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CAPILLARY SUPERCRITICAL FLUID CHROMATOGRAPHY–MASS SPECTROMETRY

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SUMMARY

The physical and chemical characteristics of supercritical fluids have prompted the development of supercritical fluid chromatography (SFC) for the analysis of labile and less volatile compounds. High-resolution chromatographic separations with efficiencies approaching those of gas chromatography and high speed analyses are possible in capillary SFC using pressure programming methods and narrow bore columns. Further refinement of the SFC–mass spectrometry (SFC–MS) interface provides the basis for extension to more polar fluid systems with greater solvating power and the selectivity and sensitivity of mass spectrometric detection. The use of polar modified fluids has been facilitated by advances in understanding of supercritical fluid phase behavior. Fluid mixtures have been prepared for analysis of more polar, higher molecular weight analytes, that allow mild chromatographic temperatures and full exploitation of selectivity offered through control of fluid pressure (*i.e.*, density). Continuing development of the SFC–MS interface has led to designs which can be near routinely applied with fluids such as carbon dioxide, and providing enhanced transport of truly nonvolatile compounds to the mass spectrometer ionization region. These advances also include an SFC interface to a high resolution, dual electric magnetic sector instrument, allowing supercritical fluid solvents to be exploited for on-line extraction–mass spectrometry for characterization of complex, often otherwise intractable, materials.

INTRODUCTION

Chromatography using supercritical mobile phases (supercritical fluid chromatography, SFC) allows high resolution or high speed analyses of many less volatile or labile compounds not amenable to gas chromatography[1–10]. The solvating power of supercritical fluids is directly to fluid density, and the importance of pressure in control of fluid density is well established with fine control of pressure being vital in obtaining high resolution separations for a wide range of compounds[11]. The physical characteristics of supercritical fluids also lead to higher resolution separations when

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compared to high-performance liquid chromatography (HPLC), as well as a much greater compatibility with gas phase detectors. Although capillary SFC with flame ionization detection (FID) has been shown to be applicable to even relatively high molecular weight compounds[5,7] when using fluids giving negligible detector response, the increased interest in fluids and fluid mixtures not compatible with FID[1,12] requires the use of a detector not affected by the chromatographic mobile phase. Mass spectrometry (MS) provides a sensitive and selective detector[1–4] that also allows a variety of techniques to enhance selectivity in an analysis (*e.g.*, alternate ionization modes, high-resolution and MS–MS)[3,4,9,10,13]. With the use of fused-silica capillary columns for chromatography[14,15] and the development of the direct fluid injection (DFI) interface for SFC–MS[9,10,16], the analytical capability of SFC–MS, is currently being realized.

The direct fluid injection interface is based on the rapid expansion of the supercritical mobile phase into a region where ionization can occur. Since proper conditions produce a gas following expansion, conventional electron impact (EI) and chemical ionization (CI) methods are readily adapted. The most vital component of the SFC–MS interface is the capillary restrictor with dimensions selected to yield the desired SFC linear velocity for the chromatographic conditions. Restrictors can be short with a small inner diameter (I.D.) or longer with a larger I.D. Currently there is no one ideal restrictor design for SFC–MS but a number of designs have been investigated[17], each having distinct advantages and disadvantages. The current work will discuss the use of the DFI interface in coupling capillary SFC with MS with particular emphasis on the role of the capillary restrictor in the fluid expansion process. Current applications of the interface, including the interface with high-resolution MS, and new approaches to overcome limitations on the interface imposed for non-volatile compounds will be highlighted.

EXPERIMENTAL

Details of the equipment used for capillary SFC–MS have been described previously[1,2,10,13,18]. A computer-controlled syringe pump was used to generate pressure regulated flow of purified and distilled fluids. Temperature regulation of the chromatographic column was provided by Hewlett-Packard gas chromatograph ovens, and a Valco C14W HPLC injection valve with a 60-nl rotor volume was used for sample introduction. Capillary columns were prepared as previously described[1–3].

Schematic illustrations of the DFI interfaces for high-resolution MS and for operation under high flow-rate conditions are shown in Figs. 1 and 2, respectively. The schematic diagram of the high resolution interface (Fig. 1) shows design modifications that permit coupling of the air-heated DFI probe with the high voltage (up to 8 kV) ion source of a VG ZAB mass spectrometer[18]. Electrical isolation of the DFI probe tip, which is operated at source potential, is maintained by a Vespel segment used to couple the tip to the 1.27-cm (O.D.) stainless-steel probe body. Further, paths for the chemical ionization plasma to contact ground potential are eliminated by the zero dead volume (ZDV) seal on the fused-silica capillary restrictor. This design eliminates high voltage "arcing" which would preclude operation of the CI ion source. The design also includes provisions for direct heating of a capillary stainless-steel tube used to sheath the fused-silica capillary restrictor.

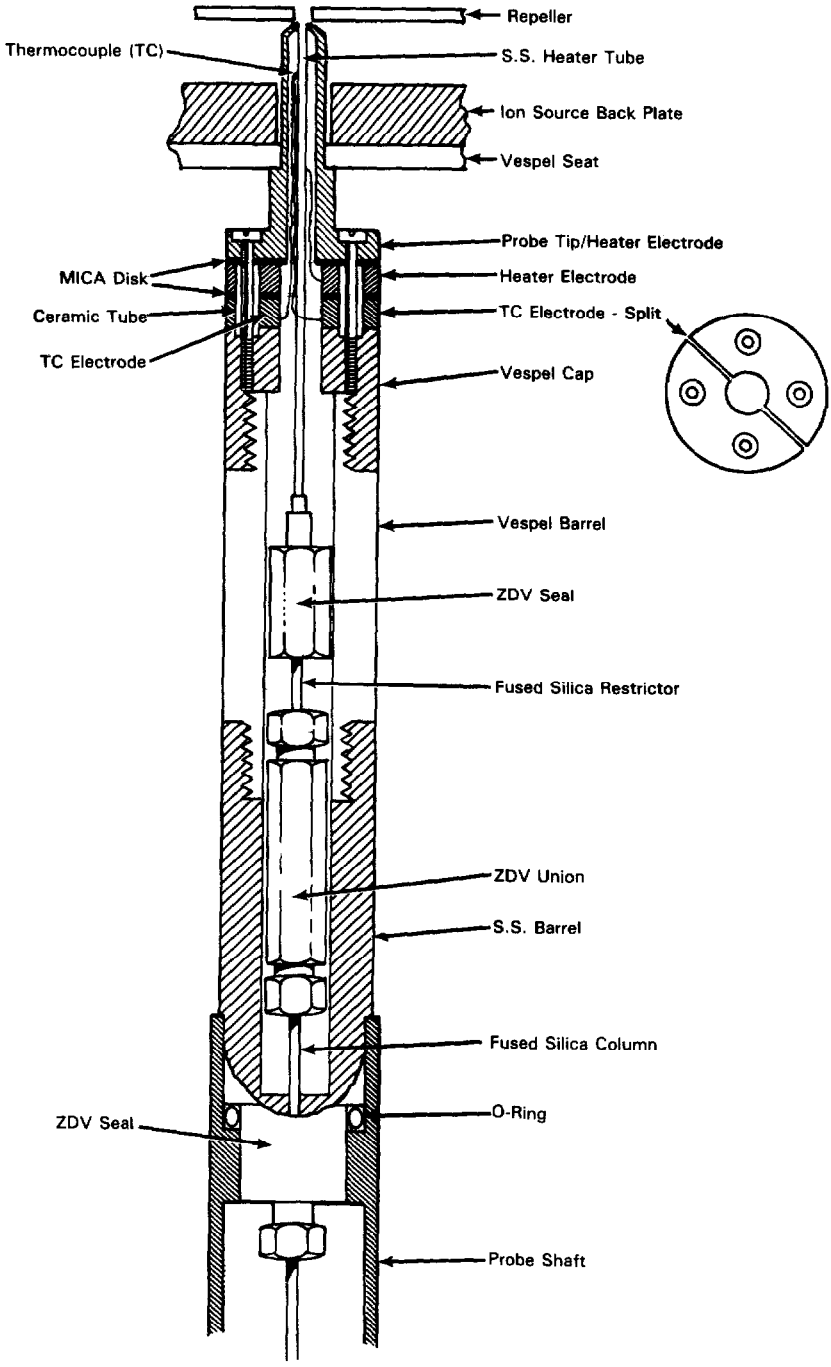

Fig. 1. Detailed schematic diagram of the SFC–MS interface for the VG ZAB (high voltage) CI source.

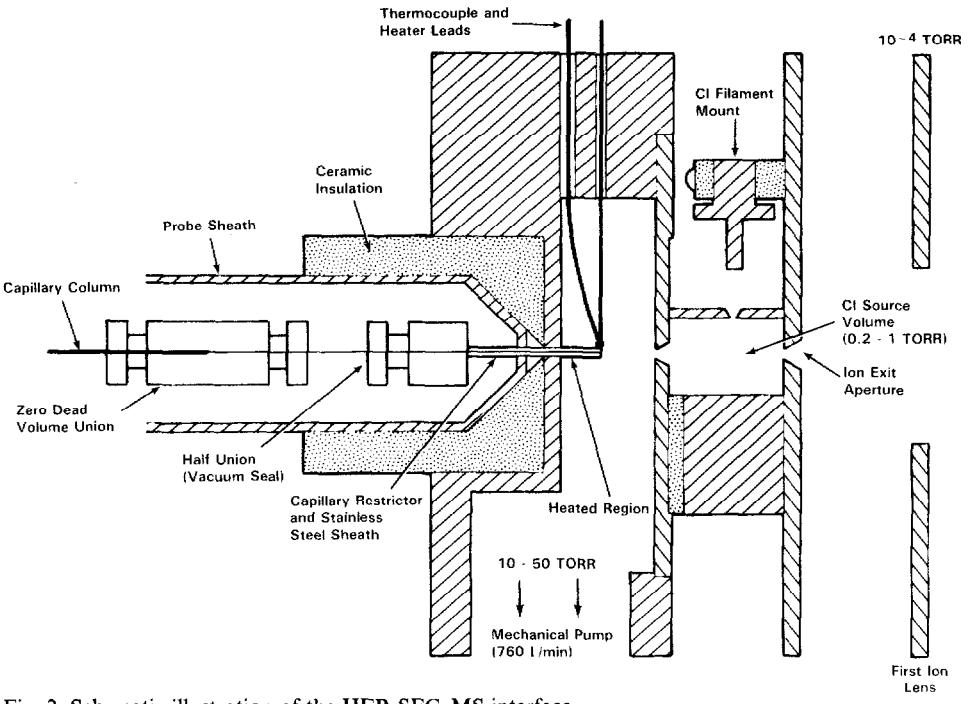

Fig. 2. Schematic illustration of the HFR SFC–MS interface.

The high flow-rate (HFR) interface (Fig. 2) has the capillary column connected to a capillary restrictor using a zero dead volume union. Capillary restrictors used for this interface consisted of a 5–10-cm length of 25–50 μm I.D. fused-silica capillary tubing with a drawn region, similar to that described by Chester *et al.*[5], typically 3–10 mm in length, and an exit diameter of 8–10 μm. A vacuum seal was made to the probe body via a "half union" fabricated using a capillary stainless-steel sheath which extended approximately 0.7 cm beyond the end of the probe (Fig. 2). The restrictor sheath provided mechanical protection for the fragile drawn restrictors and fits inside a larger 0.7-mm I.D. stainless-steel capillary that aligns with an aperture in the CI source repeller electrode. This electrode served to separate the expansion region from the CI source volume. The larger capillary was directly attached to the expansion volume so as to mate with the DFI probe. With heater and thermocouple wires welded to the free end of this capillary heater, the design provided direct resistive heating of the 0.7-mm I.D. capillary which in turn heated the capillary protection sheath and the capillary restrictor. Flow-rates of 100–200 μl/min for carbon dioxide (liquid) were obtained without any degradation of source performance with this interface (compare with *ca.* 20 μl/min for earlier SFC–MS instrumentation[17]).

RESULTS AND DISCUSSION

The combination of physical properties (viscosity and diffusion rates), combined with variable solvent properties, are the basis for the advantages of SFC. Physi-

cal properties of a supercritical fluid are variable between the limit of normal gas and liquid by control of pressure, with solvent characteristics different at each density. Typically, supercritical mobile phases for chromatography are at densities from 0.1 to *ca.* 0.8 of liquid density, with diffusion coefficients substantially greater than liquids. Viscosity similarly mirrors diffusivity and is typically 10–100 times less than for liquids[19]. Density of a supercritical fluid will be typically 10^2–10^3 times greater than that of the gas at ambient pressures; consequently the "liquid-like" density of the fluid results in greatly enhanced solubilizing capabilities. Table I gives the critical parameters for a number of supercritical fluid solvents.

For some of the more interesting problems that might be applicable to SFC–MS (*i.e.*, more polar analytes), use of a more polar supercritical fluid is desirable. However, the high critical temperatures of the polar fluids (Table I) limits the usefulness of these compounds as pure solvents. These compounds can be utilized in SFC as fluid mixtures to enhance solvating power or change chromatographic selectivity, with only minor increases in the critical temperatures of the non-polar fluids.

The phase behavior of binary systems is highly varied and much more complex than single component systems and has been well described for selected binary systems (ref. 19, and references therein). It is vital that fluid mixtures for SFC be selected so that they can be mixed and pumped as a single phase (most conveniently at ambient temperatures). Particular attention is required when operating over a range of pressures, as typical in capillary SFC, so as to avoid producing a two-phase system. Comparison with simple predictions in the absence of actual phase equilibria shows that considerable error can result, which can lead to inadvertent operation in the vapor–liquid region of the phase diagram. These considerations are much more important when pressure programming methods are used and can be comparatively unimportant for packed column separations using isobaric methods. An additional concern relevant to SFC–MS is that the fluid be maintained as a single phase without loss of the solute until the point of injection into the mass spectrometer, which often occurs at a higher temperature than used for the separation.

TABLE I

COMMON SFC SOLVENTS

Compound	*Boiling point (°C)*	*Critical temperature (°C)*	*Critical pressure (bar)*	*Critical density (g/cm^3)*
Carbon dioxide	−78.5	31.3	72.9	0.448
Ammonia	−33.4	132.4	112.5	0.235
Water	100	374.2	218.3	0.315
Nitric oxide	−88.6	36.5	71.7	0.45
Ethane	−88.6	32.3	48.1	0.203
Ethylene	−102.7	9.2	49.7	0.218
Propane	−42.1	96.7	41.9	0.217
Pentane	36.1	196.6	33.3	0.232
Benzene	80.1	288.9	48.3	0.302
Methanol	64.7	240.5	78.9	0.276
Isopropanol	82.5	235.3	47.0	0.273

The range of solvating power of practical supercritical fluids for SFC–MS is of primary importance and ultimately determines the limits of application. The solute typically exhibits a pressure above which solubility increases significantly. The region of maximum increase in solubility as a function of pressure is near the critical pressure where the change in density with pressure is greatest. This results from the nearly linear relationship between log (solubility) and density for dilute solutions of non-volatile compounds (up to concentrations where solute–solute interactions become important). In contrast, where volatility is extremely low, and at densities less than or near the critical density, increasing temperature will typically decrease solubility[10]. However, there can be an increase in "solubility" at high temperatures where solute vapor pressure can become significant. Thus, while highest supercritical fluid densities at a given pressure are obtained near the critical temperature, greatest solubility (within given experimental pressure limitation) will often be obtained at somewhat lower densities but higher temperatures. The role of supercritical fluid solubility in SFC–MS cannot be understated, as retention in the non-selective stationary phases generally used in capillary SFC typically mirrors fluid phase solubility. Further, fluid phase solubility plays an important role in the successful interface of SFC with MS.

Restrictor performance for capillary SFC–MS

The direct fluid injection interface is based upon the rapid expansion of the supercritical fluid mobile phase into a region where ionization can occur. Since proper conditions produce a gas after expansion, conventional EI and CI methods are readily adapted. The fluid expansion process through the pressure restrictor is the vital step (and primary problem area) of the technique which defines both the capabilities and ultimate limitations. More detailed discussion of factors affecting restrictor performance has been published[20].

Restrictor performance constitutes the most vital component of an SFC–MS interface. At present, most SFC and SFC–MS utilizes some form of capillary restrictor with the dimensions empirically selected to give the desired SFC linear velocity for the chromatographic temperature and pressure range. The capillary restrictor can be short with a relatively small inner diameter or longer with a larger I.D., providing a fast expansion or a relatively slow expansion through a tortuous path. The ideal restrictor for SFC–MS would provide the following characteristics: (a) uniform pulse-free flow, (b) immunity from plugging, (c) be easily replaced or provide for variation of flow-rate and (d) provide for complete transfer of labile or non-volatile solutes to the detector without pyrolysis or formation of analyte particles. A wide variety of restrictor designs have been studied to date, each with advantages and disadvantages. There exists, currently, no one ideal restrictor for capillary SFC–MS, particularly for nonvolatile compounds. However, work has led to interface designs which are nearly routine for use with volatile and less volatile materials in a range of supercritical fluids.

A vital property of SFC–MS restrictors is their effectiveness for transporting "non-volatile" compounds to the ion source. Success depends on the restrictor design, fluid pressure and temperature, the particular demands imposed by the ionization method, and under some conditions, the volatility or melting point of the "non-volatile" compounds.

It has been observed[5,21] that FID of less volatile or higher-molecular-weight

compounds can cause large spikes in the signal with a frequency on the order of 0.1–10 s^{-1}. Similar phenomena can also be observed under some conditions (usually for a very hot ion source) with MS detection. It has been suggested that origin for the spiking process is "clustering", and has been shown that incorporation of a suitably long time constant (a few seconds) with FID can produce a reasonable chromatogram[21]. Also observed is that increased fluid temperature delays the onset of the spiking phenomena to later eluting (and typically less volatile) compounds and suggested a "spiking delivery rate threshold" which varies with solute volatility[22]. Heating of the fluid through relatively long restrictors with FID is also effective[25], as is heating a region just prior to the restrictor[23].

For truly non-volatile compounds two distinct modes of operation appear feasible, the first leading to the spiking by a "precipitation" process, and the second resulting in a "nucleation regime" where it is unlikely. In the spiking mode, the non-volatile analyte tends to collect on restrictor walls and (if the local temperature is above the analyte melting point) flows towards the end of the restrictor. The liquid will collect at the end of the restrictor and be periodically entrained in the high shear gas flow and transported to the detector. This is a complex process with details which likely depend on the liquid viscosity and restrictor geometry. Solid particle agglomerates also appear to form by a related mechanism.

The fluid expansion process has been directly observed and various materials expanded from supercritical fluid solutions through 5–75 μm I.D. fused-silica capillaries have been collected and analyzed. In one set of experiments, polycarbosilane, which has a mean molecular weight of approximately 1430, a melting point of *ca.* 240°C, and is not volatile but decomposes to yield silicon carbide at >900°C, was studied. The molten polycarbosilane solute was observed to collect at the fused-silica capillary exit and be periodically entrained in the gas flow[20]. For polycarbosilane in pentane at 350°C and 100 bar, short fibers were formed (Fig. 3b). The high shear forces can apparently also elongate polymer droplets to yield fibers. The particle size (either fibers or spheres, depending upon the solute, fluid, and restrictor conditions) was found to increase with capillary diameter. These observations are consistent with the observed FID spiking phenomena and suggest a process involving the restrictor walls and solute melting point.

The second mode of operation producing much smaller particles occurs when analyte nucleation is delayed to near the end of the restrictor. Fig. 3a shows polycarbosilane collected under such a set of conditions (30 ppm pentane solution at 240 bar, 250°C). The major requirement for operation in the "nucleation mode" is to maintain solvating conditions to near the end of the restrictor, which is facilitated by the use of very short restrictors and fluid conditions enhancing solubility. It is important to recognize that this does not necessarily correspond to elevated restrictor temperatures. For example, the polycarbosilane particles shown in Fig. 3b were formed at 350°C and 100 bar, while the very fine, nearly monodisperse particles (Fig. 3a) were produced at 240 bar and 250°C. The solvating power of pentane for polycarbosilane is much greater under the latter condition. In addition, the particles were formed at gas temperatures below their melting point (due to cooling upon expansion), and where adhesion to the capillary walls was apparently insignificant. Under these conditions a very long restrictor would plug rapidly, but typically would produce large particles (as in Fig. 3b) if heated to >300°C.

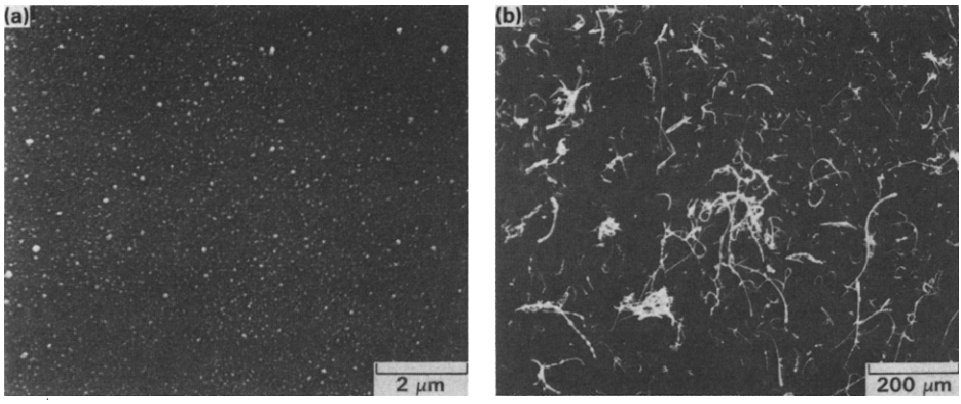

Fig. 3. Photographs showing products obtained from the expansion of supercritical polycarbosilane–pentane solutions. (a) Ultrafine polycarbosilane powder formed by expansion through a short restrictor at 250°C and 240 bar and (b) fibers collected from a solution expanded from 350°C and 100 bar.

Increased pressure always serves to enhance the transport of non-volatile analytes, but in practice maximum pressure is limited by either the SFC conditions needed to yield sufficient retention or the maximum pressure for the system. The effect of temperature on fluid phase solubility is more difficult to predict, but some guidance is provided by analyte vapor pressures. FID results with capillary SFC support these observations and have shown that the pressure and temperature of the fluid prior to the restrictor, restrictor dimensions, restrictor temperature, and possibly the temperature of the expansion region, can all impact detection[22]. Heating of the fluid just prior to expansion and heating of the restrictor itself have been shown to improve and extend detection for compounds having low volatilities. It has been shown that volatility plays a major role in detection of such analytes, both directly and indirectly, since fluid phase solubilities (at a given density) generally mirror analyte vapor pressures[4,20].

For truly non-volatile compounds heating of the fluid before or during expansion can be counterproductive, due to lower fluid densities and the resulting lower fluid phase solubilities. For non-volatile analytes, improved FID results are obtained using shorter restrictors and higher flow-rates. Larger concentrations and less soluble analytes will also lead to more rapid nucleation and particle growth. These small particles, typically well under 0.1 μm diameter for solute concentrations under 100 ppm, apparently form rapidly ($< 10^{-6}$ s) and apparently pose no difficulty for FID.

High flow-rate interface for SFC–MS

In an attempt to allow SFC–MS interfacing using conditions that delay analyte nucleation by maintaining solvating conditions of non-volatile compounds, the HFR interface was developed. Complete description of the design and performance of the interface appears elsewhere[14].

The HFR interface has the advantages, compared to earlier interfaces, of allowing SFC operation at high flow-rates, providing efficient analyte transfer to the CI region, unrestricted CI operation at optimum pressures and maintenance of normal CI reagent gas flow-rates while requiring a relatively minor increase in complex-

ity. Additional pumping is provided by a two-stage mechanical pump, similar to that required for thermospray LC–MS, and introduces no significant problems due to the volatility of most supercritical mobile phases. Actual sample size injected on column was much greater as the HFR interface permits splitless operation, sensitivity in terms of sample concentration was enhanced and the actual amount of sample utilized was unchanged (due to the waste involved in loading the high-pressure injection valve). Improved sensitivity was most obvious for higher-molecular-weight components, suggesting a possible enrichment process due to alignment of the capillary restrictor with the CI sample entrance orifice. Other factors likely contributing to the improved performance include the delayed solute nucleation, optimized CI source operation, and analyte injection into a volume of the source from which ions are more efficiently created and sampled.

The improved performance for higher-molecular-weight, less volatile components is demonstrated in Fig. 4, which shows selected ion chromatograms of a capillary SFC–MS analysis of the nonionic surfactant, Triton X-100. The separation was obtained using supercritical carbon dioxide at 100°C as the mobile phase and a 30 m × 100 μm I.D. fused-silica capillary column. The separation utilized a pressure

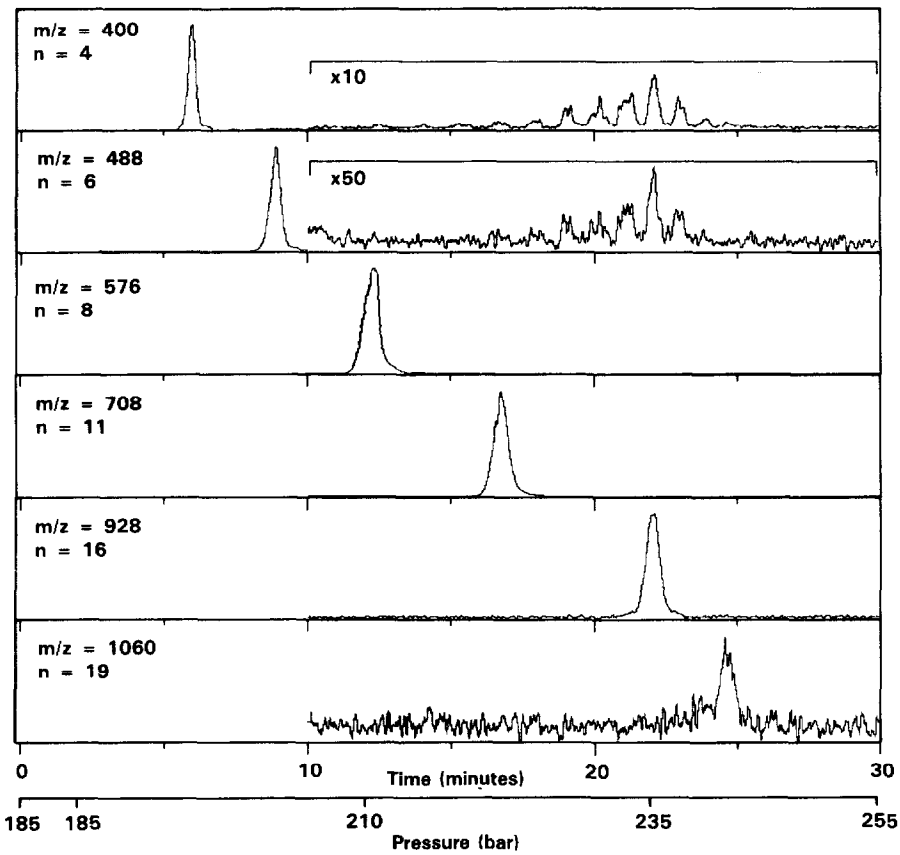

Fig. 4. Selected ion chromatograms for selected oligomers of the non-ionic surfactant Triton X-100 obtained using the HFR interface and splitless injection for capillary SFC–MS.

program of 2.5 bar/min from 185 bar starting 2 min after injection. MS detection utilized ammonia CI, but good results were also obtained using methane CI[24]. Capillary SFC with FID has shown the Triton X-100 $n = 9$ or $n = 10$ oligomer to have the greatest abundance, consistent with the SFC–MS results. Capillary SFC–MS with the previous (low flow) interface designs was limited to $n \sim 16$[17]. The selected ion chromatograms in Fig. 4 show that the $n = 16$ oligomer can be easily detected, with the $n = 19$ oligomer (m/z 1060) also readily observed, although it has a concentration at least an order of magnitude smaller than $n = 16$.

Heating of the fluid just prior to (and during) the expansion through the restrictor can facilitate transfer of less volatile compounds[5,20,23,25,26]. The improved transport to the detector is primarily associated with the enhanced vapor pressure or delayed precipitation of less volatile analytes[20]. The HFR interface may provide for improved analyte transport to the detector and remove the need for excessive heating of the capillary restrictor, which may result in pyrolysis of labile compounds. The HFR interface allowed heating of only a small segment (*ca.* 0.6 cm) of the restrictor, with the maximum heating obtained at the restrictor exit.

Application of the DFI interface to high-resolution MS

Extension of supercritical fluid introduction methods to high-resolution MS instrumentation offers the potential of enhanced selectivity and additional capabilities for characterization of unknown materials. Two practical advantages accrue from the DFI interface to magnetic sector mass spectrometers; higher mass range without the discrimination against higher-molecular-weight ions found with quadrupole mass analyzers and the ability to obtain exact mass information on compounds introduced using supercritical DFI.

The identification of compounds in complex natural matricies can be greatly facilitated by the ability to obtain exact mass information. The identification of toxic fungal metabolites in a wheat matrix utilizing supercritical fluid extraction (SFE) and DFI MS has recently been demonstrated[13]. The benefits of such an approach include a great reduction in sample handling and preparation, facilitating analysis and simplifying interpretation. The selectivity of supercritical fluids is provided by control of fluid density (therefore, solvating power). Natural substances, however, present complications due to concurrent extraction of a broad spectrum of components (with extraction selectivity dependent on fluid composition, temperature and pressure), resulting in a relatively large "background" signal, which can ultimately determine detection limits. With the use of high-resolution MS, the interfering effects of the sample matrix not eliminated by selective ionization (based on choice of CI reagents) can be overcome.

Fig. 5 shows the high-resolution mass spectrum of the ammonium adduct ion region (m/z 384) for the trichothecene mycotoxin diacetoxyscirpenol (DAS, MW 366). DAS and T-2 toxin (MW 466) were spiked on a wheat sample, the sample extracted with a supercritical mixture of carbon dioxide and isopropanol (5%, v/v)[13] and the extract directly injected into the CI source of the ZAB mass spectrometer, adapted for the DFI interface[18]. Ammonia was utilized as reagent gas for CI. The exact molecular weights (± 3 ppm) of both DAS (Fig. 5) and T-2 toxin were determined, even in the presence of numerous, nominally isobaric interferences. This system has been operated at a resolution ($m/\Delta m$) in excess of 20000 (10% valley).

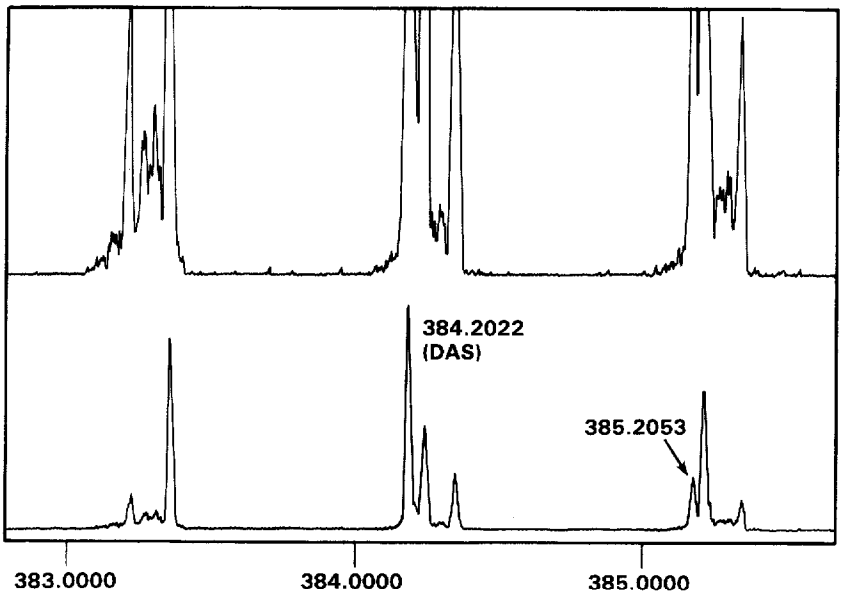

Fig. 5. An oscillographic trace of the high-resolution mass spectrum of a supercritical carbon dioxide–isopropanol (95:5) extract of wheat containing diacetoxyscirpenol (DAS) and T-2 toxin. Ammonia CI was used at 7400 resolution (5% valley) on a VG ZAB mass spectrometer.

Coupled with the previous work[13], detection limits for this analysis in the 10 ppb range appear feasible using this approach.

Along with other experiments[18], the utility of the DFI interface to high-resolution MS for exact mass determination and SFC–MS analysis of higher-molecular-weight materials, has been demonstrated.

CONCLUSIONS

The development of the DFI interface for capillary SFC with MS has advanced so that nearly routine application with the more common supercritical fluids and volatile and less volatile analytes is possible. MS provides near universal detection for capillary SFC providing both high sensitivity and selectivity and allowing operation with polar modified fluid mixtures. The use of the high flow-rate interface enhances analyte transfer of non-volatile compounds to the mass spectrometer ion source. Further advances and insight into the factors controlling the supercritical fluid expansion are required to extend the application of SFC–MS to the truly non-volatile materials.

ACKNOWLEDGEMENTS

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