent remaining after depressurization could redissolve the solute.

Examples of solutes precipitated using liquid injection are summarized in **Table 3**. These examples include polymer microspheres, where the temperature of the precipitation vessel and the concentration of polymer in the solution play an important role in determining the morphology. There is a tendency for the polymer particles to agglomerate when the temperature is higher than the glass transition temperature of the polymer. Also, a high polymer concentration in solution produces fibres. On the other hand, micron-sized particles with a narrow size distribution can be obtained by adjusting the conditions of co-solvent and injection devices.

The liquid solution injection device plays a key role in SAS operations. The injector is designed to produce very small liquid droplets that expand in the precipitation vessel. Various geometries have been proposed to achieve this, including nozzles, capillaries, vibrating orifices and co-axial capillaries. The precipitation vessel must be designed to mix two phases and to

Table 3 Substances processed using SAS with liquid injection

Compounds	*Solvent*[a]	*Antisolvent*	*Morphologies, particle size (μm)*
Polymers and biopolymers			
Poly (L-lactide)	CH_2Cl_2	CO_2	Spheres, 1–10
Polystyrene	Toluene	CO_2	Spheres, 0.1–20 Microballoons
Polyacrylonitrile	DMF	CO_2	Microfibrils, hollow fibres
Pharmaceuticals			
Insulin, catalase, trypsin, lysozyme	DMSO, DMF	CO_2	Spheres, 1–5
Methylprednisolone acetate	THF	Ethane	Crystals, 2.5–8.5
Hydrocortisone acetate	DMF	CO_2	Crystals, 2.5–8.5
Salmeterol xinafoate	Acetone	CO_2	Crystalline modification, 1–10
Sodium cromoglycate	Methanol	CO_2	Spheres, 0.1–20
Tetracycline	NMP	CO_2	Spheres, 0.15–0.6
Salbutamol	DMSO	CO_2	Long rods, 1–3 length
Catalysts, inorganics			
Red lake C, pigment yellow 1, pigment Blue 15	Acetone	CO_2	Spheres, > 0.6
Barium acetate, copper acetate	DMSO	CO_2	Spheres, 0.1–0.4
Yttrium acetate	DMSO	CO_2	Spheres, 0.1–0.3
Samarium acetate, neodymium acetate	DMSO	CO_2	Spheres, 0.1–0.3
Zinc acetate	DMSO	CO_2	Spheres, 0.05–0.02

[a] DMF, dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; NMP, *N*-methyl-2-pyrrolidone.

provide heating/cooling. Filtration of the particles at high pressures also requires special equipment.

In summary, both RESS crystallization and SAS crystallization appear to be promising methods for generating supersaturation and therefore represent alternatives to conventional crystallization. Such alternatives may prove attractive in applications such as polymer and pharmaceutical processing, or in particle design for drug delivery. It is possible to obtain a variety of morphologies and particle sizes in these processes by proper choice of conditions and expansion devices. However, *a priori* design of supercritical crystallization processes is not yet possible because the interaction between phase equilibria, expansion paths, and crystallization kinetics in these processes is not yet well understood.

See also: **II/Crystallization:** Control of Crystallizers and Dynamic Behaviour; Polymorphism.

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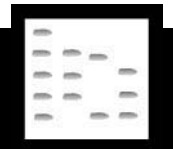
SUPERCRITICAL FLUID EXTRACTION–SUPERCRITICAL FLUID CHROMATOGRAPHY



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Introduction

The transfer of extracted analytes to a chromatography column can be either offline or online. In offline analysis, the extracted analytes are collected and then an aliquot is manually transferred to the chromatography system. Online analysis is where the extracted analytes are automatically transferred to the analytical column. The intrinsic problems with offline collection are that sample loss and contamination are possible, the process is difficult to automate and the sample must be diluted with solvent to allow transfer, resulting in higher detection limits. Coupling extraction and chromatography minimizes many of these problems. Supercritical fluid extraction (SFE) and supercritical fluid chromatography (SFC) are ideally suited for coupling together as the most frequently used solvent, carbon dioxide (CO_2), is the same for both techniques. In the case where pure CO_2 is used, the extracted analytes can be deposited at the start of the analytical column simply by reducing the pressure, and chromatography started by increasing the pressure again. Capillary SFC (cSFC) benefits particularly from online methods. The columns are small and easily overloaded, particularly with injection solvent. For example, a 1-μL injection occupies 0.5 m of a 50-μm i.d. column. Larger injections can easily cause band broadening and peak splitting. The limitation of injection size increases the detection limit. A logical method of solving the intrinsic problems of offline collection and cSFC is to link them online.

Samples for which SFE–SFC is Applicable

The main alternatives to SFC are GC and HPLC. Online coupling of SFE and HPLC is difficult, as the presence of gaseous CO_2 is incompatible with HPLC