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Hyphenation of high-temperature liquid chromatography with high-pressure electrospray ionization for subcritical water LC-ESI-MS†

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High-pressure electrospray ionization (HP-ESI) performed under super-atmospheric pressure allows a stable and efficient electrospray of pure aqueous and/or superheated solutions even under a μL min^{-1} flow rate regime. In this paper, we report the direct coupling of the HP-ESI source to high-temperature liquid chromatography (HT-LC) operated at ≤30 μL min^{-1} flow rates. In addition to ESI, the ion source functions as a back-pressure regulator to keep the mobile phase in the liquid phase when the column is heated to >100 °C. Under an ion source pressure of 7 bar, the LC column can be operated up to 160 °C. LC is performed under isocratic elution, and besides the isothermal mode, the temperature of the column can also be programmed to increase the selectivity while keeping the ion source at a constant temperature. For a given solution flow rate, the analytical time can be shortened by increasing the column temperature. HT-LC-ESI-MS using pure water as the mobile phase with a capillary column is also demonstrated.

Introduction

Operating the analytical column at a high temperature increases the efficiency and speed of liquid chromatography. Heating the liquid to a temperature much higher than room temperature changes some of its properties. When the liquid is heated, surface tension and viscosity decrease, and solutes diffuse faster in the liquid. These changes favor the separation of analytes if those solutes do not decompose and if the stationary phase remains stable at high temperature. The theoretical framework of high-temperature liquid chromatography (HT-LC) was introduced as early as the 1980s.[1] The increase in solute diffusivity in the liquid promotes the mass transfer between the stationary and mobile phases and that reduces the contribution of the C-term in the van Deemter equation, which allows a column to be operated at high eluent velocity without losing the number of theoretical plates. It had been pointed out that the analytical speed of GC is generally higher than room temperature LC because analytes diffuse faster in a gas than in a liquid.[2] The improvement in diffusivity at high temperature thus makes the analytical speed of HPLC on par with GC.[3]

For a given pumping pressure, the reduction in eluent viscosity allows one to operate LC at a higher flow rate, or to use either longer columns or columns packed with smaller particles. For a liquid like water, the dielectric constant (polarity) also decreases with temperature,[4,5] and at elevated temperature, water behaves as if it is an organic solvent.[6] In LC, a change of column temperature has an equivalent effect of a change in acetonitrile concentration on retention.[7] This forms the basis for temperature programming as an alternative to gradient elution. A recent analysis showed that even for an isothermal operation, it was advantageous to set the temperature to the highest possible value that can be tolerated by the instrument and analytes to optimize the peak capacity.[8]

At present, most commercial silica-based stationary phases are not thermally stable at high temperature and the typical operation is limited to below 80 °C. Alternatives to silica for high-temperature application are zirconia[9] and graphite particles.[10] Conveniently, these particles are also stable under harsh pH conditions and have become commercially available recently. Using zirconia-based particles, the potential of HT-LC for sub-minute analysis had been demonstrated by the Carr group by flowing the eluent at 15 mL min^{-1} through a 50 mm long column with a 4.6 mm inner diameter.[11] Temperature mismatching of the eluent before and after entering the column is a key issue that affects the resolution and elaborate efforts have been made for the pre-heating of the eluent in

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addition to post-column cooling and back pressure regulation. Back pressure regulation is needed to prevent the boiling of eluent within the column if the temperature exceeds the normal boiling point. For relatively low flow rate operation such as that in chip-based HT-LC, the preheating loop was unnecessary because the heating was quick enough and the radial dispersion is negligible for narrow columns.[12] The column packed with 100% carbon is free of column bleeding because the particles have no bonded phases, and the retention is due to to the dispersive and charge induced interaction with the graphite surface.[10] Besides small molecules, the separation of proteins using high-temperature LC with a polymer-based column has also been reported.[13] Besides high throughput analysis, HT-LC using superheated water has also emerged as a promising green LC method.[14–16]

The common detection method for HT-LC is UV detection, but it has also been coupled to a flame detector.[15] The coupling of HT-LC to MS had been performed using pneumatically-assisted ESI at >100 μL min^{-1} and with the use of flow restrictors of 50–64 μm.[10,17] The pressure drop across the flow restrictor (owing to the Hagen–Poiseuille law) under the flow regime of several hundreds of μL min^{-1} was enough to provide a back pressure to the column to avoid the boiling of eluent. However, the back pressure generated by the restrictor depends on the viscosity and varies with the liquid flow rate. Under the flow regime of several tens or several μL min^{-1} and with the reduced viscosity at high temperature, the pressure drop across the restrictor was insufficient for elevated temperature operation. The addition of the restrictor and cooling loop introduces an additional dead volume to the system that causes the post-column broadening.

Although the conventional flow regime LC-MS is in the order of several hundred μL min^{-1}, the efficiency of ESI and its tolerance to contaminants is higher under a lower liquid flow rate.[18–20] Spraying samples sparingly at a few μL min^{-1} or less is ironically more sensitive than introducing a large amount of sample in a short time. Although flow splitters can be used to divert the extra eluent to waste, it would be economical and more sensitive to employ a μL min^{-1} flow rate for the whole LC and ESI system to reduce the sample and solvent consumption and matrix effects.[21,22]

In this work, endeavors have been made to hyphenate the low flow HT-LC directly to ESI-MS *via* a high-pressure ion source. The high-pressure ESI (HP-ESI) source with an operating pressure of >1 atm was first developed in our laboratory to prevent the unwanted electrical discharge when dealing with pure water solution and to increase the desolvation efficiency.[23] Under a moderate pressure of <7 bar, direct coupling to a mass spectrometer can be performed with a modified ion transfer tube without the addition of extra pumping. Compared to a solution prepared in organic solvents, ion abundance of hydrophobic contaminants was reduced and a much cleaner spectrum could be obtained using pure aqueous solution.[24] Under super-atmospheric pressure, solutions can also be heated above their normal boiling points (*e.g.* 100 °C for water), and stable ESI of the superheated solution had been demonstrated up to a solution temperature of 220 °C under 22 bar.[25] The technique has been applied to rapid non-enzymatic digestion mass spectrometry in which the digestion products were ionized *in situ* with ESI,[26] and the overall time for digestion and ESI-MS acquisition could be as short as 3 s.[27] Here, HT-LC was coupled directly to HP-ESI without using a flow restrictor and post-column cooling. Under a super-atmospheric pressure operation, the ion source itself functioned as the pressure regulator to the LC system to prevent the liquid from boiling within the column.

Experimental section

High-temperature liquid chromatography system

The schematic of the HT-LC-HP-ESI system is shown in Fig. 1. The photographs of the experimental configuration are shown in ESI Fig. S1 and S2.† The automatic sample injector and the liquid pump unit were from Shimadzu (Nexera 2, Shimadzu, Kyoto, Japan). Two columns were tested in this study. One was a 100 mm × 1 mm i.d. column packed with porous graphitic carbon of 3 μm diameter. This column used all metal components for sealing and could be safely used up to 200 °C. Another one was a 100 mm × 0.1 mm i.d. capillary column packed with 5 μm graphitic carbon. Both columns were from Thermo Fisher Scientific. A stainless-steel capillary of 0.1 mm i.d. and 1.6 mm o.d. (Supelco, Sigma Aldrich, St Louis) was used optionally for the pre-heating of eluent before entering the analytical column. The column and the pre-heating capillary were embedded within heating blocks made of aluminum. The aluminum blocks were attached with a cartridge heater and platinum temperature sensors. All gaps were filled with silicone/zinc oxide based thermal conductive grease. The temperatures of the column and the preheater were controlled using temperature regulators (Omron, Kyoto, Japan). The ESI capillary was connected directly to the outlet of the column using a PTFE sleeve and a stainless steel ferrule. The inlet to the preheater capillary or the column (when preheater was not in use) was connected to an automatic sample injector using a ~20 cm long fused silica capillary of 50 μm inner diameter. This provided a sufficient electrical isolation for the column as

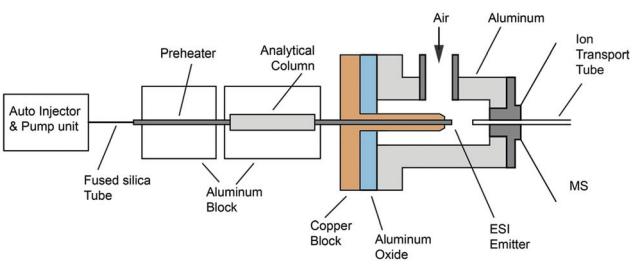

Fig. 1 Schematic of the hyphenation of high-temperature LC with high-pressure ESI-MS. The ion source is pressurized with air from a compressor. A preheater is used for 1 mm i.d column. For 0.1 mm i.d. capillary column, the fused silica tube from the injector is connected directly to the analytical column.

well as the ESI capillary from the ground. Only a single liquid pump was used and all chromatographic separations were performed isocratically.

High-pressure electrospray ionization source

The HP-ESI source employed previously for subcritical water ESI was used.[26] In brief, the ESI emitter (stainless steel capillary of 0.1 mm i.d. and 0.2 mm o.d. from Nilaco, Tokyo, Japan) was housed inside an ion source chamber made of aluminum alloy. The ESI capillary was embedded within a copper heater block to control the liquid temperature before emerging to the ESI emitter tip. The ion source was pressurized with air and the ion source pressure could be varied depending on the column temperature. In this study, the maximum pressure was 7 bar (absolute pressure), and the maximum column temperature was 160 °C. The generated ions were introduced to mass spectrometry *via* a homemade ion transfer tube. Unless otherwise stated, the i.d. of the ion transfer tube was 0.25 mm.

Mass spectrometer

The experiment was conducted using a benchtop Orbitrap mass spectrometer (Exactive, Thermo Fisher Scientific, Bremen, Germany). The settings for the Exactive-Orbitrap were as follows: the temperature for the ion transport tube was 300 °C, the inlet capillary and tube lens voltages were 50 V, and the skimmer voltage was 20 V. The maximum ion injection time was 100 ms. Extracted ion chronograms were accumulated to construct the chromatograms. In this study, all analytes were detected as protonated species $[M + H]^+$.

Sample preparation

The mobile phase containing HPLC grade acetonitrile and 0.1% v/v formic acid were from Fisher Scientific (Hampton, USA). The sample for mixture I (metoprolol, acebutolol, propranolol, quinidine) and mixture II (sulfaguanidine, sulfathiazole, sulfamerazine, sulfamonomethoxine) was from Sigma Aldrich (St Louis, USA) and was used without further purification. Methamphetamine was from Sumitomo Dainippon Pharma, Osaka, Japan. Pure water was produced using Simplicity UV (Millipore, Burlington, USA). The final solution of mixtures I and II was prepared in 10^{-5} M for each analyte in the solutions, and 0.1 μL was injected using the automatic injector. Raw urine collected from a volunteer was diluted 10-fold using pure water. Methamphetamine solution (0.5×10^{-7} M) was prepared in the diluted raw urine and was injected directly into the column with the automatic injector. All samples were filtered using a 0.2 μm PTFE syringe filter ((Millipore, Burlington, USA) prior to analysis. Informed consent was obtained from all individual study participants prior to the research procedure.

Results and discussion

Boiling of liquid at the ESI emitter had an adverse effect on the spray stability. When the ion source is operated at a solution flow rate of several to several tens μL min^{-1}, the liquid was in good thermal equilibrium with the emitter capillary. At 100 °C emitter temperature, the spray became unstable and the bumping or bursting of the liquid took place. The liquid at the sprayer could even evaporate completely if the ion source was further heated to >100 °C without generating gaseous ions (ESI Fig. S3†). Even by cooling the ion source, the boiling of eluent within the heated column could still take place if the backpressure was insufficient. One such example is shown in ESI Fig. S4,† in which the ion source was placed under atmospheric pressure and at room temperature while the column temperature was kept at 100 °C. The bubbles due to the cavitation of the eluent within the column can be seen emerging from the ESI capillary into the liquid cone (Taylor cone) at the emitter tip. The bubbling eased when the ion source was pressurized with nitrogen or air.

Usually, when the column temperature was raised under non-boiling conditions, the viscosity of the eluent reduced and it was accompanied by a drop of pump pressure and a reduction in retention time for analytes. When the boiling took place within a column, it was noticed that the pump pressure increased, and the retention trend reversed, *i.e.* the retention time became longer accompanied by a broadening of peak width. Severe bleeding/leaking of graphite particles was also observed (ESI Fig. S5†) when the column was operated for a few minutes under boiling conditions, probably due to the failure of frit.

To prevent the boiling, a conventional strategy used so far in high-temperature liquid chromatography is to add a flow restrictor, a post-column cooler, and in the case of UV detection, a pressure regulator to the system line. While such an arrangement is suitable for >100 μL min^{-1} operation, the flow restriction is not appreciable for low flow rate and high-temperature operation and it introduces unnecessary dead volume to the system. Here, we used the high-pressure ESI method as the straightforward remedy to this problem.

For the columns of the diameter of >1 mm operated at liquid flow rates above 1 mL min^{-1}, there was a concern about temperature difference between the incoming eluent and the columns. The radial temperature gradient and the resultant gradient in viscosity and solute velocities are thought to be the reason for peak broadening.[28] A pre-heater tube was usually used to overcome the temperature mismatch. Yan *et al.* calculated that the heater tube needed a minimum length of 34 cm to achieve thermal equilibrium for a flow rate of 5 mL min^{-1}.[11] Here we employed a pre-heater with a heating path of 10 cm for the operation of the column of 1 mm inner diameter at 30 μL min^{-1}. For the capillary column of 0.1 mm i.d. and the flow rate of ≤10 μL min^{-1}, the peak broadening effect owing to the radial temperature gradient was much smaller. In addition to that, the thermal equilibrium of a narrow column could be established in a very short time owing to the much smaller heat load, therefore the pre-heating of the eluent was found to be unnecessary, in agreement with other studies that used a capillary or chip-based column.[12,29]

The operation of high-temperature LC-ESI-MS was first tested with a column of 1 mm inner diameter. Compared to

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other columns of conventional dimension (2.1 to 4.6 mm) this column can be operated below 50 μL min^{-1} which is suitable for the electrospray even without the assistance of pneumatic sheath gas. Fig. 2 shows the chromatograms of four sulfonamides acquired at different column temperatures using this column. The temperature of the preheater capillary was the same as the column. The mobile phase (isocratic) was the standard 50% ACN (v/v) with 0.1% formic acid at a flow rate of 30 μL min^{-1}. At 50 °C, all four sulfa drugs could be eluted within 20 min. Although it was possible to speed up the analysis by increasing the flow rate of the mobile phase, the stability and the efficiency of ESI would be affected. By keeping the flow rate constant, the analytical speed could be increased by a factor of ~3.5 by operating the column at 160 °C (Fig. 2). The temperatures of the ion source chamber and the ESI capillary were kept constant at 160 °C for all measurements to avoid the dependence of ESI performance on the column temperature. At 160 °C, the system pressure was approximately 3 MPa, which is less than one-tenth of the typical liquid pump limit, therefore the use of finer LC particles in the future was possible to further reduce the theoretical plate height for resolution enhancement for a given column length.

Fig. 3 shows a similar reduction in retention time for another set of pharmaceutical drugs: metoprolol (1), acebutolol (2), propranolol (3) and quinidine (4). For these compounds, the LC analyses are usually performed under >7 pH condition which is not an optimum condition for positive ESI. Using a carbon stationary phase, these compounds were well separated isocratically using 50% v/v ACN in 0.1% formic acid. However, the order of elution was different from that of a standard ODS column. Under conventional LC with a standard C18 phase, acebutolol (2) precedes metoprolol (1) and quinidine (4) precedes propranolol (3). In addition to the hydrophobic interaction, the retention mechanism of graphitic carbon also involves the charge induced dipole–dipole interaction, and the surface effect from the planar nature of graphite, thus the selectivity is different from silica-based phases. The characteristic study of this type of column is not the scope in this paper, and its features are well documented in the literature.[30] While the standard silica-based column is not thermally

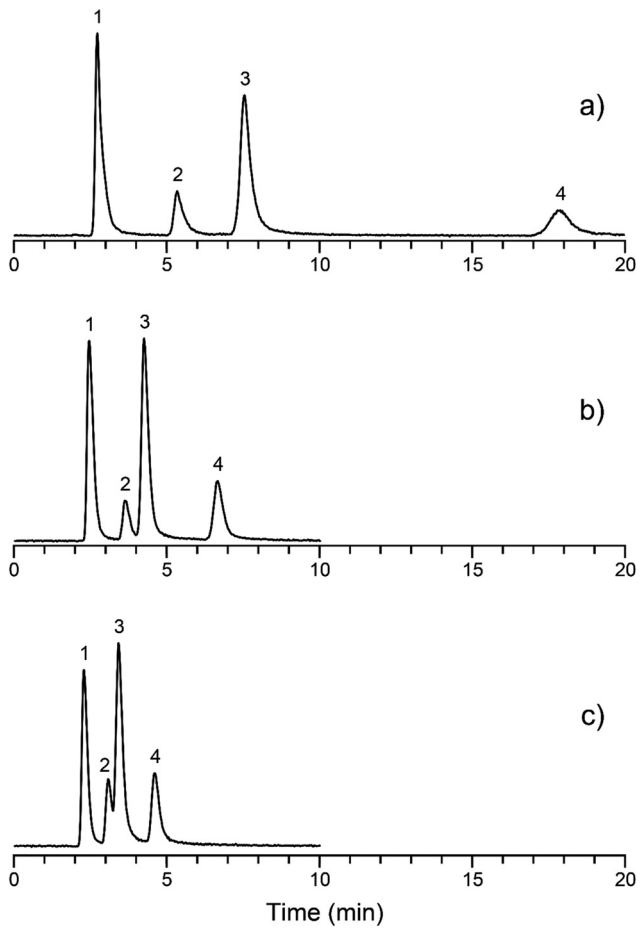

Fig. 2 Chromatograms showing the effect of column temperature using a column of 1 mm i.d. diameter. (a) 50 °C, (b) 120 °C, (c) 160 °C. Peaks are 1: sulfaguanidine, 2: sulfathiazole, 3: sulfamerazine, 4: sulfamonomethoxine. Mobile phase: 50% v/v ACN with 0.1% formic acid at 30 μL min^{-1} flow rate.

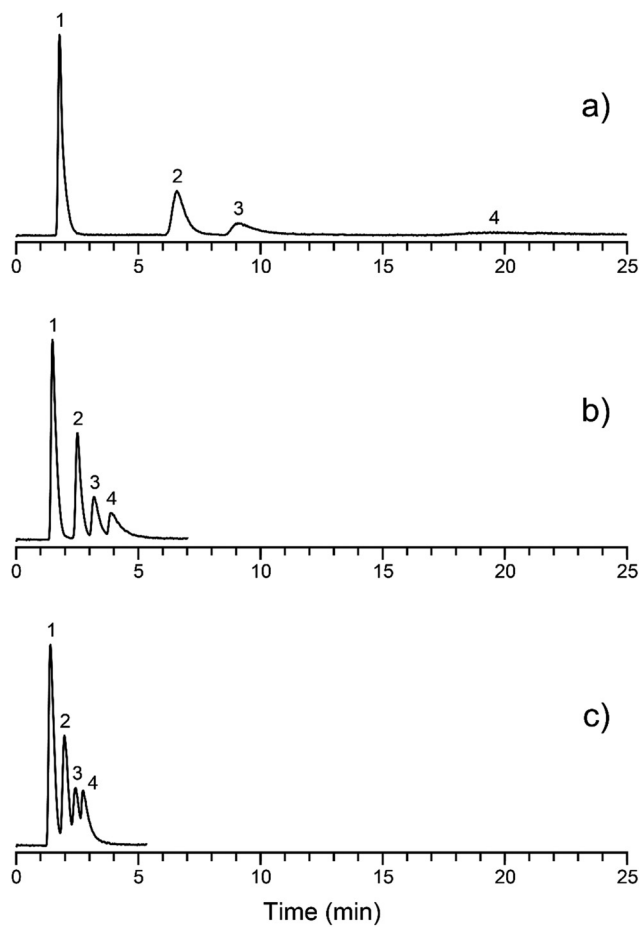

Fig. 3 Chromatograms of pharmaceuticals at different column temperatures using a column of 1 mm i.d. (a) 50 °C, (b) 100 °C, (c) 140 °C. Peaks are 1: metoprolol, 2: acebutolol, 3: propranolol, 4: quinidine. Mobile phase: 50% v/v ACN with 0.1% formic acid at 30 μL min^{-1} flow rate.

resistant to high temperature, there exists a zirconia phase (PBD) that is reported to have the same characteristic as the standard ODS phase. At present, we had not been able to acquire the commercial zirconia column with dimensions suitable for microliter per min flow rate operation, but particles from the commercial column can be custom repacked into a capillary column. Such endeavor will be pursued in future work.

The operation of high-temperature LCMS using a capillary column is relatively challenging because it is difficult to prevent evaporation and boiling at low solution flow rates even with the use of a flow restrictor. The high-pressure ionization method provides a straightforward solution to the problem and the ion source can be coupled directly to the outlet of the column. Fig. 4 shows the LC-ESI MS using a capillary column (10 cm i.d. 0.1 mm) with 5 μm particles under isocratic conditions. Pre-heating the eluent for the capillary column was unnecessary and removing the preheater capillary had actually reduced the dead time and pre-column dispersion. The solution flow rate here was 3 μL min^{-1}. This value was chosen in view of the flow stability of the present liquid pump, and the yet minimized pre/post column dead volume. Under the typical 50% ACN isocratic elution, the tested compounds were eluted too rapidly, and the theoretical plate number was not enough to resolve the peaks. To increase the selectivity, the organic component of the mobile phase was reduced. At a column temperature of 150 °C, it was found that the ACN could be reduced to ~5% (w/w) to separate the sulfa drugs in less than 10 minutes. Less consumption of organic solvents, particularly the hazardous acetonitrile in LC, is beneficial for reducing the running cost and providing a green approach for analytical chemistry.

The use of superheated water as the LC mobile phase had been a subject of study in green chemistry. However, the elution strength of the subcritical water, though is much higher than that at room temperature, is still smaller than that of the standard LC solvent. In practice, the elution using pure water for hydrophobic compounds takes a relatively long time to complete or needs to be operated at much higher flow rates (in the case of conventional columns) that may not be well supported by the ion source. The use of a capillary column has the benefit of keeping the volumetric flow rate lower even at high linear velocity. Fig. 5 shows the HT-LC-ESI-MS of sulfa drugs using pure water as the mobile phase. The flow rate was set to 10 μL min^{-1} to elute the compounds on a reasonable timescale. At this flow rate and with the column of 0.1 mm inner diameter, the linear velocity (~21 mm s^{-1}) of the mobile phase was equivalent to that with a flow rate of approximately 21 mL min^{-1} for a 4.6 mm column. For safety, and to prevent

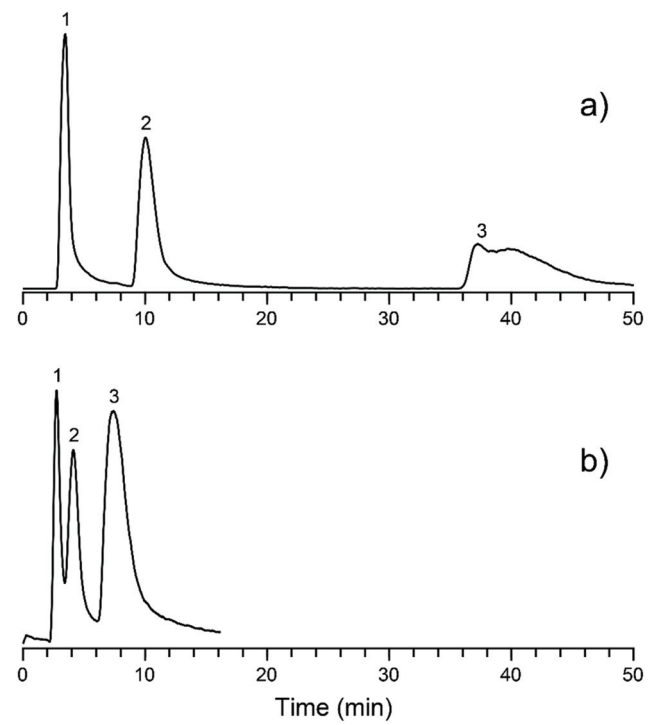

Fig. 4 Chromatograms obtained using a capillary column with 0.1 mm inner diameter at different column temperatures. (a) 60 °C, (b) 150 °C. The mobile phase: 5% (w/w) ACN at 3 μL min^{-1}. Peaks are 1: sulfaguanidine, 2: sulfamerazine, 3: sulfamonomethoxine.

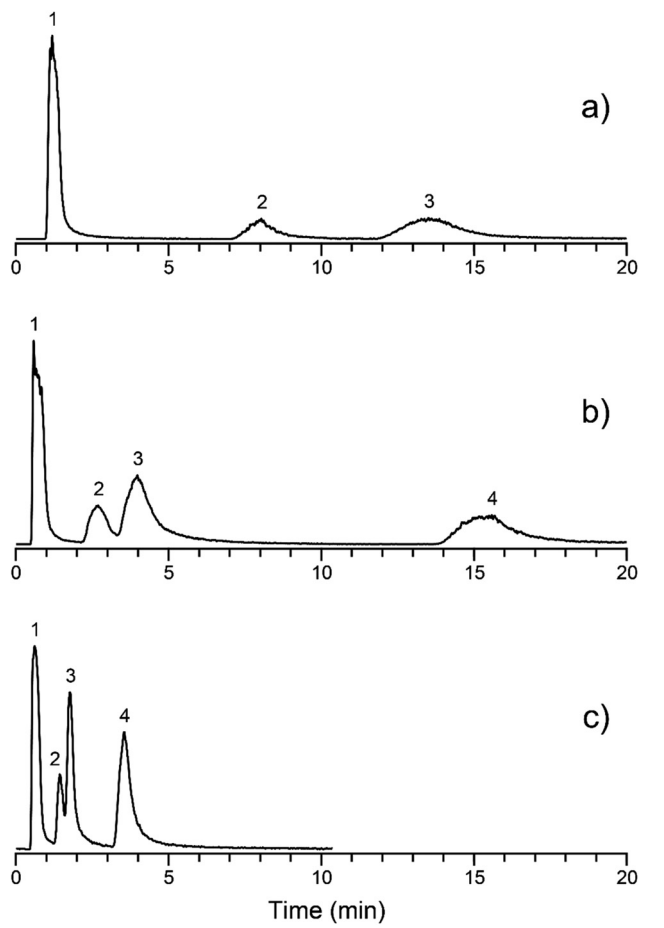

Fig. 5 Chromatograms obtained using pure water as the mobile phase at different column temperatures. (a) 80 °C, (b) 120 °C, and (c) temperature gradient from 120 °C to 150 °C at 12 °C min^{-1}. The flow rate of pure water is 10 μL min^{-1}.

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the failure of the fused silica transfer line, the upper limit of the system pressure was set to 25 MPa, which was approximately half of the maximum pressure of the normal grade HPLC pumps. The minimum temperature of the column was approximately 80 °C in order to operate the LC system below the pressure limit.

At 80 °C, one of the compounds, sulfamonomethoxine was strongly retained and could not be eluted even with over one-hour elution time. This compound was eluted with pure water at >100 °C. At 120 °C, the retention time was approximately 15.5 min. The retention time was reduced to <4 min, by increasing the column temperature to 150 °C. Under an isothermal operation of 150 °C, sulfathiazole (2), and sulfamerazine (3) were both eluted in less than 1.5 min, and could not be well resolved owing to the limited theoretical plate number of the column and the post column dispersion which had not yet been minimized. Here, we used the temperature gradient strategy to improve the separation of (2) and (3). The starting column temperature was set at 120 °C, and upon the injection of sample, the column temperature was ramped to 150 °C at 12 °C min^{-1}. To repeat the measurement, a cooling fan was employed to cool the column back to 120 °C before the next injection for the verification of reproducibility. The system pressure for 10 μL min^{-1} pure water flow rate at a column temperature of 150 °C was 13 MPa, thus further reduction in particle size or column i.d. is still possible.

Fig. 6a shows the detection of 100 fmol methamphetamine prepared in diluted raw urine using the high-temperature capillary HT-LC-HP-ESI-MS. The column temperature was 140 °C and the ion source pressure was 4 atm. Here, an ion transfer tube of 0.5 mm was used to increase the ion transmission, and a booster pump was used to keep the pressure in the first pumping stage under normal operating conditions. The methamphetamine doped urine sample was injected directly without additional clean-up and the mobile phase used in this measurement was 9% (w/w) acetonitrile aqueous solution and the flow rate was 10 μL min^{-1}. As a comparison, the detection of the same amount of sample was performed using a standard pneumatically assisted ESI under atmospheric pressure (Fig. 6b). To prevent the boiling of eluent, a flow restrictor (i.d. 50 μm) was placed in between the column and ESI source. An over hundred μL min^{-1} solution flow rate was necessary to create the sufficient back pressure to the column. The capillary column was not suitable for this high flow rate operation, thus was replaced by the column of 1 mm inner diameter. The column preheater was also re-installed. The flow rate was set to 400 μL min^{-1} to obtain approximately the same retention time with that of capillary LC in Fig. 6a. The extracted ion chromatographs of the protonated methamphetamine are shown in the insets of Fig. 6a and b. In Fig. 6, the peak intensity acquired by a low flow rate mode is approximately 10 times higher than the high flow operation. The results clearly show the advantage of microflow capillary LC-MS in dealing with a small amount of sample. There is a rich literature on the reduction of the matrix effect and enhanced sensitivity in the low flow ESI owing to the generation of smaller precursor charged droplets. Those benevolent effects become more significant for the electrospray operated at a sub-microliter per minute flow rate. Operating the high-temperature LC in that flow regime is in principle feasible using the present high-pressure ESI approach, but it requires a compact and integrated design of the column and ion source in addition to the liquid delivery and injection systems of sufficiently small dead volume.

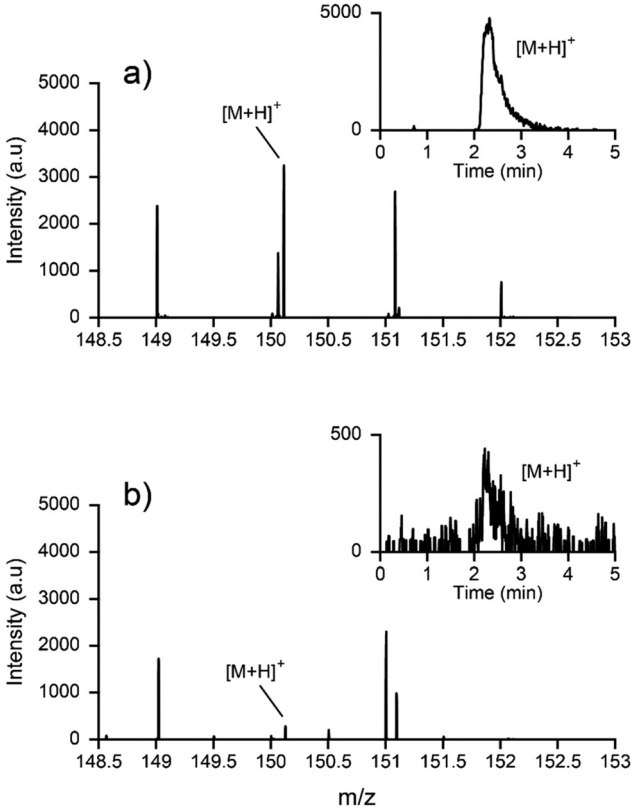

Fig. 6 Detection of 100 fmol methamphetamine in diluted raw urine by (a) high-temperature capillary LC-MS (column i.d.: 0.1 mm) using HP-ESI under 4 bar, and (b) high-temperature LC-MS (column i.d.: 1 mm) using pneumatically assisted ESI under atmospheric pressure. Column temperatures: 140 °C, mobile phase: 9% (w/w) acetonitrile aqueous solution, solution flow rates: 10 μL min^{-1} for HP-ESI (a) and 400 μL min^{-1} for pneumatically assisted ESI (b). Insets show the EIC for the protonated methamphetamine.

Conclusion

A direct method to hyphenate high-temperature liquid chromatography with mass spectrometry *via* a high-pressure ESI source had been demonstrated. The super-atmospheric pressure operation (7 bar in this study) allowed the LC to be operated up to 160 °C to keep the eluent in the liquid state both within the column and at the ESI emitter. Subcritical water LC-ESI-MS was demonstrated using a capillary column. Operating the column at high temperature and employing the temperature gradient could speed up the elution and improve

the selectivity of the analysis even at constant flow rate operation. The post-column broadening effect can be further minimized by having a short ESI emitter connected directly to the outlet of the column or by embedding the capillary column into the ESI heater block. The fully integrated HT-LC-HP-ESI will be reported in the future.

Conflicts of interest

There are no conflicts to declare.

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