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Simultaneous analysis of some amphetamine derivatives in urine by nonaqueous capillary electrophoresis coupled to electrospray ionization mass spectrometry

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Abstract

A nonaqueous capillary electrophoresis method, coupled to UV and electrospray mass spectrometry (ESI-MS), is described for the simultaneous analysis of Ecstasy and other related derivatives. Several electrophoretic and ESI-MS parameters were systematically investigated, such as electrolyte nature and concentration, organic solvent and sheath liquid compositions, nebulization gas pressure and drying gas flow-rate. The best results were achieved with an acetonitrile–methanol (80:20, v/v) mixture containing 25 m*M* ammonium formate and 1 *M* formic acid, an applied voltage of 30 kV and a separation temperature of 15°C. Under optimized CE–ESI-MS conditions, separation of the investigated drugs was performed in less than 6 min, with a high efficiency. Method precision based on migration time and peak area was determined and the limits of detection, which depend on the tested compound, were established between 20 and 70 ng ml^{-1} in the selected ion monitoring mode. Finally, the described method was successfully applied to the analysis of amphetamines in urine after a liquid–liquid extraction. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Nonaqueous capillary electrophoresis; Mass spectrometry; Amphetamines; Ecstasy

1. Introduction

Amphetamine and other related derivatives are powerful stimulants of the central nervous system and are often misused by recreational users [1]. A chronic abuse of so-called ''designer drugs'' often leads to hallucinations and psychosis, as well as dysphoria and depression upon withdrawal. Therefore, their analysis is of great importance in clinical and forensic analysis.

In our laboratory, several chromatographic [2–4] and electrophoretic methods [5,6] coupled to spectrophotometric detectors were developed and validated for the separation of amphetamine and related compounds. In particular, capillary zone electrophoresis (CZE) coupled with a diode array detector was successfully applied to the analysis of amphetamines sold on the black market as tablets of various composition [7]. However, because of the relatively low sensitivity afforded by the short optical path length of the capillary, the dosage of these drugs in biological matrices (e.g. urine, serum) by capillary electrophoresis coupled with UV detection (CE–UV) remains a challenge. Among the different strategies investigated to enhance sensitivity in CE, the on-line coupling of CE with electrospray ionization mass spectrometry (ESI-MS) was found to be a promising alternative [8,9]. In this context, a CE–ESI-MS method was developed and successfully applied to

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determine ecstasy and derivatives in urine samples [10,11].

Nonaqueous capillary electrophoresis (NACE) has recently gained increased popularity [12–17]. Different selectivity, high efficiency, rapid analysis time and better solubility and stability of some compounds in organic solvent than in water are the main reasons for this success. NACE has been found to be a good alternative for the analysis of pharmaceuticals and their metabolites which are difficult to separate in aqueous media. However, NACE–UV may present a lack of sensitivity due to UV-absorption of many organic solvents [12]. Therefore, the on-line coupling of NACE with electrospray ionization mass spectrometry is a promising combination of powerful separation and detection techniques, particularly in terms of selectivity and sensitivity. The application of on-line NACE–MS to the analysis of drug metabolites and peptides has recently been demonstrated [16,18–23].

In this contribution, a NACE–ESI-MS method is reported for the analysis of amphetamine and related compounds possessing similar structures and charge to mass ratio. Several electrophoretic and ESI-MS parameters are systematically investigated, such as concentration of the electrolyte, organic solvent and sheath liquid composition, nebulization gas pressure and drying gas flow-rate. Repeatability and sensitivity of the method are also discussed. Results obtained with NACE–ESI-MS are compared to those obtained by CE–ESI-MS in aqueous media. Furthermore, the optimized method is applied to the analysis of six amphetamines in urine samples after a liquid–liquid extraction.

2. Materials and methods

2.1. Chemicals

Standard solutions of 1 mg ml^{-1} of amphetamines (A, MA, MDA, MDMA, MDEA, MBDB, MDPA; Fig. 1) in methanol were purchased from Alltech (Deerfield, IL, USA). Analytical reagent-grade ammonium formate, formic acid, ammonium acetate and acetic acid were obtained from Fluka (Buchs, Switzerland). HPLC-grade methanol (MeOH), acetonitrile (MeCN) and isopropanol were supplied by Romil (Kölliken, Switzerland). All other reagents and solvents were analytical-grade reagents from Fluka (Buchs, Switzerland). Ultra-pure water was supplied by a Milli-Q RG unit from Millipore (Bedford, MA, USA).

2.2. Instrumentation

2.2.1. Capillary electrophoresis

CE experiments were performed with a $HP^{3D}CE$ system (Hewlett-Packard, Waldbronn, Germany) equipped with an on-column diode-array detector, a 1100 mass spectrometer MSD HP, an autosampler and a power supply able to deliver up to 30 kV. A CE Chemstation (Hewlett-Packard) was used for both CE and MS instruments control, data acquisition and data handling. The separation was performed in a fused-silica capillary (Composite Metal Service, Worcestershire, UK) of 75 cm (22 cm from inlet to UV detector)×50 μm I.D. To maintain a stable electrospray, a 20 mm portion of the polyimide coating was removed from the outlet edge of the capillary. This procedure was found effective to provide better mixing characteristics at the probe tip. All experiments were carried out using the cationic mode (anode at the inlet and cathode at the outlet). A constant voltage of 30 kV, with an initial ramping of 500 V/s, was applied during analysis. The capillary was thermostated at 15°C. Samples were kept at ambient temperature in the autosampler and injected by applying a pressure of 50 mbar for 4 s. The UV detection was carried out at 200 nm with a bandwidth of 10 nm.

Before its first use, the fused-silica capillary was sequentially washed with 1 *M* sodium hydroxide, 0.1 *M* sodium hydroxide, Millipore water and separation buffer for 5 min each. Between analyses, the capillary was flushed with the running buffer for 2 min. When not in use, the capillary was washed with 0.1 *M* sodium hydroxide, water and then dry stored. As a solution electrolysis can alter the running buffer and subsequently change the electroosmotic flow (EOF), the separation buffer was replaced every 6 to 10 runs.

2.2.2. Mass spectrometry

The electrospray mass spectrometry measurements were carried out in the positive ionization mode were

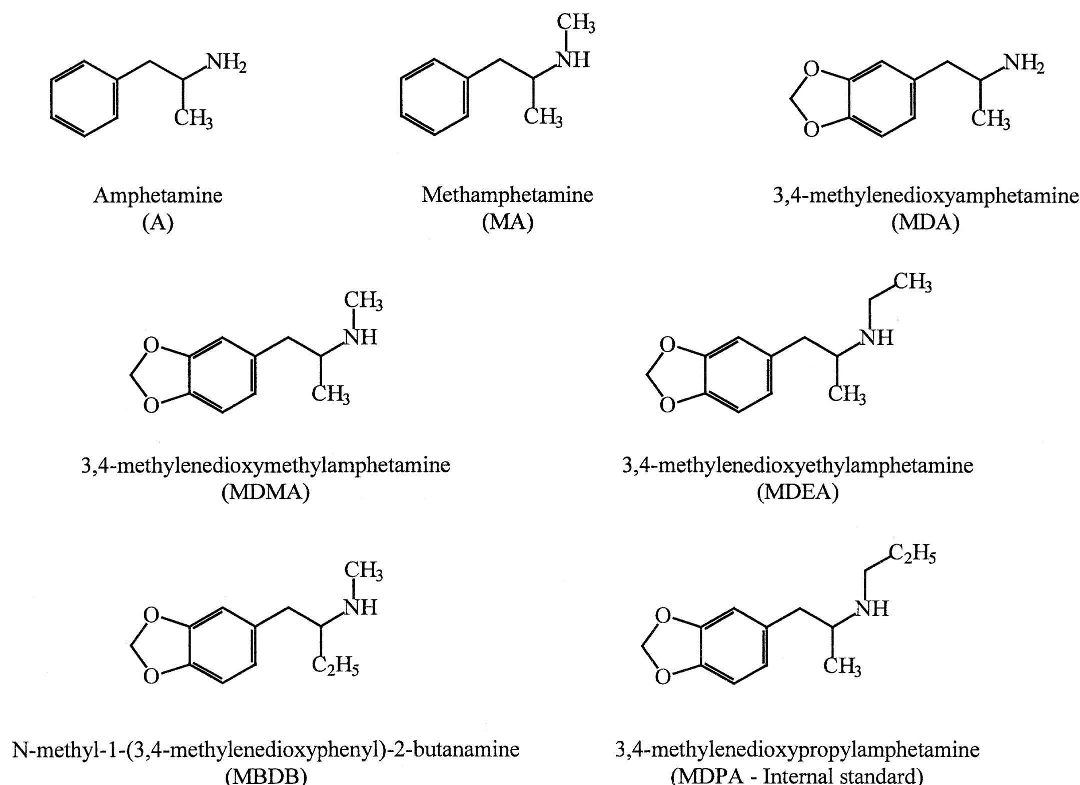

Fig. 1. Structures of ecstasy and related amphetamines.

performed in a single quadrupole instrument HP Series 1100 MSD (Hewlett-Packard, Palo Alto, CA, USA), which has an upper mass limit of 3000 amu. In order to couple the $HP^{3D}CE$ instrument with the mass spectrometer, a CE–MS adapter kit from Hewlett-Packard was used. This triple tube ESI-MS interface provides both a coaxial sheath liquid make-up flow and a nebulization gas to assist droplet formation. Drying and nebulization gases were both nitrogen. The coaxial sheath liquid was delivered at 3 μl min^{-1} by a Harvard Model 22 syringe pump (South Natick, MA, USA). The ESI capillary was set at +4.0 kV. Unless otherwise stated, the nebulizing pressure and the drying gas flow-rate were set at 4 p.s.i. and 4 l min^{-1}, respectively (1 p.s.i.=6894.76 Pa). The gas temperature was set at 150°C and the fragmentor voltage at 70 V. The coaxial sheath liquid consisted of isopropanol–water (50:50, v/v) in presence of 0.5% formic acid. MS detection was carried out in the selected ion monitoring (SIM) mode for the positive molecular ion. The selected masses were acquired with a dwell time of 68 ms on each mass to charge ratio, which were 136 for A, 150 for MA, 180 for MDA, 194 for MDMA, 208 for MDEA and MBDB and 222 for MDPA.

2.2.2.1. Buffer and sample preparation

The nonaqueous buffer was a mixture of MeCN–MeOH (80:20, v/v) containing 25 m*M* ammonium formate and 1 *M* formic acid unless otherwise specified. Before use, the electrolyte solutions were filtered through a 0.40 μm microfilter (Supelco, Bellefonte, PA, USA) and degassed in an ultrasonic bath for 10 min.

The amphetamine mixture was prepared by dissolution of individual compounds in a methanol–running buffer (90:10, v/v) mixture to give a final concentration of 1 μg/ml each. Working standard solutions were prepared daily, but remain stable for at least one week at 5°C.

2.2.3. Urine sample preparation

The liquid–liquid extraction (LLE) procedure used for urine samples was the following: 1 ml of urine was spiked with 10 μl of amphetamines mixture (A, MA, MDA, MDMA, MDEA, MDPA; 10 μg/ml each) in a 10 ml conical polypropylene tube. 1.5 ml of sodium borate buffer (100 m*M*, pH 9.2) and 7.5 ml of chlorobutane were added to the solution. After shaking for 20 min with a Turbula, the mixture was centrifuged at 1500 rpm (ca. 125 *g*) for 5 min and then frozen. The organic layer was transferred to a polypropylene tube and acidified with 100 μl of a HCl methanolic (2%, v/v) solution to prevent amphetamine evaporation. The solution was evaporated to dryness under a gentle flow of nitrogen at a temperature of 40°C. The dry residue was diluted in 50 μl of methanol–buffer (90:10) and vortex-mixed for 30 s. The sample was transferred into a 100 μl vial and was injected twice. Sample solutions were stable for more than a week at 5°C and no degradation was observed for all tested amphetamines during analysis.

3. Results and discussion

In a previous paper [24], a NACE–UV method was described for separation of the investigated amphetamines (Fig. 1). Baseline separation of six amphetamines, including A, MA, MDA, MDMA, MDEA and MDPA, was achieved using a methanolic solution containing 100 m*M* trifluoroacetic acid (TFA) and 50 m*M* ammonium acetate. As the main objective of this study was to achieve a fast separation and use electrospray ionization mass spectrometer, the method was slightly modified. In fact, the presence of TFA in the separation buffer is known to suppress the MS signal and affect negatively the separation efficiency, due to ion-pair formation. Thus, several MeCN–MeOH mixtures containing 25 m*M* ammonium formate and 1 *M* formic acid were tested for separation of the investigated drugs. As a result, a MeCN–MeOH (80:20, v/v) mixture containing 25 m*M* ammonium formate and 1 *M* formic acid was found to be a good compromise in terms of selectivity, high efficiency and short analysis time.

3.1. Influence of ESI-MS parameters

In a previous article [10], optimization of ESI-MS parameters was investigated (by mean of an experimental design) for the analysis of amphetamines in aqueous CE. It was demonstrated that only a few parameters significantly influenced the MS detector response. Therefore, sheath-liquid composition, nebulization pressure and drying gas flow-rate only were optimized in NACE–ESI-MS.

3.1.1. Sheath-liquid composition

Sheath liquid is used to connect electrically the CE outlet to ground potential at the sprayer and boost the flow through the ESI needle [25–27]. The use of a water–isopropanol mixture containing 0.5% formic acid was found appropriate for optimal electrospray ionization conditions [10,28]. In order to determine the effect of isopropanol percentage on the MS signal sensitivity and stability, different isopropanol–water compositions were tested while keeping the formic acid percentage constant. At a high isopropanol percentage (80%), the CE current was not stable and current breakdown was observed. By decreasing the isopropanol percentage, both CE and ESI currents were stable. Moreover, as shown in Fig. 2, an isopropanol–water (50:50, v/v) mixture in presence of 0.5% formic acid gives the highest ion abundance signal as well as the most stable conditions. A decrease of sensitivity by a factor 2, observed with a sheath liquid containing 80% water, may be explained by the fact that water is less volatile than isopropanol. Therefore, an aqueous solution of 50% isopropanol, containing 0.5% formic acid, was used throughout the study.

The make-up flow-rate was also studied. As expected, higher flow-rates result in lower signal-to-noise ratio, because of dilution of the separated compounds, whereas lower flow-rates affect negatively spray stability. Thus, a compromise was reached with a flow-rate set at 3 μl min^{-1}. It can be seen that results for sheath liquid composition and rate obtained with nonaqueous media are identical to those obtained in an aqueous medium.

3.1.2. Nebulization pressure

Addition of a nebulization gas, combined with a high voltage, is generally necessary to assist solvent

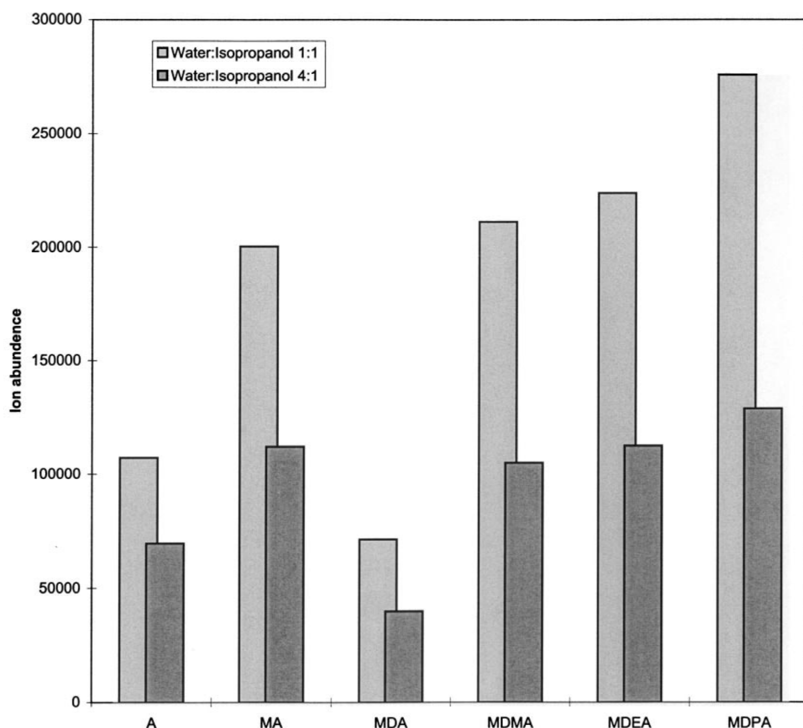

Fig. 2. Ion abundance as a function of isopropanol percentage in sheath liquid composition. Studies were performed in presence of 0.5% (v/v) formic acid.

evaporation. However, gas has been reported to have an aspirating effect which influences separation quality because of a pressure-induced flow [29]. To investigate the effect of the nebulization gas on separation performance, the pressure was varied between 2 and 8 p.s.i. As shown in Fig. 3, both migration time and resolution were significantly affected by the pressure of the nebulization gas. In fact, the migration time of MDPA, the last migrated amphetamine, was reduced from 6.5 to 5 min when the pressure was increased from 2 to 8 p.s.i. This migration time decrease was attributed to the aspirating effect into the capillary [23,30]. Moreover, the resolution between MDMA and MDEA was greatly impeded at a high pressure (8 p.s.i.).

Furthermore, sensitivity decreased slightly by lowering the pressure from 8 to 4 p.s.i., but reduced significantly from 4 to 2 p.s.i. In fact, at a lower pressure, large charged droplets are generated which may explain the sensitivity decrease. As a compromise, a nebulization pressure set at 4 p.s.i. was selected to achieve high sensitivity and acceptable resolution. Similar results were observed in aqueous media.

3.1.3. Drying gas flow-rate

The drying gas is generally used to accelerate buffer desolvation, increase MS sensitivity and avoid the entrance of undesirable ions into the mass spectrometer. Thus, the effect of the drying gas flow-rate was studied between 4 and 12 l min^{-1}. Migration time and resolution were not affected (electropherograms not shown). However, sensitivity was clearly reduced by increasing the drying gas flow-rate as illustrated in Fig. 4. No test was performed below 4 l min^{-1}, since a minimum flow-rate is required to maintain a positive pressure in the spray chamber and avoid unfiltered air flowing into the spray chamber and vacuum system. The drying gas flow-rate was then fixed at 4 l min^{-1}. Similar results were observed in aqueous media.

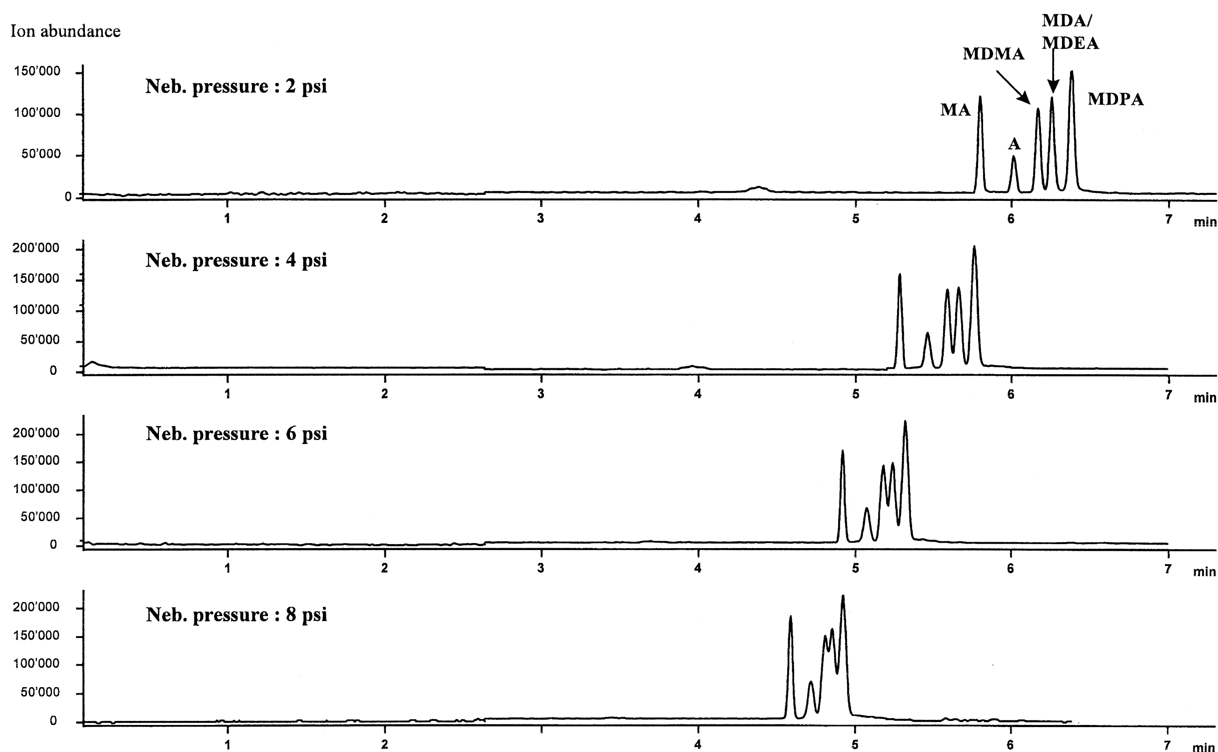

Fig. 3. Reconstituted ion current (RIC) of a standard amphetamine mixture (1 μg ml^{-1}) at different nebulizing gas pressures. Experimental conditions: MeCN–MeOH (80:20, v/v) containing 25 m*M* ammonium formate and 1 *M* formic acid, 15°C, 30 kV (ramp at 500 V s^{-1}), 50 mbar for 4 s, fused-silica capillary of 75 cm×50 μm I.D. For other conditions, see Section 2.2.

3.2. Buffer electrolyte

In presence of MeCN–MeOH (80:20, v/v) containing 25 m*M* ammonium formate and 1 *M* formic acid, the migration order was: MA<A<MDMA<MDEA=MDA<MDPA (Fig. 5a). It has to be noted that MDEA and MDA were not resolved under these conditions. However, in the SIM mode, all amphetamines can be determined without ambiguity by scanning the protonated molecular ion for each amphetamine (Fig. 5b). As reported in Fig. 5c, the use of on-line UV detection did not allow the determination of investigated amphetamines at this low concentration (1 μg/ml).

It is noteworthy that the use of organic solvent instead of water results in migration order inversion of A, MA and their methylenedioxy derivatives MDA and MDMA. Organic solvents have been reported to considerably affect compound migration order, because of solvatation changes [24]. These findings may be of considerable importance for quantitative purposes as it is desirable to have the minor compound in front of the major one. In order to investigate further electrolyte effect on separation performance, an electrolyte composition of 25 m*M* ammonium acetate and 1 *M* acetic acid was selected, while keeping the organic solvent composition constant. Such a modification had no significant effect on sensitivity. However, in the presence of an acetate buffer, a change in migration order was observed: MA<A<MDEA<MDMA=MDPA<MDA (data not shown). Thus, by a simple variation of electrolyte composition, a significant change in selectivity can be achieved. This behaviour may be explained by ion-pair formation in presence of acetate. Various electrolyte concentrations were investigated. As a result, 1 *M* formic acid was found to be a good compromise for a low electric current (19 μA) as

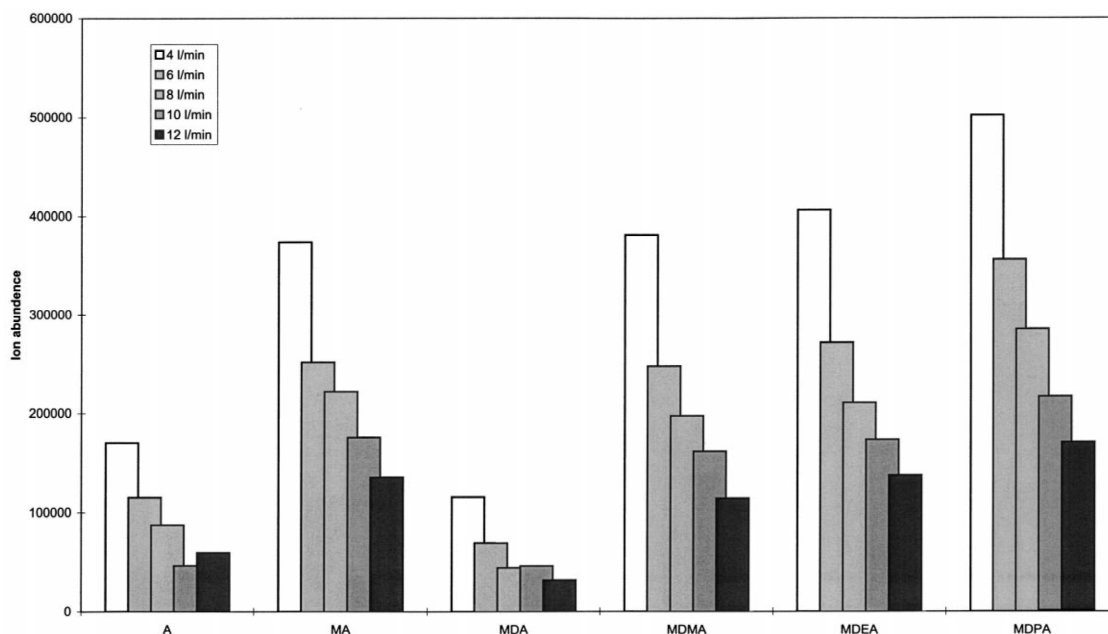

Fig. 4. Influence of drying gas flow-rate on ion abundance.

well as high efficiency through sample stacking effect. In comparison to an aqueous media, the generated electric current is lower in the presence of a methanol–acetonitrile mixture, allowing better CE–MS compatibility [31].

MDEA and MBDB are two positional isomers (Fig. 1). Since these isomers were not resolved by aqueous CE, a collision-induced dissociation (CID) approach was reported to differentiate these drugs [10]. To investigate their separation in nonaqueous media, several MeOH–MeCN mixtures containing 25 m*M* ammonium formate and 1 *M* formic acid were tested. 100% MeCN was found effective in separating these isomers and MDEA migrated before MBDB (data not shown). However, resolution was insufficient for quantitative purposes and, as in aqueous CE, the CID approach was selected.

Since modifying MeOH–MeCN ratio was worthless for quantifying these two isomers, a solvent mixture presenting the highest ϵ^2/η ratio was chosen [12]. Therefore a MeCN–MeOH (80:20, v/v), with 25 m*M* ammonium formate and 1 *M* formic acid, was selected as the appropriate buffer for our purpose.

3.3. Quantitative performances

3.3.1. Efficiency

Under optimized conditions, the generated electric CE current was low (19 μA), which considerably reduces Joule heating and facilitates successful CE–ESI-MS coupling. Subsequently, high peak efficiencies (N~120 000) were obtained for all the tested analytes. Indeed, in spite of the large non-thermostated part of the capillary between CE and ESI-MS, no significant band broadening was observed.

3.3.2. Repeatability

In order to assess method repeatability, replicate injections ($n=8$) of the amphetamine mixture were carried out. As shown in Table 1, the relative standard deviation of uncorrected migration time and peak area measurements were 0.5% and 15%, respectively. To improve method precision, an internal standard (MDPA) was found necessary to compensate the poor precision observed with hydrodynamic injection.

By adding an internal standard, the corrected migration time and peak area ratio RSD were

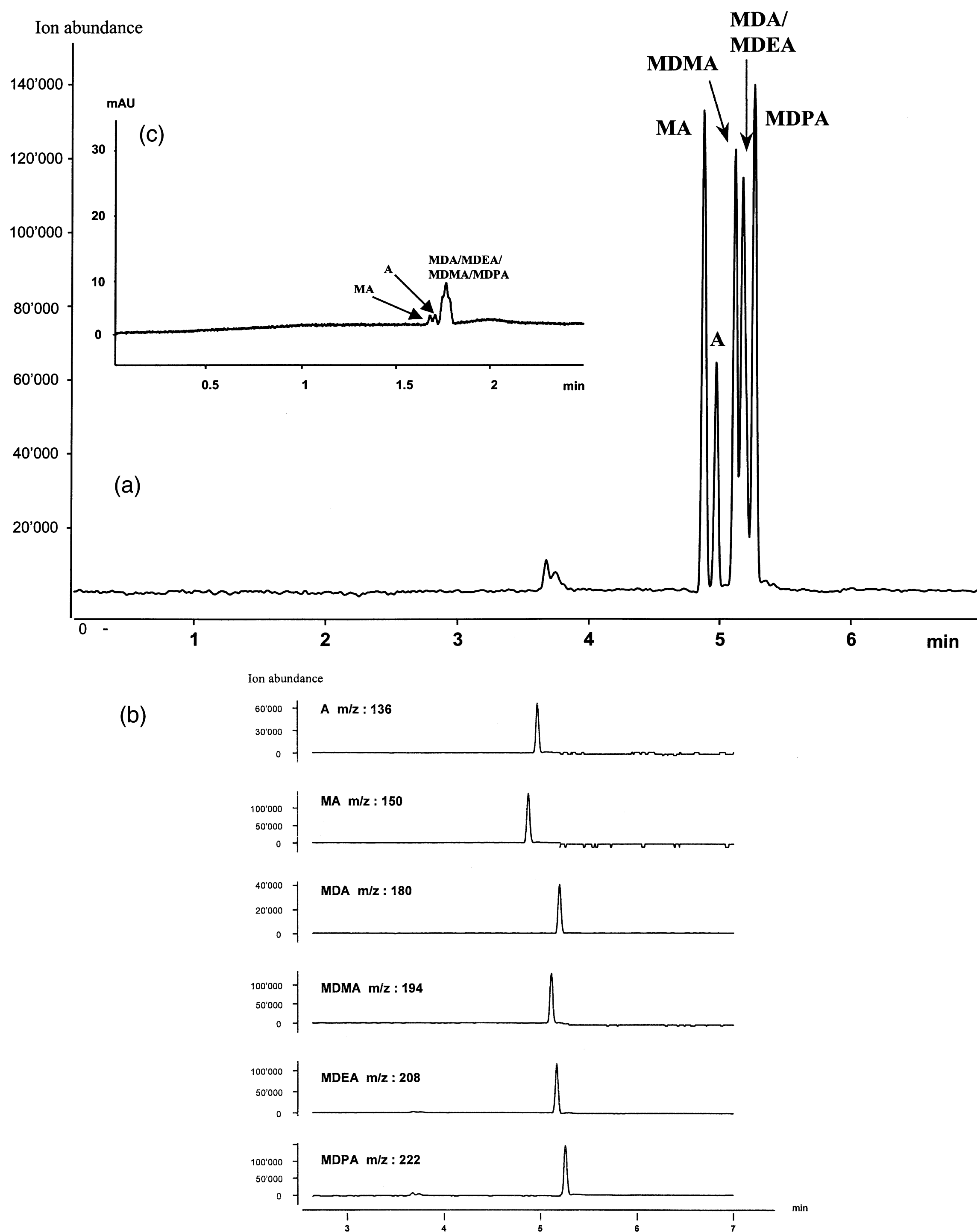

Fig. 5. (a) RIC of a standard amphetamine mixture (1 μg ml^{-1}) obtained in the SIM mode. (b) Extracted ion current for each amphetamine. (c) On-line UV detection obtained at 200 nm. Experimental conditions: MeCN–MeOH (80:20, v/v) containing 25 m*M* ammonium formate and 1 *M* formic acid, 15°C, 30 kV (ramp at 500 V s^{-1}), 50 mbar for 4 s, fused-silica capillary of 75 cm (22 cm to UV detection)×50 μm I.D.

Table 1
Relative standard deviation ($n=8$) of migration time and peak area of investigated amphetamines (1 μg ml^{-1}), with and without the addition of an internal standard

Amphetamine RSD (%) ($n=8$)	Without internal standard		With internal standard (MDPA)	
	Migration time	Peak area	Corrected migration time	Corrected peak area
A	0.48	14.6	0.04	5.7
MA	0.47	10.1	0.05	3.3
MDA	0.51	12.0	0.01	2.5
MDMA	0.50	10.4	0.03	4.3
MDEA	0.50	12.9	0.02	5.6

significantly improved [RSD inferior to 6% (Table 1)]. Thus, despite the risk of solvent evaporation of volatile organic solvents, low RSD values indicate that the method can be used for quantitative determination of amphetamines.

3.3.3. Limit of detection

Limit of detection (LOD) was estimated as three times the signal-to-noise ratio. LOD was determined by injecting test mixture solutions of various concentrations. The estimated limits of detection are reported in Table 2. These results suggest that sensitivity depends on the amine function in the amphetamine structure as drugs with a secondary amine (e.g. MA, MDMA, MDEA and MDPA) exhibit higher proton affinity and thus greater sensitivity.

3.4. Application to a urine sample

To assess the potential of the developed method in analysing Ecstasy and its derivatives in biological matrices, a spiked urine sample was analysed following a LLE. Urine is a complex matrix containing various amounts of salts and endogenous amine-based compounds. Therefore, it is necessary to apply a sample preparation procedure before analysis. After spiking a blank urine sample with 6 amphetamines (A, MA, MDA, MDMA, MDEA and MDPA) at a concentration of 100 ng ml^{-1} each, a simple and fast LLE was accomplished. Samples were injected twice according to the CE–ESI-MS experimental conditions and gave electropherograms (Fig. 6) which showed no interference by endogenous compounds.

4. Conclusions

In this study, successful on-line coupling of NACE with ESI-MS is demonstrated for the separation of amphetamine and other related derivatives. Different parameters, such as electrolyte and sheath liquid compositions, nebulization gas pressure and drying gas flow-rate, were optimized and a successful CE–MS separation obtained with a running buffer of MeCN–MeOH (80:20, v/v) containing 25 m*M* ammonium formate and 1 *M* formic acid. The sheath liquid used in the ESI-MS interface was a mixture of isopropanol–water (50:50, v/v) in presence of 0.5% formic acid. Migration time, resolution and sensitivity were critically affected by nebulization gas pressure and drying gas flow-rate. Although baseline resolution was not obtained for the 6 investigated drugs, the use of an MS detector al-

Table 2
Limits of detection of investigated amphetamines

	Amphetamine					
	A	MA	MDA	MDMA	MDEA	MDPA
LOD (ng ml^{-1} injected)	60	30	70	20	20	20

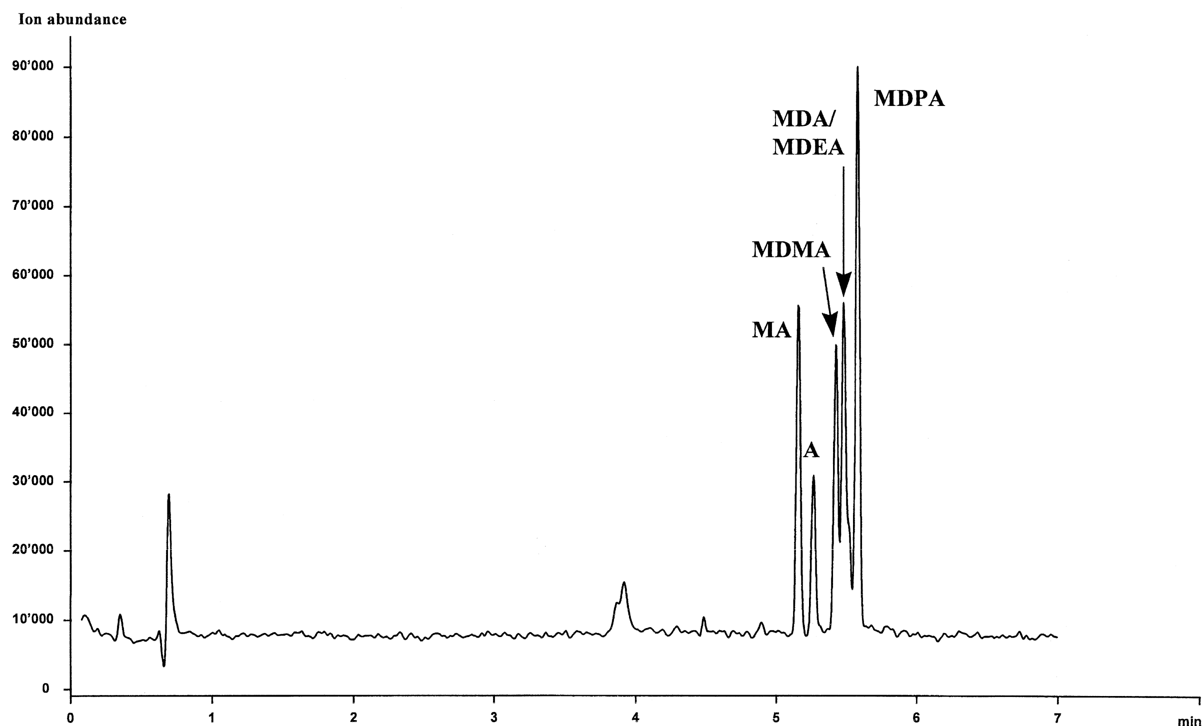

Fig. 6. RIC of a spiked urine sample (100 ng ml^{-1}) after liquid–liquid extraction. Experimental conditions as stated in Fig. 5.

lowed to determine each drug without ambiguity. Moreover, in the SIM mode, each amphetamine can be quantified. The quantitative performances of the method were also evaluated, and showed high sensitivity as well as good repeatability in terms of migration time and peak area ratio. In comparison to already described aqueous CE–ESI-MS methods, the use of organic solvent allowed different selectivities and resulted in efficiency improvement. In addition, the generated electric current is very low in the presence of methanol–acetonitrile mixture, allowing good CE–MS compatibility. Finally, a urine sample spiked with 6 amphetamines was analyzed after a simple liquid–liquid extraction and showed no interference by endogenous compounds.

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