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PROBLEMS IN INTERFACING OPEN-TUBULAR LIQUID CHROMATOGRAPHY AND MASS SPECTROMETRY

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SUMMARY

The improvement of the detection limits in coupled open-tubular liquid chromatography and mass spectrometry (OT-LC–MS) has been studied. The minimum detectable quantities with the present system constitute the major challenge in OT-LC–MS coupling, and various aspects and results are discussed from this point of view. The selection of appropriate interfaces for OT-LC–MS, the ionization conditions, the application range of the selected interfaces, the reduction of external peak broadening and the minimum detectable quantities obtained are considered.

INTRODUCTION

The coupling of liquid chromatography and mass spectrometry (LC–MS) has attracted considerable interest in recent years and has been extensively reviewed[1–5]. Various types of LC columns have been interfaced with MS instruments. The use of LC columns with small inner diameters (< 3 mm) has been advocated by many workers, irrespective of the actual inner diameter of the column. However, different diameters lead to different advantages. "Microbore" columns (0.5–2 mm I.D.) can be used to solve some of the problems with the use of high LC flow-rates. Because of the 10–20-fold reduction in flow-rate in comparison with conventional 4.6 mm I.D. columns, direct microbore LC–MS interfacing is possible, avoiding the need for splitting or for substantial modifications to the vacuum system. As a result, lower detection limits can be achieved[6,7]. Microbore columns also offer advantages when mobile phases with high water contents have to be used with transport-type LC–MS interfaces[8]. Further reduction of the column diameter does not result in improvements as far as flow-rate-related problems are concerned, but there are other advantages. Packed capillary columns (100–500 μm I.D.) are advantageous, as their low flow-rates permit the on-line acquisition of electron-impact spectra[9,10], whereas open-tubular columns (5–30 μm I.D.) are advantageous for fast separations of complex mixtures that require very high plate numbers[11].

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In the past 4 years we have investigated the coupling of open-tubular liquid chromatography (OT-LC) and mass spectrometry[12–14]. Two other research groups have also reported on OT-LC–MS[15–18]. Although OT-LC–MS has great potential, several problems have to be solved before its widespread use can be expected. In this paper we discuss further results on various aspects of OT-LC–MS coupling. Attention is focused on the improvement of the detection limits, which, in our opinion, is the major challenge in OT-LC–MS. Related topics that are dealt with are the selection of appropriate interfaces for OT-LC–MS, the ionization conditions, the application range of the selected interfaces and external peak broadening.

SELECTION OF INTERFACES

More than 15 different interfaces for the (semi) on-line coupling of LC and MS have been described[1–5]. In order to select interfaces suitable for use under the conditions prevailing in OT-LC–MS, a few of the most successful interfaces were examined more thoroughly. A brief discussion of this examination will explain our selection of the capillary inlet and the direct liquid introduction (DLI) interface for further investigations.

The various LC–MS interfaces described in the literature can be divided into two groups, with direct or indirect introduction of the column effluent. The most important example of an indirect introduction interface is the moving-belt system[19]. We did not select this type of interface for OT-LC–MS for three reasons: (1) in the literature the importance of the uniformity of the liquid film on the belt has been stressed; we are pessimistic about the possibility of forming a uniform liquid film with the extremely small flow-rates used in OT-LC (0.05–10 nl/s); (2) the contribution of external peak broadening due to the interface is too large for high-efficiency separations[20,21]; and (3) a moving belt system is a complex mechanical device which is fairly expensive.

Of the direct introduction interfaces, the capillary inlet interface, in which the column effluent evaporates from a capillary tube into the ion source, has been selected because of its simplicity and cheapness. Results on OT-LC–MS with a capillary inlet interface have also been reported by Ishii *et al.*[15] and Tijssen *et al.*[17]. Owing to the necessity to evaporate the column effluent, the range of applicability of this interface is limited to fairly volatile compounds[7,14]. Other direct introduction interfaces, having a broader applicability range, *e.g.*, the direct liquid introduction (DLI) interface[22,23] and the thermospray interface[24], are less compatible with the flow-rates used when the open-tubular columns are operated at near to kinetic optimum linear velocities. The use of a DLI-type interface in combination with an open-tubular column has been demonstrated by Tijssen *et al.*[17]. They used a conical tip instead of a diaphragm. Because of the relatively high flow-rate necessary to form the liquid jet from a conical tip of practical dimensions, this approach severely limits the kinetic performance of the open-tubular column[17]. A pneumatic nebulizer[18,25] is also applicable under these conditions. The results of OT-LC–MS with a pneumatic nebulizer, as demonstrated by Smit *et al.*[18], look very promising. However, the slit between the open-tubular column and the gas inlet tube in a concentric nebulizer must be very narrow, resulting in problems with the production, the handling and the adjustment of such nebulizers.

Therefore, it was decided to adopt the DLI interface, which was at that time

(1982) the most successful LC–MS interface, to the conditions prevailing in OT-LC–MS[12]. In our DLI interface an additional liquid flow, the so-called make-up liquid, is mixed with the column effluent in a small chamber behind the diaphragm used for the nebulization of the liquid.

EXPERIMENTAL

The experimental set-up used in our laboratory has been described in detail in previous papers[12,14]. Fig. 1 shows schematic diagrams of the two interfaces used. The experimental procedure, described for studying the range of applicability of the capillary inlet interface[14], has also been used in comparable experiments with the DLI interface.

Previously reported data on the external peak broadening in the OT-LC–MS system with the DLI interface have been recalculated using the values for the column diameter calculated from experimental data on pressure drop and peak residence time (see Table I). Hence the data given in the tables in a previous paper[12] differ from those used here. However, the conclusions drawn earlier are still valid.

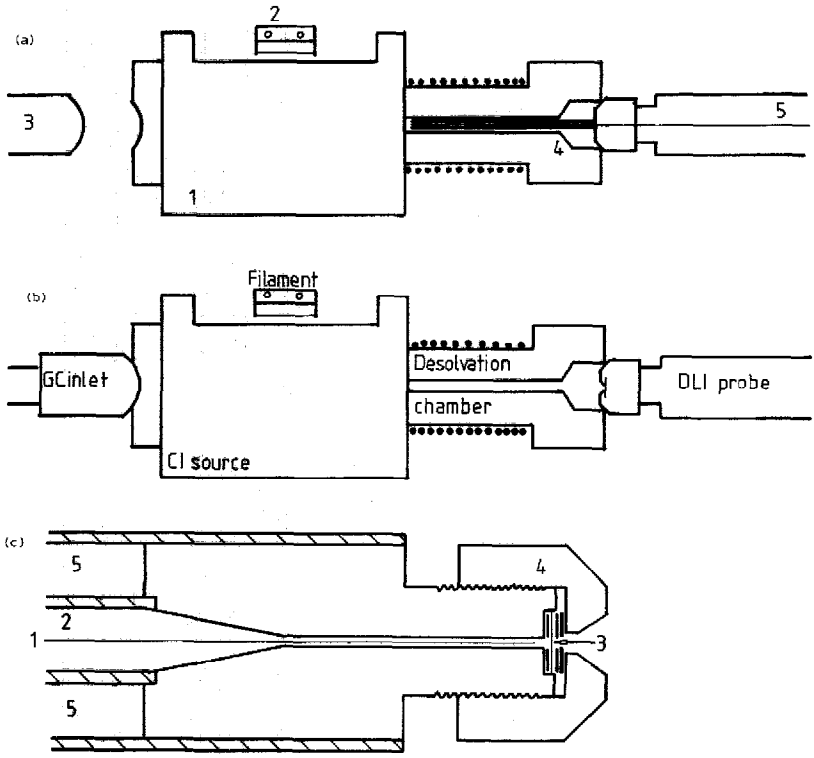

Fig. 1. Schematic diagrams of OT-LC–MS interfaces. (a) Capillary inlet interface. 1 = CI source block; 2 = filament; 3 = GC inlet; 4 = external heater assembly; 5 = water-cooled capillary inlet probe. (b) DLI interface, showing the DLI probe, the heated Macor desolvation chamber, the CI source and the GC inlet line. (c) The laboratory-built DLI probe. 1 = open-tubular column; 2 = make-up liquid; 3 = nickel diaphragm enclosed between two PFTE spacers; 4 = stainless-steel nut; 5 = cooling-water jacket.

TABLE I

CALCULATED VALUES OF THE COLUMN DIAMETER, d_c

Viscosity of methanol = $0.57 \cdot 10^{-3}$ Pa s.

Column No.	*Stated d_c (μm)*	*Average calculated d_c ± S.D. (μm)*
1	25	28.0 ± 0.4
2	10	10.7 ± 0.3
3	5	7.1 ± 0.2

RESULTS AND DISCUSSION

External peak broadening

Considerable attention has been paid to the study of the external peak broadening. The aim of the research project in our laboratory, of which the OT-LC–MS investigations form a part, is the development of detection systems for OT-LC, giving a (lower than) 1-nl contribution to external peak broadening. The 1-nl limit is a result of theoretical calculations on the performance of open-tubular columns in comparison with packed columns, as made by Knox and Gilbert[11].

Peak-deconvolution methods, based on the exponentially modified Gaussian (EMG) model of the chromatographic peak, have been used to evaluate the external peak broadening in our system without a prior knowledge of the precise inner diameter of the column or of the diffusion coefficient of the solute in the mobile phase. By comparison with theoretically expected values, the various sources of external peak broadening have been elucidated[13]. The results indicate that the peak broadening in the interfaces is small, whereas considerable contributions from injection and the electronics have been observed. Still, external peak broadening can be made smaller than a 1-nl volume contribution, as can be seen from the data in Table II.

TABLE II

EXPERIMENTAL EXTERNAL PEAK BROADENING IN THE OT-LC–MS SYSTEM

Solvent, methanol; solute, toluene. Linear velocity, u, and external peak broadening, σ_{ext}.

Column	*u (mm/s)*	*Capillary inlet σ_{ext}*		*DLI: σ_{ext}*	
		s	*nl*	*s*	*nl*
6.82 m × 28.0 μm I.D.	27	0.34	5.8	0.49	7.9
	7	0.82	3.4	0.62	2.6
2.03 m × 10.7 μm I.D.	12	0.26	0.30	0.31	0.33
	4	0.67	0.19	0.50	0.18
1.81 m × 7.1 μm I.D.	10	0.18	0.07	0.21	0.09
	2	0.47	0.05	0.68	0.04

TABLE III

COMPARISON OF THE PLATE HEIGHTS AND PLATE NUMBERS OF A 2.03 m × 10.7 μm I.D. OPEN-TUBULAR COLUMN, MEASURED WITH THE CAPILLARY INLET INTERFACE OR THE DLI INTERFACE

Linear velocity (mm/s)	*Inlet*	*Plate height (μm)*	*Plate number*	*Resolution*
4 ($1.8u_{opt}$)	Theory	3.6	560 000	1.0
	Capillary inlet	5.0	410 000	0.85
	DLI	5.6	360 000	0.8
12 ($5.6u_{opt}$)	Theory	9.0	230 000	1.0
	Capillary inlet	14.0	145 000	0.8
	DLI	24.0	85 000	0.6

In Table III, plate heights measured for a 2.03 m × 10.7 μm I.D. column with a capillary inlet and a DLI interface are compared with the theoretical plate heights according to the Golay equation for two linear velocities. Effects on plate numbers and resolution are also shown. At a linear velocity of 4 mm/s, which is about twice the optimum velocity, the external peak broadening results in a decrease in plate number and resolutions of 27 and 14%, respectively, when the capillary inlet interface is used, and of about 36 and 20%, respectively, when the DLI interface is used.

The capillary inlet interface is expected not to contribute to peak broadening. With volatile solutes no indications of peak broadening in the interface have been found, whereas with less volatile solutes broad and irregular peak profiles have been observed, which are probably due to insufficient heat transfer, slow evaporation and thermal decomposition.

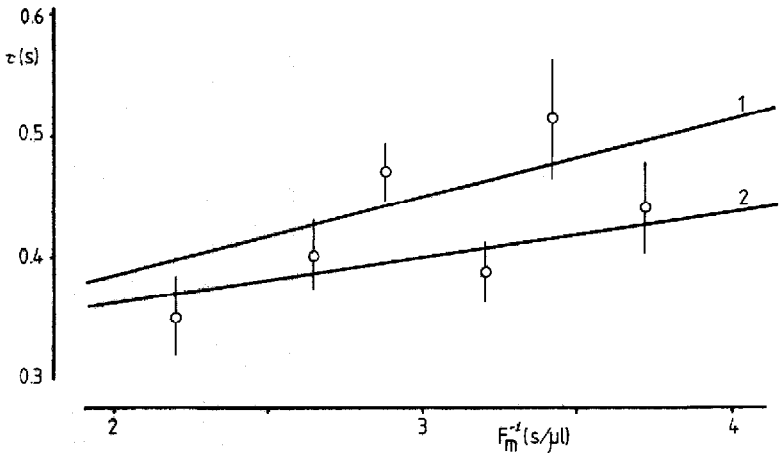

Fig. 2. Plot of the total experimental time constant, τ (s), *versus* the reciprocal of the make-up flow-rate, F_m^{-1} (s/μl), with (○) experimental values. 1, Theoretical for a 100 nl mixing chamber; 2, theoretical for a 70 nl mixing chamber.

In the DLI interface a small mixing chamber is present. The contribution to peak broadening of this volume depends on the make-up flow-rate (200–500 nl/s), which exceeds the column flow-rate (0.1–10 nl/s). The expected linear relationship between the overall external peak broadening and the reciprocal make-up flow-rate was observed experimentally (Fig. 2). The results indicate a volume of 80–100 ml for the mixing chamber. The DLI interface, operated with a 500 nl/s make-up flow, will give a 5% contribution to peak broadening when the column peak standard deviation is 0.44 s. It can be concluded that no problems are to be expected from peak broadening in the interface.

Whereas the peak broadening due to the interface is small, and that due to the electronics can be made sufficiently small, the peak broadening in the injection and splitting system still needs further reduction. The injection volumes used in our experiments are 2–5 times higher than those allowed when a 5% contribution due to injection is accepted. Attempts to work with smaller injection volumes, by using either higher split flow-rates or 0.5-μl internal loop valves in combination with a moderate splitting, have not been very successful. Although many experiments have been performed successfully with the described split injection system, sometimes very asymmetric peaks have been observed, the asymmetries of which are dependent on flow-rate. The peak shapes can often be improved by reassembling the splitting and injection section, although visually no changes were made in the geometry of the splitting device. These results indicate that the geometry of the splitting and injection section piece is critical. However, the parameters that control these incidental occurrences are not well understood. Further work is in progress.

Fig. 3 shows a plot of the ratio of the maximum acceptable injection volume and the flow-rate *versus* the column peak standard deviation for various percentage

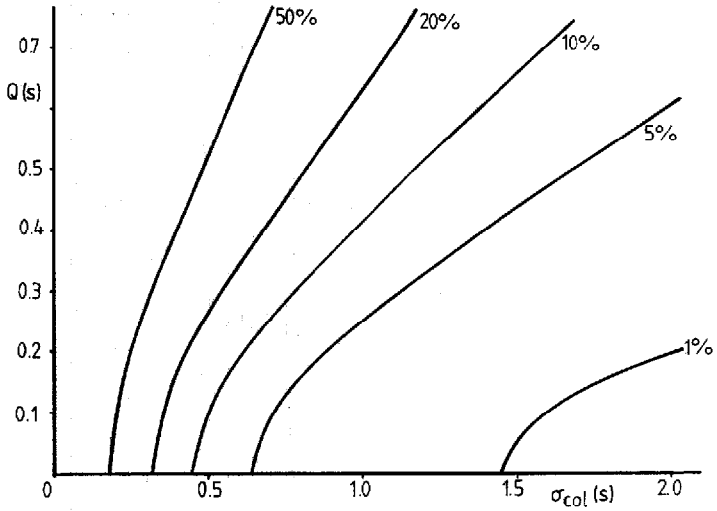

Fig. 3. Plots of the ratio of the maximum accepted injection volume and the flow-rate, Q (s), and the column peak standard deviation, σ_{col} (s), for various percentage contributions. This plot can be used to calculate the maximum tolerable injection volume for a particular column and flow-rate at a particular percentage contribution. Values of 0.14 and 0.15 s were assumed for the time constants of DLI interface and the electronics, respectively.

contributions. It reflects the observed importance of the injection volume in the present external peak broadening. This plot can be used to calculate the maximum tolerable injection volume for a particular column and flow-rate, while accepting a certain percentage contribution of external peak broadening.

Range of applicability

Our investigations of the range of applicability of the two interfaces support the trends outlined in literature. With the capillary inlet interface, compounds with boiling points below 500°C and molecular masses below 350 g/mole can be determined. Therefore, the applicability is limited to non-polar and moderately polar compounds of not too high molecular mass, for which LC is preferred to GC. Thermally labile compounds tend to decompose in the interface[14]. From the results of Alborn and Stenhagen[9] it appears that a combination of low pressure in the ion source and high electrostatic fields in a sector instrument can extend the range of applicability of the capillary inlet interface.

The DLI interface has been adopted in order to broaden the range of applicability. Several compounds that cannot be analysed successfully with the capillary inlet interface, such as glucose, theophylline and androst-4-ene-3,17-dione, show good CI spectra with the DLI interface. The broad applicability range of the DLI interface can also be seen from results reported in literature[23]. The range of applicability of a pneumatic nebulizer appears to be comparable to that of a DLI interface[18,25].

One of the problems with the DLI interface, and probably also with the pneumatic nebulizer, is the poor heat transfer to the liquid droplets under vacuum to assist in the evaporation of the solvent[3]. This limitation was fully recognized when the use of the DLI interface was extended to higher flow-rates[26]. In our search for better detection limits in OT-LC–MS, the question arises of whether most of the solute molecules are efficiently desolvated and completely available for the chemical ionization process, or whether a (large) part of the solute leaves the ion source as neutral, highly solvated molecules. In the former instance the ionization efficiency can be improved by optimizing the ion-source pressure or by increasing the residence time of the molecules in the source, whereas in the latter instance improvements in detection limits can probably be better achieved by more efficient desolvation. The difficulties that Arpino and Beaugrand[26] encountered with the DLI interface in producing filament-off ionization, which is easily achieved with a thermospray interface, are probably indicative of insufficient desolvation. These observations may shed some light on the importance of heat transfer aspects and droplet size distribution for the thermospray method. Although on the introduction of thermospray the influence of pre-formed ions in solution and liquid-ion evaporation has been emphasized[27,28], it now appears that conventional chemical ionization and gas-phase ion chemistry also play an important role in the thermospray ionization process[29–31]. These observations stress the necessity for efficient desolvation of the droplets. The widened range of applicability of the thermospray interface cannot yet be obtained with DLI methods.

Some preliminary experiments have been performed to study the possibilities of thermospray nebulization for OT-LC–MS. It is possible to achieve thermospray nebulization from narrow-bore fused-silica capillaries[32]. However, linear velocities in the column should exceed 0.5 m/s for successful direct thermospray nebulization,

and such velocities are too high for chromatographic purposes. Of course, it may be possible to use a make-up flow-rate to assist in the nebulization process. Such an approach will certainly extend the potential of OT-LC–MS.

The evaporation of liquid droplets can also be improved by nebulization of the liquid in an atmospheric pressure chamber. Examples of this approach, which would also necessitate the use of a make-up liquid in OT-LC–MS coupling, were given by Willoughby and Browner[33] for a monodisperse aerosol generating interface (MAGIC) and by Whitehouse *et al.*[34] for an electrospray interface. Evaluation of their results in terms of improvements in detection limits is not yet possible.

In our opinion, the use of a make-up liquid is certainly not the best solution to the problems present in interfacing OT-LC and MS. It is in fact similar to the situation in the early days of capillary GC–MS: addition of gas at the end of the capillary column in order to be able to use conventional jet separators. However, at present the use of make-up liquid appears to be the most practical approach for the application of various interfaces in OT-LC–MS.

Ionization conditions

In our experiments we use open-tubular columns of I.D. 7–28 μm. The columns are operated at linear velocities near to the kinetic optimum velocity, resulting in flow-rates between 0.12 and 18 nl/s. The pressure in the ion-source housing of the modified vacuum system[14] can be kept below 1.5 mPa with methanol flow-rates up to 14 nl/s. When under these conditions an open EI source is used, it is possible to obtain electron-impact spectra. With the tighter CI source used in most experiments the EI conditions are met at lower flow-rates (below 2 nl/s). It must be pointed out that at the low end of the mass spectrum peaks of solvent ions will interfere with the solute spectrum. Apart from intense interfering peaks from the methanol spectrum, *e.g.*, at *m/z* 15, 29, 31 and 32, some peaks at *m/z* 45 and 63 are also observed. The latter ions are probably due to an ion–molecule reaction of *m/z* 31 with neutral methanol followed by loss of water.

With the DLI interface, substantially higher flow-rates are introduced, resulting in CI conditions in the ion source. The solvent spectra observed under these conditions closely resemble those reported for DLI[35,36]. Fig. 4 shows an example of the methanol reagent gas spectrum. The spectrum contains an intense peak of a protonated methanol molecule at *m/z* 33, and several solvent cluster ions at higher masses, the relative intensities of which greatly depend on the temperature and the pressure in the ion source. The solute spectra are typical CI spectra: intense peaks

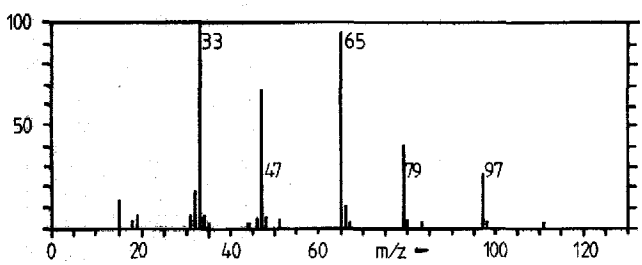

Fig. 4. Typical reagent gas spectrum of methanol under CI conditions. Temperature of ion source and desolvation chamber, 150°C.

from protonated molecules and little fragmentation. Some examples are shown in Fig. 5.

In an attempt to optimize the system for better detection limits, the influence of the ion-source pressure has been studied in more detail. The pressure in the ion source can be varied in three ways: by changing the size of the ion-source apertures, by varying the distance between the DLI probe tip and the desolvation chamber and by varying the flow-rate. Changing the size of the ion source apertures is inconvenient in our system, as these apertures cannot be varied from outside the vacuum system.

Sugnaux *et al.*[37] have shown the potential of ion-source pressure regulation by varying the distance between the DLI probe tip and the desolvation chamber. In our design, the probe tip fits closely to the desolvation chamber (*cf.*, Fig. 1b). In agreement with the observations of Sugnaux *et al.*[37], it has been found that withdrawing the probe tip 1 mm from the desolvation chamber results in a drastic change in the spectrum of the reagent gas. A more gradual change in the spectrum of the reagent gas with this distance has been observed in some preliminary experiments with a modified desolvation chamber, which envelop the DLI probe tip. A modest improve-

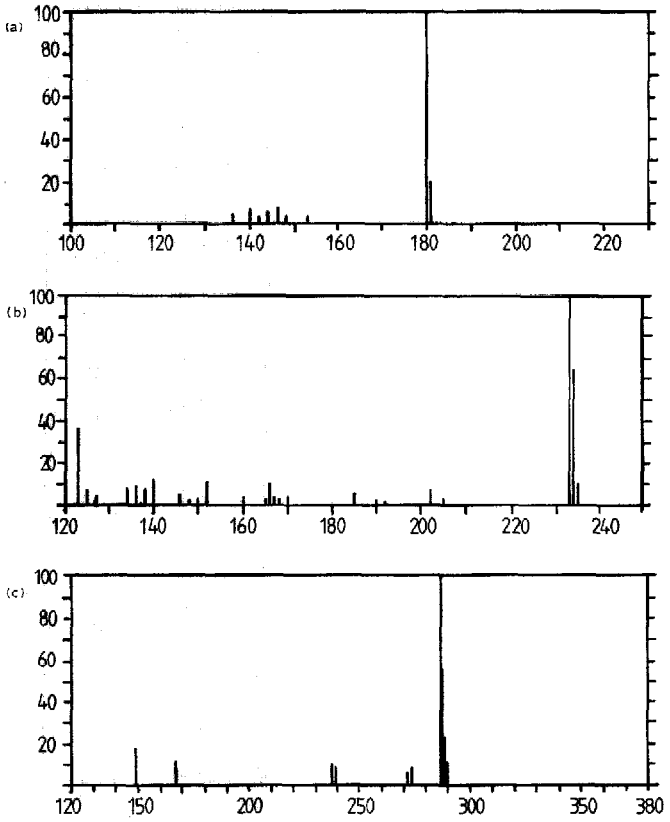

Fig. 5. CI mass spectra for various compounds (high flow-rate region). CI reagent gas, methanol; temperature of ion source and desolvation chamber, 170–200°C. (A) Phenacetin [N-(*p*-ethoxyphenyl)acetamide]; (B) diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea]; (C) androsten-4-ene-3,17-dione.

ment (a factor of 3–10) in the signal-to-noise ratio of the selected ion peak of toluene (*m/z* 93) has been observed in the latter instance.

The influence of the flow-rate on the CI reagent gas spectrum has also been studied. With the capillary inlet interface flow-rates up to 100 nl/s can be used. Higher flow-rates result in pressure fluctuations, probably owing to freezing of the solvent as a result of insufficient heat transfer. With the DLI interface equipped with a 4 μm I.D. diaphragm it is possible to introduce amounts of liquid at between 0.15 and 0.6 μl/s. Using these two interfaces flow-rates between 10 and 580 nl/s of methanol have been introduced, and the reagent gas spectra have been studied. The ion source has been made as tight as possible in these experiments. The protonated methanol, $[M + H]^+$ at *m/z* 33, is the base peak of the spectrum over the entire range of flow-rates. On increasing the flow-rate, the relative abundances (normalized at *m/z* 33) of the typical EI peaks at *m/z* 15, 29, 31, 45 and 63 decrease, whereas the relative abundances of the peaks of protonated molecule and ion clusters at *m/z* 47, 65, 79 and 97 increase. Fig. 6 shows a plot of the relative abundances of the peaks at *m/z* 31 (the base peak in the methanol EI spectrum) and 47 (the $[CH_3OH\ CH_3]^+$ ion) as a function of the flow-rate and the pressure in the ion-source housing. An increase in the total ion current with increasing flow-rate was also observed. However, owing to some fluctuations in the electron current at some of the higher flow-rates, the above results cannot be discussed in terms of absolute peak intensities. This would have given even more information on the ion plasma.

Detection limits

The minimum detectable quantities (MDQ) found in our experiments (with selective ion monitoring) with the capillary inlet and the DLI interface are similar: 1–10 pg for volatile solutes, such as toluene and aniline, and 30–80 pg for less volatile solutes, such a phenacetin and caffeine. Although MDQs in the low picogram range

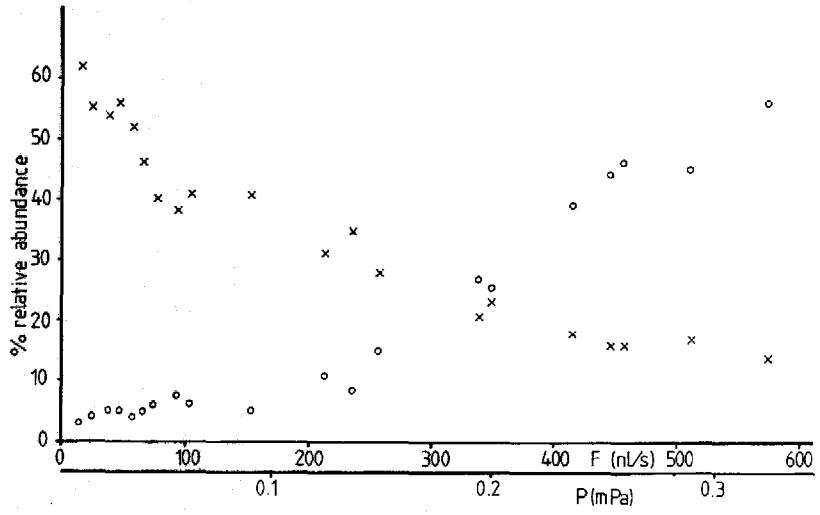

Fig. 6. Relative abundance of the mass peaks at *m/z* 31 (×) and at *m/z* 47 (○) as a function of the flow-rate, *F* (nl/s), or the pressure in the ion source housing, *P*. All values are normalized to *m/z* 33.

seem impressive, the concentration detection limits are completely inadequate for successful operation of OT-LC–MS. For example, the MDQ of about 5 pg observed for aniline (see Fig. 7) corresponds to a concentration of 5 μg/ml, when 3.5 nl is injected on to a 6.82 × 28.0 μm I.D. column. Considerably lower MDQs are necessary for a mass spectrometer to be used as a detector in OT-LC. This conclusion will be considered in more detail.

The detection limit in terms of mass flow, S_m (kg/s), of a mass-flow sensitive detector, such as a mass spectrometer, can be written as

$$S_m = \frac{3\ N_d m}{R_d \sqrt{2\pi}\ \sigma_t}$$

where N_d is the detector noise, R_d the detector response, m the mass of solute injected on to the column and σ_t the peak standard deviation in time units. Reviewing the results reported in the literature on coupling of conventional and microbore LC columns and MS shows that mass-flow detection limits between 0.1 and 100 pg/s are observed, whereas we obtained 5–100 pg/s for OT-LC–MS.

The mass-flow detection limit required to detect a signal from an injection of 1 μg/ml on to an open-tubular column giving 10^6 plates has been calculated. The injection volume for a particular column was chosen by using Fig. 3, thus taking into account the external peak broadening of the complete DLI-OT-LC–MS system. The results are presented in Table IV. It can be concluded that the mass-flow detection limit must be improved by two orders of magnitude in order to be able to detect 1 μg/ml of solute from a 10 μm I.D. column, and by even more for columns of smaller inner diameter and/or lower concentration detection limits.

Further, it must be emphasized that the MDQs reported here were measured with unretained peaks. Retention will lead to larger peak variance. The mass flow of solute at the peak maximum is proportional to the reciprocal of the peak standard deviation in time units. The peak height is a measure of the mass flow at the peak maximum when a linear detector response is assumed. Fig. 8a shows a plot of the relative peak height as a function of the capacity factor for a typical open-tubular

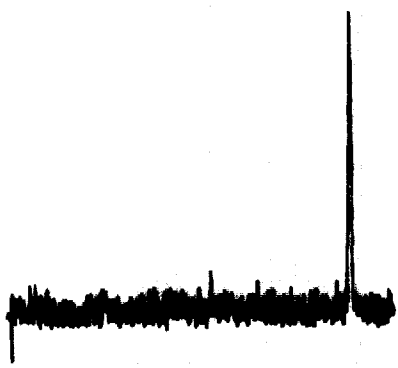

Fig. 7. Chromatographic peak of aniline near the MDQ. Conditions: injection of 3.5 nl of 5 μg/ml aniline on to a 6.82 m × 28.0 μm I.D. open-tubular column; DLI interface; mobile phase and make-up liquid, methanol.

TABLE IV

REQUIRED MASS-FLOW DETECTION LIMITS, S_m, TO DETECT 1 μg/ml OF SOLUTE FROM AN OPEN-TUBULAR COLUMN GIVING 10^6 PLATES (OPERATED AT 10 mm/s)

σ_{tot} = Total peak standard deviation; V_{inj} = injection volume.

Column	*Contribution (%)*	V_{inj} *(nl)*	σ_{tot} *(s)*	S_m *(pg/s)*
11 m × 10 μm I.D.	5	0.212	1.113	0.23
	10	0.345	1.166	0.35
	20	0.526	1.272	0.49
3 m × 5 μm I.D.	50	0.0047	0.42	0.0134

column (constant injected mass). The peak heights decrease very rapidly with increasing retention. At a capacity factor of 2 the peak height is reduced to about 13% of the height of the unretained peak.

External peak broadening also affects the attainable MDQ, although this effect is less pronounced than the effect of retention. Fig. 8b shows a plot of the relative

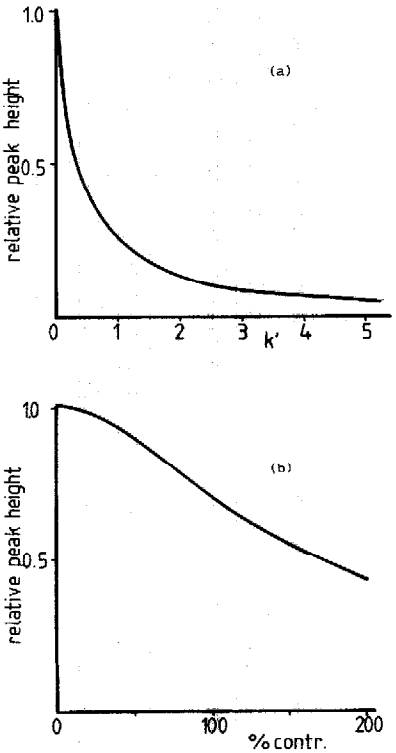

Fig. 8. (a) Relative peak height as a function of capacity factor, k' (unretained peak has peak height 1.0). Conditions: column, 5 m × 10 μm I.D.; film thickness, 0.125 μm; linear velocity, 5 mm/s; diffusion coefficients in mobile and stationary phase, 10^{-9} and 10^{-11} m^2/s, respectively; no external peak broadening. (b) Relative peak height as a function of the percentage contribution (a 0% contribution has a peak height of 1.0).

peak height as a function of the percentage contribution of the external peak broadening.

The MDQ in DLI-LC–MS is known to be greatly influenced by the composition of the CI reagent gas and by the distance of the probe to the ion source. Some improvements in MDQs for particular solutes are possible by optimizing the ion-source pressure and temperature, the composition of the make-up liquid, which determines the CI reagent gas, the inner geometry and the temperature of the desolvation chamber, and/or the distance between the probe tip and the ion source. However, this approach is not expected to lower the MDQ more than about 50-fold, and this is probably an optimistic estimate. The results in Table IV and Fig. 8a indicate that at least 10^3-fold improvement in mass flow detection limits is necessary. When these improvements can be achieved, the detection power of the OT-LC–MS system will still not compete with that of conventional or microbore LC–MS systems in terms of concentration detection limits. However, the very high efficiencies that can be obtained in relatively short times with OT-LC will probably compensate for this in many interesting applications.

CONCLUSIONS

In contrast to the situation in coupling conventional LC and MS, where the large amount of liquid hampers the coupling, it is difficult to select an appropriate interface for OT-LC–MS coupling owing to the very low flow-rates used in open-tubular columns. The only interface that is flow-rate compatible, the capillary inlet interface, has a too limited range of applicability[14]. Nebulizing interfaces, which give broader application, require much higher flow-rates. Our solution to these problems, *i.e.*, an additional liquid flow to achieve nebulization of the column effluent, is not the best, but about the only one available at present.

The most important problem in OT-LC–MS appears to be the mass-flow detection limit of the present equipment. At least a 10^3-fold improvement has been shown to be necessary before the widespread use of OT-LC–MS may be expected. The results on ionization conditions, applicability range and external peak broadening are all discussed here from this point of view. Although some improvements in mass-flow detection limits may be expected from optimizing the experimental parameters of the present system, *e.g.*, ion source pressure and interface geometry, a revolutionary approach to this problem in both interfacing and mass spectrometry appears to be necessary in order to solve the problems of the inadequate mass-flow detection limits.

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