Instrumentation

T. A. Berger, Berger Instruments, Newark, DE, USA

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Introduction

Supercritical fluid chromatography (SFC) is an instrumental technique in which a small volume of a sample is entrained in a solvating mobile phase, held near its critical point, and is swept through a stationary bed of particles, or a tube coated with a liquid film. The components of the mixture are separated from each other through differential solvation by the mobile phase, and retention by the stationary phase. SFC can be viewed as a transition technique between GC and HPLC.

A fluid is 'supercritical' when it is raised above its characteristic 'critical point' (a critical temperature, T_c, and a critical pressure, P_c). Most fluids used as SFC mobile phases are gases at room temperature and pressure but all are easily liquefied by raising the pressure. In a supercritical fluid, the molecules are forced close together by an externally applied pressure. Some but not all supercritical fluids act as a solvent. Changing the density of such fluids changes their solvent strength.

Packed vs. capillary columns There are two SFC techniques, using either open tubular (capillary), or packed columns, each of which exploits a different aspect of the technology. Although in 1958 Lovelock originally proposed SFC as a capillary technique, for its first 20+ years SFC was exclusively performed with packed columns. The first commercial instrumentation for packed-column SFC was introduced in 1982 as a modification kit for a HPLC. Capillary SFC was not viable until the late 1970s when stationary phases were first bonded to the surface of the column. Earlier stationary phases were washed out of the column by the SFC mobile phase. In 1981, the groups of Lee at Brigham Young University and Novotny at Indiana University, combined bonded stationary phases with SFC and published the first realistic capillary (open tubular column) SFC chromatograms.

Subsequently, a rather unfortunate controversy raged for some years as to whether capillary or packed columns were 'better'. However, the two techniques are sufficiently different that almost any attempt to compare them will show one or the other unfavourably.

Open tubular or capillary SFC (CSFC) is almost always performed using pressure programming of pure carbon dioxide as the mobile phase. CSFC can be thought of as an extension of gas chromatography (GC) to higher molecular masses, since the solvation energy of the fluids can replace thermal energy. Elution temperatures can be 200°C or more lower than in GC (i.e. carbon dioxide at 150°C vs. GC with hydrogen at 400°C). The column temperature is almost always maintained at >50°C above the critical temperature.

The fluid solvent strength can be changed in a predictable manner by programming the fluid density (usually pressure, sometimes temperature, rarely both). Carbon dioxide is compatible with the flame ionization detector (FID). The most common uses of CSFC are for the separation of light polymers, surfactants and other homologous series.

Carbon dioxide has a solvent strength similar to hexane or a fluorocarbon. Relatively nonpolar solutes such as hydrocarbons are miscible with carbon dioxide. Polar solutes such as sugars or amino acids are virtually insoluble in carbon dioxide.

Packed columns are, inherently, 10 to 100 times more retentive than capillary columns, due to their higher surface area to void volume ratio. This makes it more difficult to elute molecules from packed columns using pure carbon dioxide. On the other hand, the low polarity of carbon dioxide is incompatible with the solvation of polar molecules.

The most widely used approach to extending SFC to more polar solutes has involved the use of packed columns with binary or ternary mobile phases. Binary fluids consist of a normal liquid such as acetonitrile or methanol mixed with carbon dioxide. Ternary mobile phases consist of a fraction of a percent to several percent of a third, even more polar component, such as trifluoroacetic acid or isobutylamine, added to the liquid modifier. The use of modifiers was pioneered by Jentoff and Gouw in 1969. The use of additives was pioneered by Berger *et al.* starting in 1988.

Once a modifier is added to the mobile phase, the composition of the fluid tends to dominate over its density in determining solvent strength. Pressure programming becomes a secondary control variable. The enhanced solvent strength of modified fluids tends to be less compatible with the inherent low retentivity of capillary columns.

Packed-column SFC can be thought of as an extension of HPLC, using modifier concentration gradients of binary or ternary mixtures near (within 50°C above or below!) their critical temperature. Packed-column SFC is a form of normal-phase chromatography, complementing reversed-phase HPLC, but with

superior speed, and efficiency. The low temperatures used make packed-column SFC ideal for separation of moderately polar, thermally labile molecules. The primary detection scheme with packed columns is UV absorption.

Packed-column and capillary SFC are two different techniques sharing part of a name. As with GC and HPLC there is clearly an overlap between the two. Packed columns are sometimes used with pure carbon dioxide, pressure programming and FID detection, to perform some of the applications more commonly performed by capillary SFC. Some relatively polar solutes are soluble enough in carbon dioxide to allow elution with capillaries and pure carbon dioxide.

Unified chromatography A further problem in defining these techniques is the fact that there are no real borders between GC, SFC and HPLC. One can start an experiment, above the mobile phase critical temperature (T_c) (i.e. as GC), then raise the pressure above the critical pressure (P_c) (to SFC), then drop the temperature below T_c (to LC). In the process the name of the technique changes from GC, to SFC, to HPLC, but there is never more than one phase present, and there is never a phase transition. Changes in solute retention, viscosity, diffusion coefficients, etc., are smooth and continuous, even when the definition of the fluid changes. In packed-column SFC, modifier concentration can be programmed from 0 to 100%. At some intermediate (but not obvious) concentration, the definition of the technique changes from SFC to HPLC. The characteristics of interest in SFC are summarized in **Table 1**. SFC has additional special advantages when scaled up for preparative use.

There has been some effort to promote SFC as a form of unified chromatography. SFC instrumentation can typically also perform HPLC, and at least some GC, whereas instrumentation for the other techniques cannot perform much SFC.

Table 1 Characteristics of interest in SFC

A compressible fluid that acts as a solvent
Solvent strength changes with a physical parameter (pressure)
Very wide range of solvent strength using one binary pair of solvents
Low viscosity
long, high efficiency columns (i.e. >2 m with 5 μm particles)
low pressure drop at high flow with smaller particles
Higher speed than HPLC – higher diffusion coefficients
3–10 × higher throughput
much faster re-equilibration
rapid method development
Compatibility with GC detectors, like the FID, ECD, NPD
Transparent in the UV
Complementary selectivity to reversed-phase HPLC
Low cost, environmentally friendly solvents, easily removed

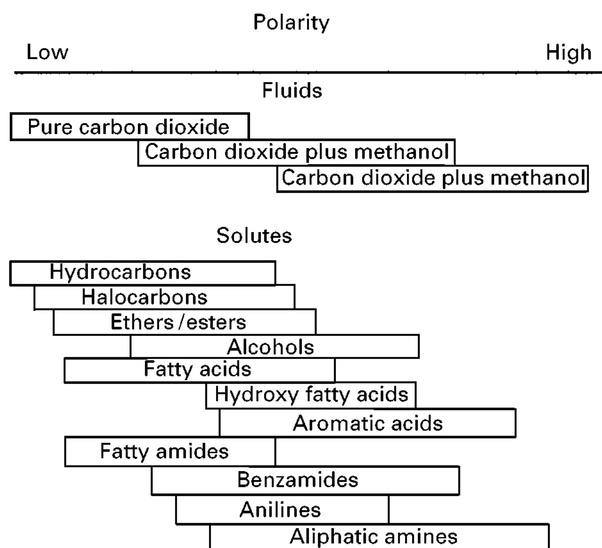

Figure 1 A summary of solute families which have been separated by SFC.

Solutes Typical samples separated by packed column SFC consist of low to moderate polarity organic solutes with relative molecular masses $\leqslant$10 000 Da. As a 'rule of thumb', solutes that can be dissolved in methanol or a less polar solvent are good candidates for SFC. On the other hand, solutes requiring water or buffered or pH adjusted water environments are a poor choice. Solute families which have been separated by SFC are summarized in **Figure 1**. Low polarity solutes are to the left, higher polarity solutes to the right. At the bottom of the figure, there is an attempt to relate the nature of the mobile phase needed to elute the various solute families.

Fluid Characteristics

Other pure fluids used A few common fluids are listed in **Table 2**. However, carbon dioxide remains the fluid of choice for SFC in spite of its inherently low polarity. It has a modest critical pressure and temperature, is inexpensive, readily available, safe, and compatible with the FID.

Some early work used supercritical pentane mixed with alcohols at >235°C. The flammability of such mixtures means that today they are rarely used. Nitrous oxide has characteristics similar to carbon dioxide but is also an extreme oxidizer. It should not be mixed with fuels such as organic modifiers. Fluids like ammonia are also obviously potentially dangerous and corrosive.

Table 2 Critical parameters of some of the pure fluids used for SFC

	Critical temp. (°C)	*Critical pressure (atm)*
Carbon dioxide	31.1	72.8
Nitrous oxide	36.4	71.5
Sulfur hexafluoride	45.5	37.0
Trifluoromethane	25.9	47.7
Ammonia	132.3	111.3
n-Pentane	196.6	41.7
Methanol	239.4	79.9
Water	374.1	217.6

Some chlorofluorocarbons have interesting properties but have been banned due to their ozone depletion potential in the environment. Several replacement fluorocarbons, especially F-134a, have recently shown potential for extending the polarity range available with a pure fluid. Sulfur hexafluoride has been used as a mobile phase, particularly in the study of hydrocarbons, but is also an ozone depleter. Its main utility is its compatibility with the FID, although a combustion product is hydrofluoric acid. Fluorocarbons exhibit the same problem.

Density At constant temperature, the log of retention in SFC is a nearly linear function of density. Changing the density of the mobile phase can result in a change in retention of 3 or 4 orders of magnitude. Using carbon dioxide as the mobile phase, the usable density range is from gas-like densities (i.e. $0.002\ \mathrm{g\ cm^{-3}}$) to a density similar to water ($>0.95\ \mathrm{g\ cm^{-3}}$). The typical pressure range is 60 to 400 or 600 bar. The typical temperature range is from 40 to 250°C, but temperatures above 150°C are seldom used.

Modifiers None of the pure fluids used in SFC are polar, and polar solutes are typically insoluble in them. Solvent polarity can be increased by adding polar modifiers, such as alcohols to the nonpolar main fluid. The increase in solvent strength is nonlinear. The addition of 2% methanol to carbon dioxide yields a fluid with the polarity one might expect from 10% methanol. This enhanced solvent strength is due to a phenomenon, sometimes called clustering, where the polar modifier molecules tend to cluster together, creating small pockets of greater than expected polarity. Polar solutes tend to be solvated within, and by, these clusters. The clusters are too small to be considered micelles or a different phase. Individual modifier molecules freely exchange in and out of the clusters.

Once a polar organic modifier is added, the composition of the mobile phase dominates over its density in determining the chromatographic retention of a solute. Gradient elution through composition programming becomes the primary means of retention control. Pressure control becomes a secondary variable. The densities of most binary fluids are unknown, and equations of state of binary pairs are inaccurate, making density programming problematic.

In SFC the composition of the mobile phase can be programmed from 0 to 100% modifier. Methanol is among the most polar liquids that is completely miscible with carbon dioxide. On Snyder's solvent strength scale widely used in HPLC, hexane has a strength of 0, water has a strength of 10.4, and methanol has a strength of 5.1. Thus, the solvent strength can be programmed over approximately half the solvent strength scale available in chromatography, using a single binary pair of common solvents. Changing the identity of the modifier can change selectivity.

Additives The polarity range amenable to SFC has been extended significantly by the use of ternary mobile phases consisting of carbon dioxide, methanol, and a low concentration of a much more polar substance called an additive. Without an additive most primary aliphatic amines and most polyfunctional acids will not elute or elute with severe tailing. The inclusion of additives often results in elution of symmetrical peaks with high efficiency. Additives appear to function through multiple mechanisms, although much more work is still required to understand their role better. The most effective additives usually contain stronger members of the same functional group. For example, trifluoroacetic acid is usually effective in improving the elution of other acids, while isopropylamine is effective in eluting amines. Ion pairing, where an acid is added to a base or a base to an acid is seldom effective.

Viscosity One of the more interesting aspects of the fluids used as mobile phases in SFC is their low viscosity, which is more gas-like than liquid-like, even at high densities. For example, the viscosity of carbon dioxide is typically an order of magnitude lower than water. At 20°C and 200 bar the density of liquid carbon dioxide is over $0.9\ \mathrm{g\ cm^{-3}}$, yet its viscosity is 10.3×10^{-4} poise. At 20°C and atmospheric pressure, the viscosity of water is 100.2×10^{-4} poise. Low viscosity clearly produces the practical advantage of minimizing pressure drops across columns. Very long, high efficiency columns can be used. Compared to HPLC, an SFC column can be run at 2.5 times the flow with 0.25 times the pressure drop. As

the modifier concentration in binary fluids increases, the viscosity of the fluid approaches that of normal liquids.

Diffusion coefficients and speed of analysis Any one column can theoretically be used for GC, SFC or HPLC. Columns can be characterized by the number of 'plates' they exhibit. A column generating many plates can resolve more complex mixtures and is said to have higher efficiency than one generating only a few plates. Another way of describing column efficiency is plate height, H, which is the distance along the column equivalent to one plate. The total number of plates, N, a column exhibits corresponds to the total length, L, divided by the plate height, H ($N = L/H$).

The van Deemter equation, which can be written as: $H = A + 2[D/u] + k[u/D]$, relates the plate height, H, to the solute binary diffusion coefficient in the mobile phase, D, and the linear velocity of the mobile phase through the column, u. Plots of H vs. u show that the minimum value of H (yielding maximum resolving power for a given column) is the same, regardless of the technique, but the optimum speed for pushing the mobile phase through the column depends on the diffusion coefficient of the solute in the mobile phase.

In GC, values for D are of the order of 0.1 to 1 $cm^2 s^{-1}$. In HPLC, a typical D is of the order of $10^{-5} cm^2 s^{-1}$. Diffusion coefficients in SFC range from 0.01 down to $10^{-4} cm^2 s^{-1}$. As usually practised, SFC is at least 100 times slower than GC but up to 10 times faster than HPLC. As the modifier concentration is increased in binary fluids, diffusion coefficients approach those in HPLC.

Instrumentation

By the early 1970s, it was generally recognized that HPLC was simpler, easier and more generally applicable than SFC. As an indication of how widespread that conclusion was, no commercial equipment for SFC existed until around 1982. By 1985, commercial SFCs for use with capillary columns appeared. More recently, several companies have introduced instrumentation specifically designed for packed-column SFC or for both packed- and capillary-column SFC.

Instrumentation for Capillary SFC

A schematic representation of the instrumentation required for capillary SFC is shown in **Figure 2**. In capillary SFC, the main method for changing retention is to change the mobile phase density. Pressure is the primary control variable, temperature is a secondary control variable. The pump is used as a pressure source. Pressure or density programming is used much like temperature programming is used in GC. Both negative and positive temperature programmes have been used.

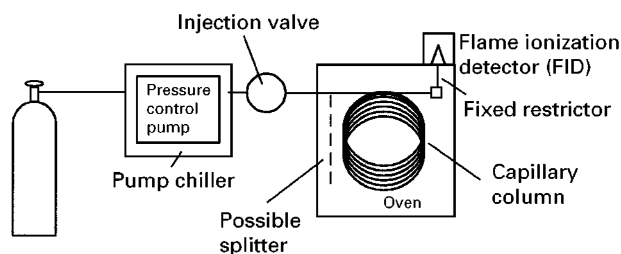

Figure 2 Schematic representation of instrumentation required for capillary SFC.

Columns The most commonly used capillary columns are 50 or 100 μm i.d. and 10 m long, they are made of fused silica tubing. A wide range of stationary phases are available, including many that are more polar than those used in GC. The optimum mobile phase flow rate is inversely related to the density of the fluid and is of the order of 0.1 to 1 $cm\ s^{-1}$.

Pumps The most common pumping systems for CSFC are built around 100 to 250 cm^3 syringe pumps, capable of generating pressures of 400 to 600 atmospheres. Syringe pumps are ideal for controlling pressure. When combined with a computer, the pressure of the pump and the temperature of a column oven can be used to calculate the pressure profile required to generate density ramps.

Syringe pumps can be difficult to fill with a single phase. Any gas present must be re-liquefied before the pump can deliver high pressures. Liquefying the gas can require most of the piston displacement. It has become a common practice to purchase carbon dioxide in cylinders with a helium headspace, raising the pressure to a point where the carbon dioxide is always a liquid. In addition, the syringe is chilled using a recirculating bath, further helping to liquefy the fluid.

Capillary columns are seldom used with mixed mobile phases, due partly to the inherent low retentivity of the columns and partly to instrumental difficulties using syringe pumps to generate composition gradients. Syringe pumps cannot control both pressure and (relative) flow simultaneously. When modified fluids are used with syringe pumps they are usually either premixed in a cylinder or made by adding a known volume of a liquid modifier to the syringe then filling with the main fluid (no composition gradients).

Neither binary fluids premixed in a cylinder nor helium headspace should be used. As such cylinders are used up, the concentration of modifier and/or helium in the carbon dioxide changes, changing the fluid solvent strength. Retention can change by a factor of 2 between a nearly full and a nearly empty cylinder.

Flow control reciprocating pumps can be used as a pressure source, when used with a back-pressure regulator (BPR), as shown in **Figure 3**. The pump(s) deliver a large (i.e. 2 mL min^{-1}) flow of mobile phase to a vessel located upstream of the BPR. A tee allows some of the flow to be drawn off to the injection valve and column. The BPR can be programmed to change the pressure in the vessel. The fluid leaving the BPR can be vented or recycled to the inlet of the pump.

Injection High pressure injection valves similar to those for HPLC are used to introduce liquid samples into the chromatograph. Unfortunately, an ideal injection volume for a 50 μm i.d. column should be <4 nL (a plug 2 mm, 40 column diameters long, in the column). Since there are no fixed loop injectors with such small volumes, split injection schemes are most often used. Timed split injectors move the rotor of a 0.060 to 0.2 μL internal loop valve back and forth fast enough so that only part of the loop volume is pushed on to the column.

Traditional flow splitters use a 'tee' mounted just downstream of the valve. A piece of larger inner diameter (i.e. 0.5 mm) stainless steel (s.s.) tubing connects the valve to the tee. The column is usually pushed through the tee and up inside the s.s. tube until it touches the valve rotor, then it is pulled back 1–2 mm. A larger volume (i.e. 0.1–0.5 μL) sample loop is switched in-line and swept with 10 to 100 times the column flow. Most of this flow and sample is vented through a restrictor mounted in the side arm of the tee.

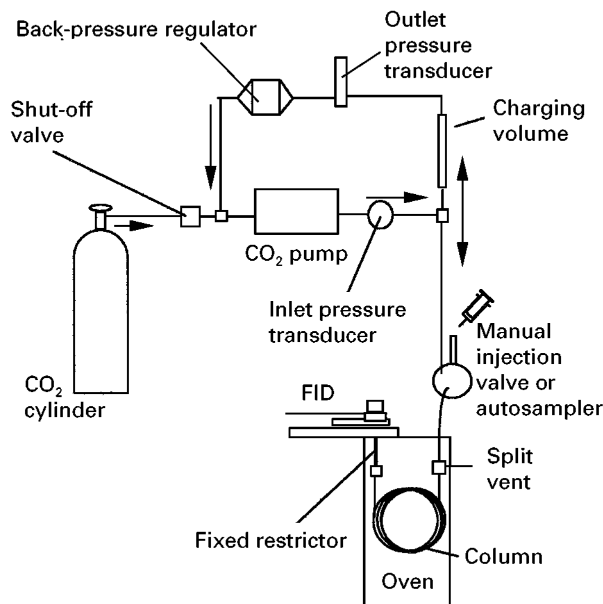

Figure 3 Flow control reciprocating pump used as a pressure source when used with a back-pressure regulator.

Split injections tend to give poor reproducibility, due mostly to the difficulty in mixing a liquid sample with a much lower density supercritical fluid a very short time before the split. Many alternate injection schemes have been developed to allow larger injections and/or better reproducibility.

Retention gaps (an empty length of deactivated capillary tubing) allow much larger injections with better reproducibility. By carefully controlling the initial temperature and pressure, the sample can be distributed as an annular film along a retention gap, with the mobile phase passing through the film, along the axis of the tube. Since the fluid rapidly becomes saturated with the sample solvent, only the solvent at the head of the gap is vaporized or dissolved. The film of solvent progressively becomes shorter, while the sample becomes concentrated in the remaining film. When all the solvent is removed, the sample components are concentrated in a narrow band on the retention gap, and are then differentially eluted with a density programme.

Ovens The temperature of the fluid is important in determining its density and thus the retention of solutes. However, temperature has an effect on retention independent of density. To programme an increase in density using only the temperature, the user would start at a high temperature and decrease temperature over time.

In CSFC, the temperature is almost always held at least 50°C higher than the critical temperature. With carbon dioxide as the mobile phase ($T_c \cong 31$°C) the most common temperatures used are between 100 and 150°C. Since CSFC most often uses GC detectors, along with these higher temperatures, large GC-like ovens are used.

Restrictors With CSFC, the flow of the mobile phase through the column is only indirectly controlled using fixed restrictors mounted on the outlet of the column. Increasing the column head pressure causes large changes in flow (and efficiency) in the column. There are no devices with small enough inner dimensions to allow the pump to act as a flow source (controlling linear velocity), while independently controlling the outlet pressure, without destroying the separation. There have been numerous schemes to minimize changes in flow through restrictors caused by pressure

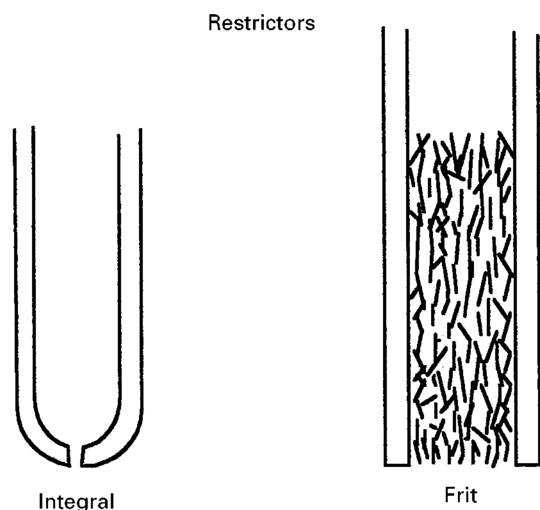

Figure 4 Two types of restrictors in common use.

changes, but they are all relatively complicated or expensive and have not been widely adopted.

There are two types of restrictor in common use: integral and frit, as shown in **Figure 4**. Integral restrictors are 1–2 μm diameter, <25 μm long pinholes formed at the end of a piece of fused silica tubing. They were originally formed on the end of the column and were integral to it. Today, they are usually made of a separate piece of tubing and attached to the column using a butt connector.

Frit restrictors consist of a porous plug of material formed inside a piece of 50 μm i.d. fused silica tubing. The plug is usually 1–2 cm long. Frits have many small tortuous paths.

Integral restrictors have better flow vs. pressure characteristics but are much easier to plug than frit restrictors. However, since the pressure drops along the full length of the frit, the density at its outlet can be low so that heavier solutes may drop out of solution and are lost inside the frit. For high molecular mass materials, the only choice is an integral restrictor. All restrictors plug over time, changing flow characteristics through the column. Restrictor performance is the weakest link in SFC instrumentation.

Detection One of the greatest advantages of CSFC with carbon dioxide is its compatibility with the flame ionization detector (FID). The FID is universal and exhibits uniform response factors for hydrocarbons, while allowing a change in solvent strength through pressure or density programming. The restrictor at the end of the column is mounted directly in the base of the detector. The fluid expands to a gas in the flame.

Although both UV and fluoresence detectors have been used in CSFC, the light pathlength is typically the column diameter (i.e. 50 μm). Standard HPLC flow cells have pathlengths 200 times longer. Both detection limits and dynamic range are, thus, compromised.

Instrumentation for Packed-column SFC

The instrumentation used for packed-column SFC can be somewhat more complex than capillary SFC as shown in **Figure 5**. Most of the hardware, including injection valves, columns and some detectors, are the same or similar to that used for HPLC. Binary and ternary fluids are the norm, although low polarity solutes can often be eluted with pure carbon dioxide. Changing the mobile phase composition is the most effective way to change solute retention. Composition gradient elution is most common, although pressure, temperature and even flow can also be programmed. Selectivity is often most easily changed by changing the temperature. Pressure is a secondary control variable.

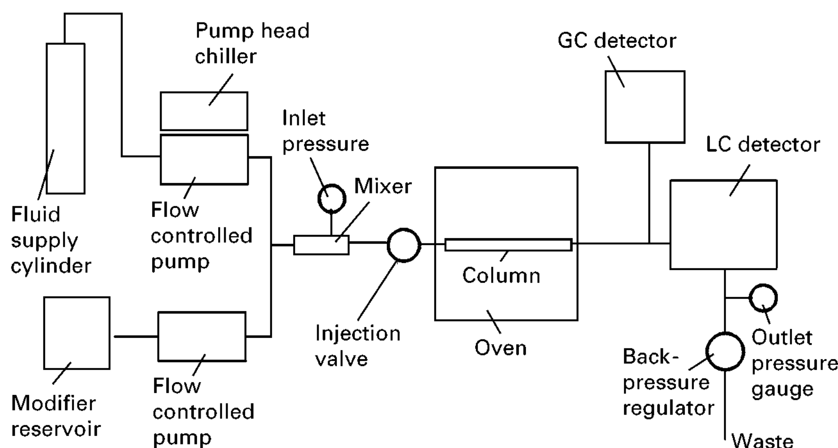

Figure 5 Instrumentation for packed-column SFC.

Columns Standard HPLC columns are used for packed-column SFC. The most common have inner diameters of 2 to 4.6 mm, and are 15 to 25 cm long. Both 1 mm and micropacked fused silica are also sometimes used. The most common packings are 3 to 5 μm diameter totally porous silica, although many other materials have been used. SFC is a 'normal-phase' technique, making the use of more polar bonded phases commoner. The biggest change from HPLC is the growing use of longer packed columns, as much as 2.2 m in length.

Pumps The most common pumping systems in packed-column SFC use multiple high pressure reciprocating pumps operated as flow control devices. Since the main fluid is supplied in a high pressure gas cylinder, gradient switching valves cannot be used to mix modifier with the fluid in SFC. One high pressure pump is used to deliver the main fluid (SF pump) and another is used to pump modifier(s). Used in conjunction with a back-pressure regulator, properly designed pumps allow independent control of flow, composition and pressure.

The head of the SF pump is chilled to ensure the fluid is pumped as a liquid. However, even as a liquid, the fluids used still have a compressibility much higher than normal liquids. To accurately pump these fluids, the pumps need both an extended compressibility compensation range, and the ability to dynamically change compressibility compensation when the pressure and temperature (and composition) are changed. Slightly modified HPLC pumps usually have an inadequate range of compressibility compensation, and never dynamically compensate for the changes in compressibility which accompany pressure and/or composition changes. Using HPLC pumps for SFC results in highly inaccurate and non-reproducible flows and compositions.

Injection Injection is accomplished using standard HPLC injection valves operated in either fixed or partial loop modes. Care must be exercised in choosing the volume and polarity of the sample solvent. SFC is usually a normal-phase technique. Common sample solvents, like methanol, are stronger solvents than the mobile phase. If too much of such a polar solvent is injected, peaks can be distorted and broadened. Injection volumes up to 10 μL can usually, but not always, be tolerated. Smaller amounts of water can be directly injected but only under carefully chosen conditions. Decreasing the polarity of the sample solvent or injecting smaller amounts reduces or eliminates the problem.

Oven The most common temperature range for packed column SFC with binary or ternary fluids is 30 to 50°C, although both higher and lower temperatures are used. With pure carbon dioxide, the temperature is usually held at $>60°C$.

Since temperature adjustment often has dramatic impact on selectivity, control of the column temperature is more critical than in HPLC. For the separation of enantiomers, subambient temperatures are often desirable. Ovens similar to GC ovens with cryogenic cooling, Peltier heated/cooled ovens, and recirculating baths are all used.

Pressure control Pressure is controlled using a back-pressure regulator mounted at the downstream end of the system. The BPR is used in conjunction with a pressure transducer and feedback loop. Early regulators were mechanical but today are electromechanical, allowing complex programming of the system outlet pressure. Several commercially available back-pressure regulators have small internal volumes which allow peak collection after the device.

Detection Pure carbon dioxide and the FID and often the UV detector can be used to study fats, waxes, silicones, hydrocarbons and other low polarity solutes, where modified fluids are unusual.

Many other GC detectors are compatible with both pure and modified fluids and have been used with either packed or capillary columns. These include: the electron capture detector (ECD) for the study of explosives, flame retardants, pesticides, derivatives of fatty acids, etc.; the thermionic or nitrogen–phosphorus detector (TID or NPD) for the study of pesticides, caffeine in beverages, and many small drug molecules; the sulfur (petroleum, pesticides) and nitrogen chemiluminescence (similar applications to the NPD) detectors; the flame photometric detector (FPD)(petroleum), as well as others. These detectors are often used with packed columns by splitting off a small fraction of the total column effluent through a fixed restrictor.

There are many hundreds of applications of both pure and modified mobile phases using the UV/VIS detector in the speciality chemical, petroleum, pharmaceutical and agricultural chemical sectors. Standard HPLC UV detectors, including photodiode array detectors, need only a high pressure flow cell to become compatible with SFC (fluid density in the cell approaches 0.9–1 g cm^{-3}). Carbon dioxide is completely transparent to below 190 nm. Mixed with acetonitrile or methanol, short wavelengths can be used to maximize detection limits.

Fluorescence detectors also require a high pressure flow cell, complicated by the need for light paths at 90° to each other. Several high pressure 'chiral' detectors are available for differentiating D and

L isomers. Other detectors that have been successfully used with SFC include: mass spectrometry (MS), Fourier transform infrared (FTIR), and the evaporative light-scattering detectors (ELSD). Most atmospheric pressure ionization HPLC-MS interfaces work equally well, or better, as SFC-MS interfaces.

Future Directions

SFC instrumentation is maturing. The unique requirements for pumping these fluids is slowly becoming widely understood. There are unlikely to be further dramatic improvements in the core technologies. However, a wide range of accessories will appear. As more instruments are sold, the cost of production will tend to drop, making SFC more competitive with HPLC. Development of SFC detector interfaces will continue. Recent results with both mass spectrometry and evaporative light scattering detectors, finally indicate equal or better results than in HPLC-MS, or HPLC-ELSD, but with higher throughput.

User training has been another block to the spread of SFC in industry. One of the chief advantages of packed column SFC in industrial environments, particularly in the pharmaceutical industry, is its similarity with HPLC. Technicians familiar with HPLC have little trouble developing expertise in SFC.

Until recently, SFC has been viewed as a research tool, due largely to the relatively high cost of equipment and the need for an expert operator. As equipment is becoming less expensive, and easier to use, it is beginning to be used in routine analysis. Since the number of analysts involved in research is small compared to the number performing routine analysis, the incorporation of a technique into routine analysis represents a major expansion. This trend should continue, since the surprisingly low cost of operation and environmental friendliness are becoming more widely understood and appreciated.

See also: **II/Chromatography: Supercritical Fluid:** Historical Development; Theory of Supercritical Fluid Chromatography.

Further Reading

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Large-Scale Supercritical Fluid Chromatography

P. Jusforgues and M. Shaimi,
PROCHROM SA, Champigneulles, France

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Introduction

Preparative supercritical fluid chromatography (Prep-SFC) came about at the same time as analytical supercritical fluid chromatography (SFC). During the 1960s and 1970s at the time of the early development of SFC, several authors included fraction collectors at the outlet of their analytical supercritical fluid (SF) chromatographs. However, the technological difficulties encountered kept these attempts somewhat marginal. The real interest in Prep-SFC appeared in 1982 when Perrut patented large-scale Prep-SFC with eluent recycling. Since then Prep-SFC has been studied and developed by several teams and on various scales. During the past decade commercial equipment has appeared and applications are reaching industry.

Principle

Prep-SFC is the result of the collaboration of three techniques:

- the principle of the separation is the same as in analytical SFC;
- the scale, the application and the industrial interest is the same as preparative high-performance liquid chromatography (Prep-HPLC);