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Review

Recent developments in supercritical fluid chromatography–mass spectrometry coupling

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Abstract

After some time of stagnation, research in supercritical fluid chromatography (SFC)–mass spectrometry (MS) coupling has been recently revived by investigations into the use of atmospheric pressure ionisation (API) techniques. Following a short introduction into the historical development, the present state of the art in SFC and the actual trends in the field of SFC–MS, the different interfacing methods are presented briefly discussing its advantages and drawbacks. Special attention is given to new results and recent developments including a survey of applications reported during the last few years.

Contents

1. Introduction

Following its rediscovery during the early 1980s, most of the work initially done in the field of supercritical fluid chromatography (SFC) was concentrated on the use of capillary columns. The expectation of high efficiency combined with low volumetric flow-rates which should allow for an easy interfacing to most of the common gas chromatography (GC) detectors and, in particular, also to mass spectrometry (MS) rapidly led to the development of commercially available capillary SFC (cSFC) equipment. The first reports on a successful interfacing to MS quickly followed [1,2] and during the subsequent years

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research on SFC–MS coupling remained nearly exclusively restricted to cSFC using a direct introduction method, that required only minor modifications to the available instrumentation. The large interest in this method at that time, resulting from proceedings in the separation of non-polar, high-molecular-mass compounds like synthetic oligomers and non-ionic surfactants, which previously were difficult to analyse, and the unique advantages of MS detection in the characterisation of such complex mixtures certainly contributed to this evolution.

Meanwhile, the progress of packed-column SFC (pSFC) was hampered by the lack of reliable instrumentation requiring the use of custom-built equipment. However, as eventually was recognised, cSFC suffers from inherent disadvantages, some of which severely restrict the performance of cSFC–MS [3]. Particular problems, like those related to sample introduction and the low sample capacity of microbore capillary columns led to a growing interest in pSFC, which is not plagued by such limitations. Moreover, pSFC offers additional advantages like the ability to handle polar analytes after a few percent of appropriate polar solvents have been added to the mobile phase. Similar approaches in cSFC were much less effective and technically difficult to realise. During the following years, improved instrumentation became available and pSFC developed into a versatile technique. High efficiencies approaching those of capillary columns can be easily achieved [4] and there have also been proceedings in the separation of very polar compounds [5–8]. Furthermore, pSFC provides considerable advantages in the field originally covered by normal-phase liquid chromatography (LC) [9].

Since there initially were no alternatives to direct coupling, pSFC–MS did not substantially progress. There have been several attempts using additional pumping stages to handle the high flow-rates [10–12]. However, the specific disadvantages of the direct fluid introduction still remained. Consequently, the work on SFC–MS (Fig. 1) mainly reflects the development of the direct interfacing approach culminating in the late 1980s and declining during the subsequent

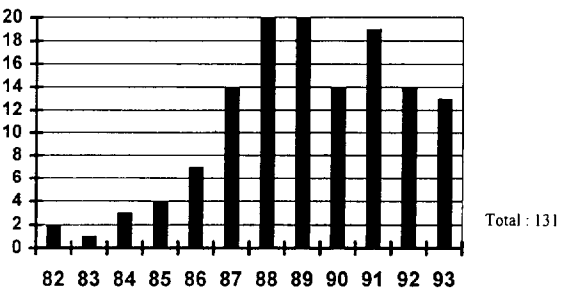

Fig. 1. Number of papers on SFC–MS during the years 1982 ("82") to 1993 ("93").

years. It was not until some years ago, that SFC began to benefit from the rapid development of atmospheric pressure ionisation (API) interfaces for LC–MS applications. These devices designed for accepting high flow-rates largely facilitate pSFC–MS and already stimulated a number of interesting investigations in that field.

2. SFC–MS with direct fluid introduction interfaces

During the last decade, the most common approach to interface SFC to MS consisted in the direct insertion of a restrictor, fixed to the end of a capillary column, into the ion source of a mass spectrometer operating in electron impact (EI) or chemical ionisation (CI) mode. For two reasons, this method, referred to as direct fluid introduction (DFI), seemed to be particularly effective. First, the low flow-rates delivered by capillary columns could be easily accommodated by the vacuum equipment of a standard mass spectrometer. Secondly, the basic requirements of the interface design —a minimal dead volume, sufficient heating of the restrictor tip to compensate for the adiabatic cooling of the rapidly expanding fluid and an appropriate inlet system to add reaction gases for chemical ionisation— could be met using commercial SFC and MS equipment without or with only minor modifications.

However, this technique suffers from inherent limitations discussed in detail in a previous paper [3]. The most severe one results from the appli-

cation of column inlet pressure programming in cSFC increasing the flow-rate and continuously modifying the ionisation conditions during the analysis. High-molecular-mass compounds not amenable to GC analysis and therefore particularly interesting in SFC have to be eluted at high pressures producing flow-rates that are not properly handled by standard vacuum systems. When working in EI mode losses in sensitivity are observed due to decreased penetration of electrons into the ion source. The ionisation is also affected by charge exchange (CE) with primarily formed $CO_2^{\cdot+}$ ions. In general, EI-CE spectra strongly resemble those obtained by EI only, but in some cases, as was reported for example in a recent study on chlorinated pesticides [13], the opposite may be found.

On the other hand, the sensitivities observed with positive CI (PCI) are usually better and the detection limits compare well with those reported for GC–MS under the same ionisation conditions [14]. However, beyond a certain column pressure the signal background rapidly increases and the transmission of sample through the mass analyser becomes poor [15–17]. Both competition of CI with CO_2 CE [18] and collisionally induced dissociation (CID) processes leading to extensive fragmentation [16,17] are discussed as the reasons for this effect.

Nevertheless, cSFC–MS in DFI mode is still used at the present, as becomes evident from the comparatively large number of applications reported during the last few years, which have been summarised in Table 1. Though, due to the disadvantages discussed above, the application range remained restricted either to the analysis of low-molecular-mass substances [13,19–21] or to such problems related to high-molecular-mass samples, where low detection limits are not needed, e.g. the characterisation of complex mixtures [22–24]. Among the publications on low-molecular-mass analytes, some fundamental work was reported on chlorinated pesticides, comparing the detection limits obtained in PCI and negative CI (NCI) mode using different reaction gases along with CO_2 and N_2O as mobile phases and providing a detailed discussion of the ionisation mechanisms [13]. Calvey et al. [20] used the DFI approach to identify thiosulfinates in garlic extracts. To prevent thermal decomposition of allicin (2-propene-1-sulfinothioic acid S-2-propenyl ester), the predominant flavor principle of garlic, the restrictor tip temperature had to be kept as low as possible requiring modifications to the interface to allow for independent heating of the restrictor tip and the ion source [20]. Furthermore, direct cSFC–MS has been applied to the trace analysis of mebeverine, a polyfunctional drug, in dog plasma following sample preparation and enrichment by solid phase extraction [21].

An interesting application to the analysis of higher-molecular-mass substances has been presented by Bücherl et al. [25]. cSFC was directly coupled to a magnetic sector instrument to identify polymer additives with molecular masses up to 1200 g/mol in supercritical fluid extracts of packaging materials. A low detection limit was not needed, because the additives occurred in these materials at rather high concentrations. Since fragmentations induced in CI mode at the high pressures needed to elute the analytes were not predictable, EI-CE ionisation was preferred yielding reliable structural informations at a comparable sensitivity. A typical EI-CE ionisation mass spectrum of an additive with the base peak at $m/z = 441$ corresponding to the loss of an ester group from the molecular ion is shown in Fig. 2. This spectrum may be compared with a spectrum of the same substance obtained by cSFC directly interfaced to a quadrupole instrument and PCI with NH_3 as the reaction gas (Fig. 3). In that spectrum, the peak of the molecular ion is more abundant, but overall fragmentation is more extensive and the structural information provided is very low.

There also were two applications of direct pSFC–MS interfacing [26,27]. One of them dealt with the group separation of diesel fuel distillates on packed capillary columns using MS to optimise the column switching times [26]. The other one described the use of 2 mm I.D. packed columns along with a modified LC–thermospray MS interface with high vacuum pumping capacity, which was operated in conventional PCI or NCI mode [27]. In the analysis of aromatic nitro

Table 1
Survey of applications recently reported on direct cSFC–MS

Analytes	Ionisation method	Mass analyser	Detection limits	Ref.
Thiosulphinates	PCI (iso-C_4H_{10})	Quadrupole	–	20
Chlorinated pesticides	EI-CE	Double focusing sector instrument	2–4 ng (both mobile phases CO_2 and N_2O)	13
	PCI (CH_4)		1–4 ng (both CO_2 and N_2O)	
	PCI (iso-C_4H_{10})		6–10 ng (CO_2), >30 ng (N_2O)	
	PCI (NH_3)		2–4 ng (both CO_2 and N_2O)	
	NCI (CO_2)		2–4 ng (CO_2)	
	NCI (N_2O)		2–4 ng (N_2O)	
	NCI (CH_4)		2–4 ng (both CO_2 and N_2O)	
	NCI (iso-C_4H_{10})		2–4 ng (both CO_2 and N_2O)	
	NCI (NH_3)		2–4 ng (both CO_2 and N_2O) Full scan range, $S/N = 3$	
Selected pesticides	EI	Quadrupole	1 ng diuron (full scan range, $S/N = 5$)	19
Mebeverine	PCI (1% NH_3 in CH_4)	Triple quadrupole	2.4 pg (single-ion monitoring, $S/N = 10$)	21
Olestra	PCI (1% NH_3 in CH_4)	Triple quadrupole	–	22
Anthracene	EI	Hybrid MS consisting of a quadrupole and an ion trap	780 fmol (full scan range, $S/N = 10$)	23
	PCI (CH_4)		78 fmol (narrow scan range, $S/N = 15$)	
Ethoxylated alcohols, poly(dimethylsiloxane)s, alkylethoxysulphates	PCI (1% NH_3 in CH_4)	Hybrid MS consisting of a quadrupole and an ion trap	– – –	23
Non-ionic surfactants	PCI (different mobile phases and reaction gases) + CID (Ar)	Triple quadrupole	MS–MS, product ion scan	24
Polymer additives	EI	Double focusing sector instrument	10–100 ng (full scan range, S/N not reported)	25

Ionisation methods: PCI, NCI = positive and negative chemical ionisation, respectively; EI = electron impact; CE = charge exchange; CID = collisionally induced dissociation.

and nitroso compounds, reasonably high sensitivities could be achieved with this combination. For example, the injection of 400 fg 2,6-dinitrotoluene produced a S/N ratio of 20 when CO_2-moderated NCI and single ion monitoring were applied. Nevertheless, it has to be remembered, that such an approach neither allows for fully exploiting the advantages of pSFC, nor compensates for the disadvantages of DFI interfacing.

Besides those applications, some of the recent work on direct coupling was dedicated to improvements in the transmission of high-molecular-mass substances. As could be shown, the application of cryopumping to the ion source region helped to significantly decrease detection limits when analysing high-molecular-mass compounds at high column inlet pressures up to 560 bar [15,22]. Compared to conventional vacuum pumping stages, cryopumping provides a more specific elimination of mobile phase molecules by condensation in a liquid nitrogen cooled trap

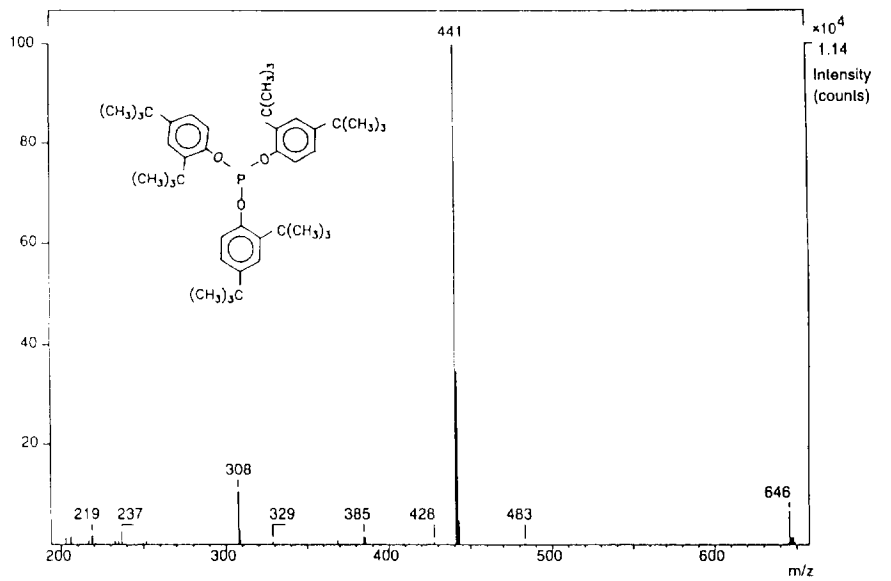

Fig. 2. Mass spectrum of a polymer additive obtained by CO_2^+ charge exchange ionisation. The SFC capillary column was directly coupled to the ion source of a magnetic sector mass spectrometer. From Ref. [25].

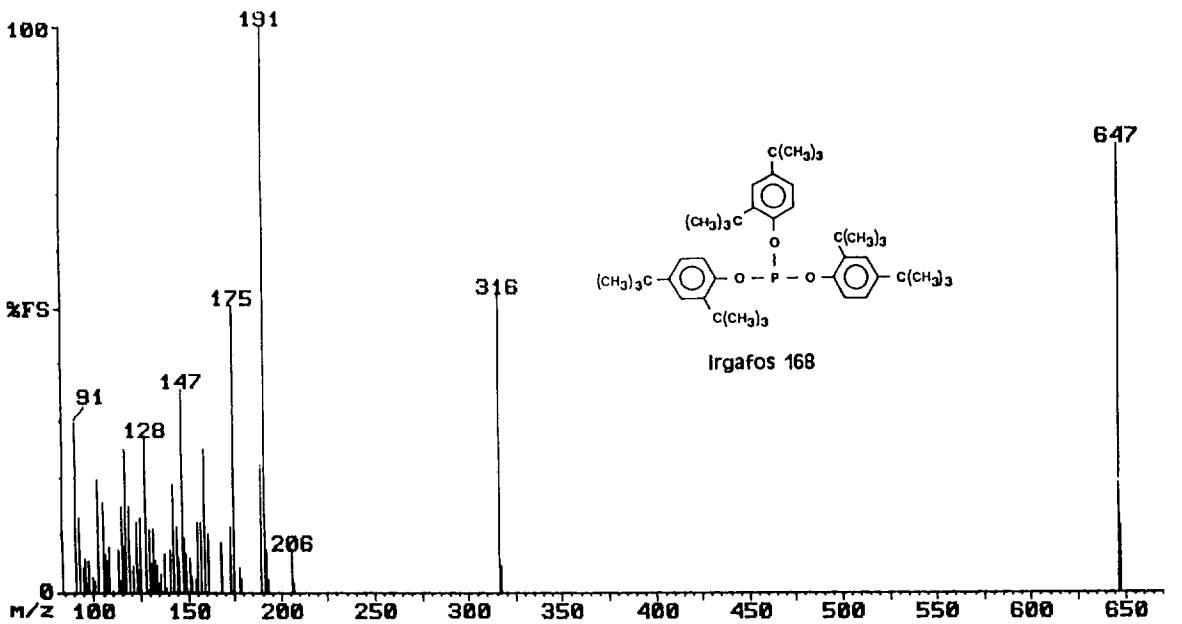

Fig. 3. Mass spectrum of the same polymer additive as in Fig. 2, obtained by proton transfer chemical ionisation. The SFC column effluent was mixed with NH_3 and directly introduced into the ion source of a quadrupole mass spectrometer (by courtesy of Fisons Instruments, Milan, Italy).

overall yielding a better sensitivity. This approach was applied to the characterisation of olestra, a mixture of fatty acid sucrose esters with molecular masses up to 3600 g/mol, yet the background noise in the CI spectra obtained for the compounds eluting at elevated pressures remained very high [22]. Interestingly, a marked influence of the restrictor design on interface performance could be noticed [15]. Amongst the common SFC restrictors, the thin-walled tapered has the most effective heat transfer characteristics and therefore provides unique advantages in the separation of some oligomer mixtures, which cannot be completely resolved using frit or integral restrictors [28]. Unfortunately, this restrictor also provides the by far largest flow-rate increase with increasing column pressures. Therefore, after replacing the tapered by a frit or integral restrictor, the system performed equally well as with the addition of cryopumping and the tapered restrictor still in place [15]. Furthermore, it was observed that cryopumping did not improve sensitivities for low-molecular-mass analytes, even at high flow-rates [13].

Other recent developments in this field include the description of a benchtop cSFC–MS system using a mass analyser originally designed for GC–MS coupling, which was equipped with additional pumping stages to accept higher flow-rates [19] and a report on interfacing cSFC to a hybrid instrument consisting of an external differentially pumped ion source, a quadrupole mass filter and an ion trap mass analyser [23]. This arrangement was conceived to prevent mobile phase and CI reagent gas molecules from penetrating to the pressure sensitive trap and the system worked reasonably well when tested with anthracene. However, despite these efforts, the fragmentation still remained unusually extensive.

3. SFC–MS using plasma ion sources

Some recent papers were dealing with the coupling of cSFC to microwave-induced plasma (MIP) [29] or inductively coupled plasma (ICP) mass spectrometry [30–32] to sensitively and selectively detect heavier elements. The interfacing was accomplished by simply introducing the capillary restrictor, secured in a metal tube allowing for the coaxial addition of a make-up gas flow, into the base of the respective plasma device. However, only the design of the MIP instrumentation met the critical restrictor heating requirements. In the cSFC–ICP-MS setup used, the restrictor tip, located inside the ICP sprayer tube, could not be heated, leading to serious peak deformation and irreproducible retention times when applying steep pressure gradients [30,32].

A summary of the reported applications is given in Table 2. The detection limits for the halogenated and the organometallic compounds were not better than those obtained with GC–MIP-MS [33] and GC–MIP-atomic emission spectrometry [34] respectively. Though, since

Table 2
Summary of applications reported on cSFC–MS using plasma ion sources

Analytes	Ionisation	Detection limits	Ref.
Organotin compounds	ICP	200-800 fg (single ion monitoring, 3σ calculation)	30
1-Chloronaphthalene	MIP	100 pg Cl (single ion monitoring, $S/N = 2$)	29
1-Bromo-2-methylnaphthalene		25 pg Br (single ion monitoring, $S/N = 2$)	
Tetrabutyllead	ICP	0.5 pg (single ion monitoring, 3σ calculation)	31
Tributyllead acetate		10 pg (single ion monitoring, 3σ calculation)	
Diethylmercury		3 pg (single ion monitoring, 3σ calculation)	

Ionisation methods: ICP = inductively coupled plasma; MIP = microwave-induced plasma. A single quadrupole mass analyser was used in all cases.

many organometallic compounds are thermally unstable, there still remains an advantage of the SFC approach.

4. SFC–MS using atmospheric pressure ionisation techniques

The most interesting proceedings in the field of SFC–MS during the last few years resulted from investigations in the use of API sources. These devices originally designed for LC–MS coupling accept high flow-rates, which may be largely varied without influencing the ion production mechanisms. From this point of view, cSFC too becomes interesting again and in fact, a major part of the work on SFC–API-MS has been performed on capillary columns. However, it should be remarked, that MS coupling does not assist in eliminating the inherent problems of cSFC at all. A summary of the applications reported on SFC–API-MS is given in Table 3. Usually, the performance of the systems was demonstrated by injecting standard mixtures of high-molecular-mass analytes and the detection limits reported are in general about three orders of magnitude lower than those achievable in DFI mode under comparable chromatographic conditions.

To interface SFC to an API source, commercial LC–MS equipment can be used without modification requiring only the restrictor introduction. Some problems may arise, when the instrumental design provides no appropriate restrictor heating, as will be discussed in the section below. A present limitation in the use of API sources results from the frequent application of mobile phase composition programming in pSFC. While variations in the overall flow-rate at a constant modifier concentration are easily accommodated, the MS sensitivity is seriously affected by even small changes of the atmospheric composition, no matter which particular ionisation technique is applied [35,36].

4.1. SFC–MS with atmospheric pressure chemical ionisation

There are two fundamentally different processes that can be utilised to ionise the solutes in an SFC effluent at atmospheric pressure. First, the ionisation can be carried out in the gas phase, which is most commonly done by directing the sample vapour through a corona discharge maintained at the tip of a needle electrode. This technique, referred to as atmospheric pressure chemical ionisation (APCI) requires the complete vaporisation of the column effluents, which is accomplished by both heating the restrictor and coaxially adding a nebulising gas assisting in the initial formation of liquid drop-

Table 3
Summary of applications reported on SFC–MS using atmospheric pressure ion sources

Ionisation	Column	Mass analyser	Analytes	Detection limits	Ref.
APCI	Capillary	Quadrupole	Polycyclic aromatic hydrocarbons	40 pg chrysene (single-ion monitoring, $S/N = 3$)	37
APCI	Capillary	Triple quadrupole	Anthracene	1 ng (single-ion monitoring, $S/N = 3$)	38
			Trilaurine	10 pg (single-ion monitoring, $S/N = 3$)	
			Cholesterol	–	
			Prostaglandines	–	
APCI	Packed capillary	Double focusing sector instrument	Polycyclic aromatic hydrocarbons Fat-soluble vitamins Polyethylene glycols Polystyrenes	–	39
ES	Packed	Quadrupole	Pyridine derivatives	–	35
			Triazine herbicides	11 pg atrazine (single-ion monitoring, $S/N = 5$)	

Ionisation methods: APCI = atmospheric pressure chemical ionisation; ES = electrospray.

lets. Problems have been observed when using air as nebulising gas burning off the polyimide coating of the restrictor and producing an increased background noise [37]. The volatility of the sample seems to represent a limiting condition, but the polarities and molecular masses of most of the analytes amenable to SFC are within a range appropriate to easily meet this requirement.

Under SFC conditions, the APCI mechanism sets on with the production of $CO_2^{\cdot-}$ and $H_2O^{\cdot+}$ ions originating from the mobile phase and moisture in the ambient air respectively. Ionisation of the analytes occurs either by CE processes or by proton transfer from proton hydrate clusters formed in a complex reaction from the primary $H_2O^{\cdot+}$ ions [36]. Therefore, in order to promote proton transfer reactions and to stabilise the ion current, the nebulising gas is usually saturated with water [37,38] or a protic solvent like methanol [39], giving rise to similar reactions. If no solvent was added, the corona discharge was found to become unstable [38].

To perform SFC–APCI-MS, commercial LC–MS interfaces without modification are mostly used, but there may arise problems due to insufficient heating of the restrictor and the transfer lines resulting in peak deformation and irreproducible retention times, especially when analysing polar or high-molecular-mass substances. A more sophisticated interface (Fig. 4) designed to eliminate these problems has been described by Tyrefors et al. [38]. The restrictor was inserted into a large-I.D. fused-silica capillary, through which the nebulising gas was coaxially added. The outer capillary was held in a thermally insulated PTFE tube swept with air preheated at the SFC oven temperature. To compensate for temperature losses along the transfer line, which still occurred with this arrangement, a heating coil acting as an active insulator was added to the tube. Another heating wire was fixed to the restrictor tip to control the expansion conditions and to finely tune the flow-rates.

4.2. SFC–MS with electrospray ionisation

Furthermore, ions can be produced directly from solution droplets by electrospray (ES) ionisation of a liquid aerosol in a strong electrical field [40]. ES ionisation can be pneumatically assisted by a nebulising gas, a variant called ion spray (IS) [41]. In both cases, ionisation is accomplished by proton transfer in the liquid phase and therefore, the use of appropriate modifiers is essential in SFC–ES-MS. This represents no disadvantage, because, due to the use of

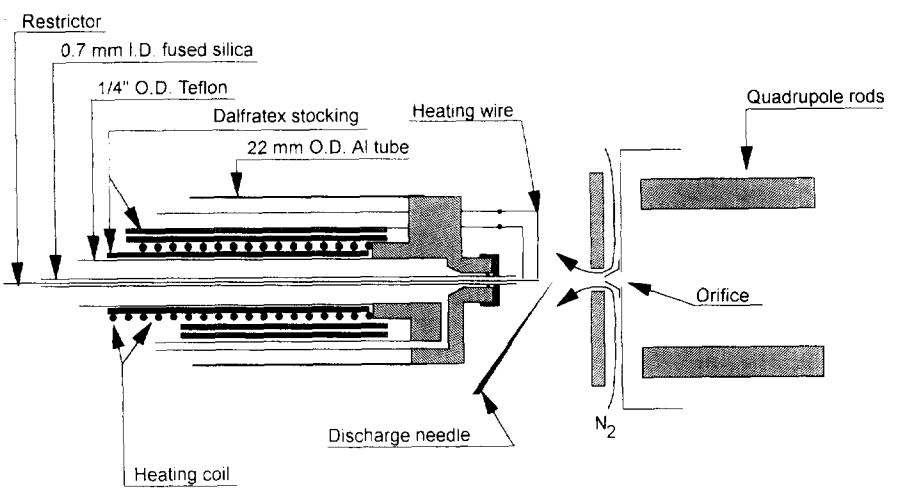

Fig. 4. Schematic representation of an SFC–MS interface for atmospheric pressure chemical ionisation induced by a corona discharge. 1″ = 1 in. = 2.54 cm. From Ref. [38].

polar modifiers, a large variety of polar compounds becomes actually amenable to SFC. However, it was observed that the solute response factors strongly depended on the concentration of the polar modifier [35], thus imposing restrictions on the choice of the chromatographic conditions. In particular, mobile phase composition gradients will be limited to a narrow range of modifier concentrations.

4.3. Miscellaneous

Besides APCI and ES ionisation, the attachment of lithium ions at atmospheric pressure has been suggested as a possible technique to perform SFC–API-MS [42]. The ions were produced by thermal vaporisation of a lithium alumosilicate bead fused to a platinum heating wire, and gas phase ion–molecule reactions led to stable lithium adducts. SFC conditions were simulated by introducing gaseous CO_2 loaded with different analytes into the ion source and a detection limit of 320 ppt (which would correspond to about 160 ppb in supercritical CO_2 at a density of 0.8 g/ml) was reported for camphor, but a practical demonstration of the coupling is still lacking.

There might be some concern to discuss thermospray (TSP) ionisation as an API technique, but the instrumental setup required for TSP ionisation is very different from that of API sources. In fact, TSP ion sources more resemble the high flow-rate interfaces designed for direct pSFC–MS and therefore, SFC–TSP-MS should be discussed along with the techniques presented in Section 2. However, since recently there have been no proceedings in that field and only one application, dealing with the analysis of conjugated bile acids using pSFC–TSP-MS [43], has been reported, a detailed discussion was omitted in this paper.

5. Conclusions

After there has been a long time of stagnation, proceedings achieved by the use of API techniques during the last few years have given a fresh impetus to the field of SFC–MS. There has now opened up a chance to interface pSFC to MS without restricting its chromatographic abilities, thereby obtaining a powerful analytical tool much more versatile than cSFC–MS, which dominated the work on SFC–MS for years. Actually, there is still few research on SFC–API-MS, at least partially due to the considerable costs of the equipment. In particular, API sources still have to be used with research-scale MS instrumentation. However, once miniaturised equipment will have been made available, one may expect, that pSFC–MS will gain a much broader acceptance.

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