ELSEVIER

Journal of Chromatography A, 979 (2002) 389–398

JOURNAL OF CHROMATOGRAPHY A

www.elsevier.com/locate/chroma

Potential of formamide and *N*-methylformamide in nonaqueous capillary electrophoresis coupled to electrospray ionization mass spectrometry
Application to the analysis of β-blockers

Laurent Geiser, Samir Cherkaoui, Jean-Luc Veuthey*

Laboratory of Pharmaceutical Analytical Chemistry, University of Geneva, Boulevard d'Yvoy 20, 1211 Geneva 4, Switzerland

Abstract

A nonaqueous capillary electrophoresis (NACE) method, coupled with either UV or electrospray mass spectrometry (ESI-MS), is described for the simultaneous analysis of seven β-blockers. The same electrolyte, namely 25 m*M* ammonium formate and 1 *M* formic acid, was used with different investigated organic solvents. In addition to frequently used organic solvents such as methanol (MeOH) and acetonitrile (MeCN), formamide and its derivatives were investigated. Formamide (FA) and *N*-methylformamide (NMF) present several interesting physico-chemical properties, one of them being a high dielectric constant (ε). Since FA and NMF possess a high UV cutoff, β-blockers with an absorbance above 250 nm were selected as model compounds in order to compare NACE–UV and NACE–MS performances. FA and NMF showed different selectivity compared to water, MeOH or MeCN, and also demonstrated a higher efficiency in terms of the number of theoretical plates (especially NMF). To overcome their unfavorable optical properties, hyphenation with MS detection appears as a promising technique, thanks to its benefits in terms of selectivity, sensitivity and universality. The practical compatibility of FA and NMF with ESI-MS detection in combination with a sheath liquid configuration was demonstrated. In comparison to UV detection, sensitivity was increased, while a high efficiency was maintained. In addition, the low and stable generated currents observed were evidences for the successful hyphenation with ESI-MS. Hence, FA and NMF seemed to be promising alternatives in NACE–ESI-MS, either used as pure organic solvent or as a mixture with MeOH or MeCN.

© 2002 Elsevier Science B.V. All rights reserved.

Keywords: Nonaqueous capillary electrophoresis; Background electrolyte composition; Beta-blockers; Formamide; Methylformamide

1. Introduction

Nonaqueous capillary electrophoresis (NACE) has recently gained increased popularity. Different selectivity, higher efficiency, faster analysis time and better solubility and stability of some compounds in organic solvent than in water are the main reasons for this success [1–5]. In particular, NACE has been found to be a good alternative for the analysis of pharmaceuticals and their metabolites that are difficult to separate in aqueous media. However, although the potential of nonaqueous solvents in CE has been largely accepted, most NACE applications

*Corresponding author. Tel.: +41-22-7026-336; fax: +41-22-7026-808.

E-mail address: jean-luc.veuthey@pharm.unige.ch (J.-L. Veuthey).

0021-9673/02/$ – see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0021-9673(02)01254-2

have been reported in acetonitrile, lower alcohols (e.g., methanol, ethanol, isopropanol) or their mixture. This is mainly due to their wide use in HPLC as pure solvents, particularly because of their low UV absorption at wavelengths commonly used with UV detection. Besides, other organic solvents [e.g., formamide (FA) and *N*-methyl formamide (NMF)] present interesting physico-chemical properties especially in terms of dielectric constant, but have found only limited applications because of their high UV cutoff (ca. 250 nm) [1]. However, the high ε^2/η ratio of NMF (about 20 000 at 25 °C) will result in higher efficiency in terms of the number of theoretical plates. FA, NMF and dimethylformamide (DMF) belong to the class of amphiprotic solvents with basic character (i.e., they enhance solute acidity and reduce analyte basicity). Their auto-protolysis constants range from 10.7 (NMF) to 29.4 (DMF), which may affect considerably the acid–base properties of the investigated analytes resulting in selectivity changes [5]. Moreover, because of its higher cohesion energy density (close to water) compared to other organic solvents, FA has proved to be useful in performing separations involving hydrophobic interactions [6]. These are most important in the case of chiral separations in the presence of cyclodextrins [7–9]. Despite these advantages, most applications with these solvents have been restricted to analytes that absorb light at considerably high wavelengths [10]. Some physico-chemical properties of water and other commonly used organic solvents are listed in Table 1 [11,12]

To extend the application range of NACE and fully exploit the advantages of these solvents, several methods were reported. Thus, to enhance sensitivity in NACE, indirect UV or fluorescence detection has been applied to the analysis of non-UV-absorbing compounds such as inorganic anions [13,14], underivatized amino acids [15] and anionic surfactants [16]. In particular, the separation of long chain fatty acids has been described in NMF–dioxane (3:1, v/v) mixture [17]. Moreover, because of its high selectivity and sensitivity, through signal enhancement, fluorescence and especially laser-induced fluorescence were found suitable for NACE applications in the presence of FA, NMF or DMF [18,19]. However, this detection mode is limited to compounds that are fluorescent, and often required tedious derivatization procedures. More recently, a contactless conductivity detection (CCD) has been described for CE with nonaqueous solvents (e.g., *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide and propylene carbonate) exhibiting strong UV absorbance below 230 nm [20]. It was demonstrated that this detection mode was very suited for the use of organic solvents, without any restrictions to their optical properties. Electrochemical detection was also found suitable for detection of compounds that are difficult to oxidize or reduce under aqueous conditions [21].

On the other hand, mass spectrometry is becoming a detector of choice in micro-separation techniques (e.g., micro-LC and CE) since it allows highly selective and sensitive analyses as well as information about the mass to charge ratio and, potentially, the structure of the separated compounds. Coupling of NACE to electrospray ionization mass spectrometry (ESI-MS) has been successfully applied to a large number of relevant compounds including nonsteroidal anti-inflammatory drugs [22] phospholipids [23], organic acids [24], amphet-

Table 1
Different physico-chemical parameters of water and selected organic solvents

Solvent	η (cP) at 25 °C	ε	ε/η (cP^{-1})	ε^2/η (cP^{-1})	pK_{auto}	UV cutoff (nm)	T_{boil} (°C)	Surface tension (10^{-2} N m^{-1})	Cohesion energy density (J ml^{-1})
Water	0.89	78.5	88.2	6924	14.0	<190	100	7.18	2291
MeOH	0.54	32.7	60.6	1980	17.2	205	65	2.21	928
MeCN	0.34	37.5	110.3	4136	–[a]	195	82	2.76	655
FA	3.30	111	33.6	3734	16.8	245	210	5.49	1638
NMF	1.65	182	110.3	20 075	10.7	245	182	3.87	992
DMF	0.80	36.7	45.9	1684	29.4	268	153	3.52	613

[a] No detectable autoprotolysis.

amines [25], fluoxetine and related compounds [26], venlafaxine and metabolites [27], tamoxifen metabolism [28] and tricyclic antidepressants [29], and a recent review was given by Yang et al. [30]. However, the majority of reports focused on the use of MeOH, MeCN and their mixture as background electrolytes without mention of FA and NMF.

β-Blockers (or adrenergic β-antagonists) are drugs that reduce the symptoms connected with hypertension, cardiac arrhythmias, headaches, and other disorders related to the sympathetic nervous system [31,32]. On an analytical aspect, β-blockers possess an UV absorbance above 260 nm, which is a spectral region where FA, NMF and DMF do not absorb strongly. Thus, these compounds are good candidates to perform NACE experiments both with UV and MS detection, with formamide and related solvents. The chemical structures of the studied β-blockers are shown in Fig. 1.

The main goal of this contribution is to demonstrate that the use of ESI-MS detection is an interesting alternative to extend the application range of NACE to organic solvents with a high absorbance UV using β-blockers as model compounds. Results obtained with formamide and related solvents are compared to those achieved with water, methanol and acetonitrile.

2. Materials and methods

2.1. Chemicals

Standard solutions of 1 g l^{-1} of β-blockers (acebutolol, alprenolol, atenolol, bopindolol, metoprolol, oxprenolol, pindolol) in methanol were a gift from the Department of Internal Medicine (University Hospital, Geneva, Switzerland). Analytical reagent-grade ammonium formate, formic acid, formamide, *N*,*N*-dimethylformamide and *N*-methylformamide were obtained from Fluka (Buchs, Switzerland). HPLC-grade methanol, acetonitrile and isopropanol were supplied by Romil (Kölliken, Switzerland). Ultra-pure water was supplied by a Milli-Q RG purification unit from Millipore (Bedford, MA, USA).

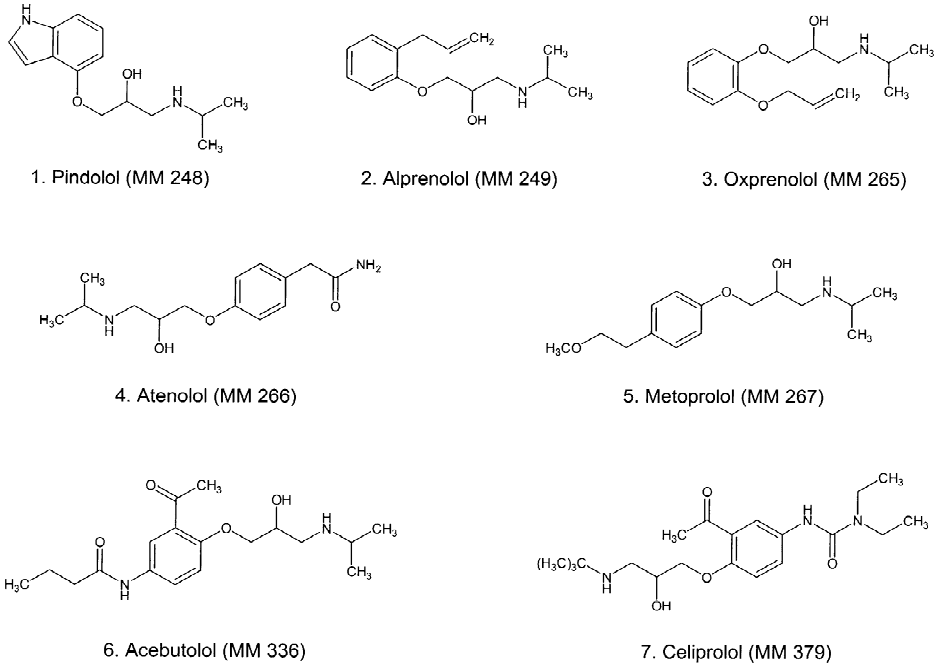

Fig. 1. Structures of β-blockers with their molecular masses (mm).

2.2. Buffer and sample preparation

Nonaqueous solvents were either MeOH, MeCN, FA, NMF, or DMF each containing 25 m*M* ammonium formate and 1 *M* formic acid. An aqueous electrolyte containing 100 m*M* formic acid (pH 2.4) was also used. Before use, the electrolyte solutions were degassed in an ultrasonic bath for 10 min.

A mixture of β-Blockers was prepared by dissolution of individual compounds in methanol to give a final concentration of 100 mg l^{-1} for CE–UV analysis and a final concentration of 1 and 10 mg l^{-1} for CE–MS analysis. Working standard solutions were prepared daily.

2.3. Instrumentation

2.3.1. CE–UV

CE–UV experiments were performed using a HP^{3D}CE system (Agilent Technologies, Waldbronn, Germany) equipped with an on-column diode-array detector, an autosampler and a power supply able to deliver up to 30 kV. A CE Chemstation (Agilent Technologies) was used for CE control, data acquisition and data handling. The separation was performed in a fused-silica capillary (Polymicro, Phoenix, AZ, USA) with an inner diameter of 50 μm and 64.5 cm total length (56 cm to the UV detector). All experiments were carried out using the cationic mode (anode at the inlet and cathode at the outlet). A constant voltage of 25 kV, with an initial ramping of 0.83 kV/s, was applied during analysis. The capillary was thermostated at 25 °C. Samples were kept at ambient temperature in the autosampler and injected by applying a pressure of 50 mbar for a few seconds depending on solvent viscosity. The injected amount was maintained at 1% of the effective capillary length. UV detection was carried out at 200 nm with a bandwidth (bw) of 10 nm (reference at 350 nm, bw 50 nm) for water, MeOH and MeCN, and at 270 nm with a bw of 10 nm (reference at 350 nm, bw 50 nm) for formamide and derivatives.

Before its first use, the fused-silica capillary was sequentially washed with methanol, 1 *M* HCl, water and separation electrolyte for 5 min each. Between analyses, the capillary was flushed with the electrolyte for 4 min. When not in use, the capillary was washed with methanol and then dry stored. As a solution electrolysis can alter the separation electrolyte and subsequently change the electroosmotic flow (EOF), the electrolyte was replaced every three to five runs.

2.3.2. CE–MS

CE–MS experiments were performed on the same CE system equipped with a single quadrupole instrument HP Series 1100 MSD (Agilent Technologies, Palo Alto, CA, USA), which has an upper mass limit of 3000 u. A CE Chemstation (Agilent Technologies) was used for CE and MS instruments control, data acquisition and data handling. The separation was performed in a fused-silica capillary (Polymicro) with 50 μm inner diameter and 58 cm total length. To maintain a stable electrospray, a 20-mm portion of the polyimide coating was removed from the outlet edge of the capillary in ESI-MS mode. This procedure was found effective to provide better mixing characteristics at the probe tip. Other CE conditions have been already stated above (Section 2.3.1).

The electrospray mass spectrometry measurements were carried out in the positive ionization mode. In order to couple the HP^{3D}CE instrument with the mass spectrometer, a CE–MS adapter kit 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 fixed at +4.5 kV. 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 drying gas temperature was fixed at 200 °C and the fragmentor voltage at 70 V. Unless otherwise stated, 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 ions. The selected masses were acquired with a dwell time of 55 ms on each mass-to-charge ratio, which were 249 for pindolol, 250 for alprenolol, 266 for oxprenolol, 267 for atenolol, 268 for metoprolol, 337 for acebutolol and 380 for celiprolol $[M+H]^+$.

3. Results and discussion

3.1. NACE–UV

As already mentioned, MeOH and MeCN are the most widely used organic solvents in NACE. Other solvents, such as formamide and its derivatives, have only limited applications, due certainly to their high UV absorbance at low wavelengths. However, as reported in Table 1, these solvents present interesting physico-chemical properties that may further enhance electrophoretic performances. In order to compare formamide and its derivatives behavior with frequently used electrophoretic solvents such as water, MeOH and MeCN, the first experiments were carried out with UV detection. Moreover, except for water, the same electrolyte, namely 25 m*M* ammonium formate and 1 *M* formic acid, was used with the investigated solvents. This electrolyte solution is suitable for CE–MS coupling and has wide application in NACE for the separation of a large variety of basic drugs [25,26]. The same electrolyte was not used in aqueous media, which would result in excessively high electric current. Hence, for aqueous experiments, a volatile electrolyte, namely 100 m*M* formic acid at pH 2.4, was used. Additionally, β-blockers have been selected as model compounds. In fact, these drugs present similar structures and exhibit UV spectra compatible with UV detection above 260 nm.

In the case of water, MeOH and MeCN, detection was performed at 200 nm, while for FA, NMF and DMF, UV detection at higher wavelength (i.e., 270 nm) was required. Moreover, since the injected amount is viscosity dependent, hydrodynamic injection time was adjusted to fill 1% of the effective capillary length. As illustrated in Fig. 2, the studied β-blockers exhibited different migration behaviors depending on the electrophoretic medium. In fact, in the absence of a modifier, the structure of the analyte and the nature of the surrounding environmental conditions mainly dictate the selectivity. The use of an aqueous solution with 100 m*M* formic acid at pH 2.4 resulted in almost baseline resolution of all studied compounds and the migration order was directly related to the molecular mass of the investigated drugs (Fig. 2A).

In comparison to water, MeCN, which is classified among aprotic solvents, showed a drastic change in migration order (Fig. 2B). In fact, while acebutolol and celiprolol (compounds 6 and 7) migrated in the last position with all other investigated solvents, their electrophoretic mobility in the presence of MeCN was higher than atenolol and metoprolol (compounds 4 and 5). Under the investigated conditions, MeOH allowed the complete separation of β-blockers in less than 15 min (Fig. 2C). It is noteworthy that FA and NMF presented the same migration order without a complete separation of all tested β-blockers (Fig. 2D,E), probably due to their basic character and similar solvation of ionic species. As shown in Table 2, despite the high electrolyte concentration, the generated electric current was extremely low. These findings are of utmost importance for achieving rapid separation through the application of high electric fields, as well as for coupling NACE with MS (see Section 3.2). The same experiments were carried out with DMF; however, the generated electric current was not stable and peak efficiency was not satisfactory. Thus, this solvent was discarded for further investigations.

Fig. 3 shows the evolution of migration time and efficiency of celiprolol in function of ε/η (A) and ε^2/η (B) solvent ratios, respectively. Water was not reported on these figures, since lower electrolyte concentration was used for this solvent in order to generate moderate current. As expected, NMF showed the highest efficiency (about 123 000 theoretical plates) and MeCN showed the fastest analysis time (approx. 5 min), and highest efficiency by unit of time (about 16 000) among the different organic solvents. However, separation time and efficiency could not be only related to pure solvent theoretical values of ε/η and ε^2/η. In CE, approximating the dielectric constant of the electrolyte solution with that of the pure solvent may not always be appropriate [6]. In fact, at higher ionic strengths, the dielectric constant of the electrolyte may be affected as the portion of the solvent oriented towards the ions increases compared to the free solvent [33]. Moreover, besides dielectric constant and viscosity, other solvent properties, such as zeta potential and purity, have to be considered. For instance, it was reported that zeta potential for MeCN was twice superior than for MeOH and FA [34]. This is in accordance with the faster analysis time obtained for

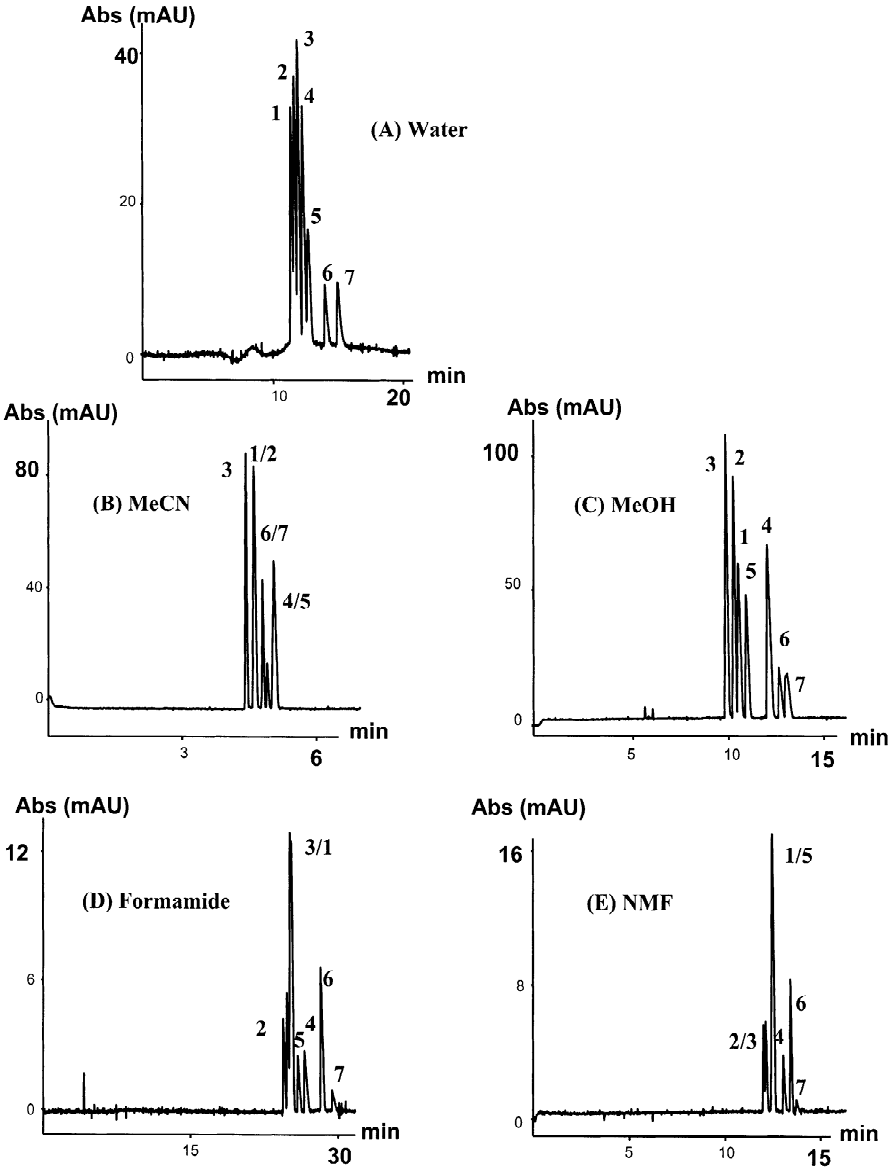

Fig. 2. On-line CE–UV detection of a standard β-blockers mixture at 100 mg l^{-1}. Experimental conditions: fused-silica capillary of 64.5 cm (56 cm to detector)×50 μm I.D., 25 °C, 25 kV, injection by pressure, 1% effective length according to electrolyte viscosity. (A) Formic acid (100 m*M*) in water; (B–E) 25 m*M* ammonium formate and 1 *M* formic acid in (B) MeCN, (C) MeOH, (D) formamide, (E) NMF. UV detection at 200 nm for (A–C); and 270 nm for (D,E). Peak numbers correspond to β-blockers, according to Fig. 1.

MeCN, compared to the analysis time expected by considering the ε/η ratio. It can also be noted that despite their high purity, amide type organic solvents may contain foreign ionic species (degradation or hydrolysis by-products). Indeed, a NACE experiment was conducted with NMF free electrolyte and generated an electric current (about 5 μA), indicating the presence of impurities in this solvent. For all these reasons, the ε/η and ε^2/η ratio listed in Table 1 provide good qualitative information about migration time and efficiencies, but practical tests are needed to exactly confirm these predictions.

Table 2
Some NACE–UV electrophoretic data with different organic solvents using celiprolol (100 μg ml^{-1}) as a model compound

Solvent	Current (μA)	Migration time (min)	Efficiency	Efficiency by unit time (min^{-1})
MeOH	14	13.0	47 000	3615
MeCN	12–17	4.4	72 000	16 365
FA	11	30.7	75 000	2445
NMF	14	13.9	123 000	8850

3.2. NACE–ESI-MS

As described above, formamide derivatives and particularly NMF showed different selectivity and very high efficiency. However, with UV detection, the use of these solvents is restricted to a limited number of compounds. Therefore, to fully take advantage of these solvents, the on-line coupling with ESI-MS was investigated. Regarding the significantly higher boiling points of formamide and its derivatives, it has been stated that they were unlikely to ESI-MS applications [1]. However, since electrospray ionization in the presence of a sheath liquid is established as the predominant technique for on-line interfacing CE with MS, the appropriate choice of the sheath liquid composition may reduce this handicap to some extent. The coaxial sheath liquid make-up flow is added coaxially to the CE capillary outlet to ensure stable electrospray as well as electrical contact at the capillary outlet.

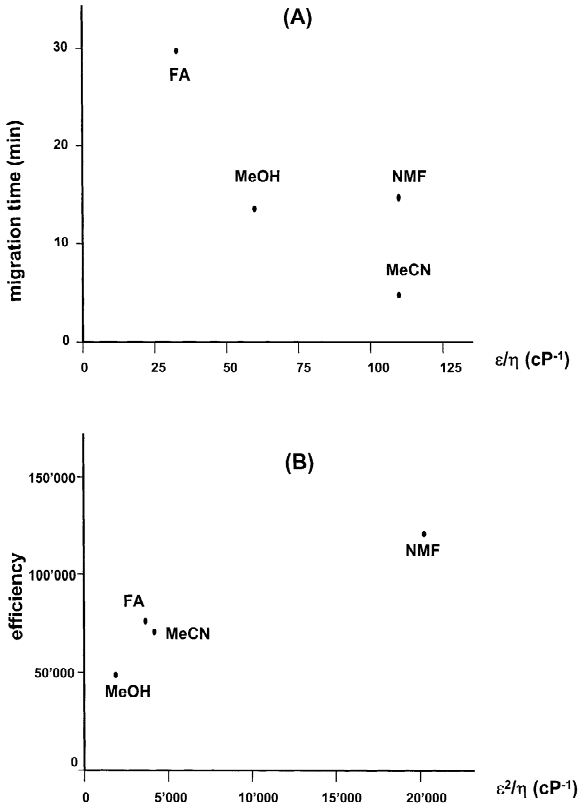

Fig. 3. Experimental results obtained in NACE–UV for four different organic solvents (MeOH, MeCN, FA, NMF) containing the same electrolyte. Experimental conditions as stated in Fig. 2. (A) Evolution of migration time in function of ε/η ratio of pure organic solvent. (B) Evolution of efficiency in function of ε^2/η ratio of pure organic solvent.

As expected, because of their low heat of vaporization and low surface tension, MeCN and MeOH showed the most abundant ESI-MS responses (Fig. 4). In the case of water, MeOH and MeCN, a sheath liquid constituted of isopropanol–water (50:50, v/v) in the presence of 0.5% formic acid was used. In contrast, with FA and NMF, the use of 100% isopropanol in presence of 0.5% formic acid was found more suitable to encompass incompatibilities due to the high boiling points of these solvents. Despite the diluting effect inherent to the use of a sheath liquid junction, CE–ESI-MS allowed an important gain in sensitivity over CE–UV by a factor of approximately 10 for β-blocker analyses with FA and NMF. Nevertheless, water, MeOH and MeCN exhibited better signal-to-noise ratios (approx. factor 10) in comparison with FA and NMF, since they are more volatile. On the other hand, while the latter are less proned to solvent evaporation and out-gassing occurrence, they are well suited for achieving stable electrospray current and may induce better stability.

With the NACE–MS coupling, very high efficiency was maintained for all investigated compounds. For all studied solvents, a significant decrease of migration times was observed in NACE–MS in comparison with NACE–UV inducing a loss

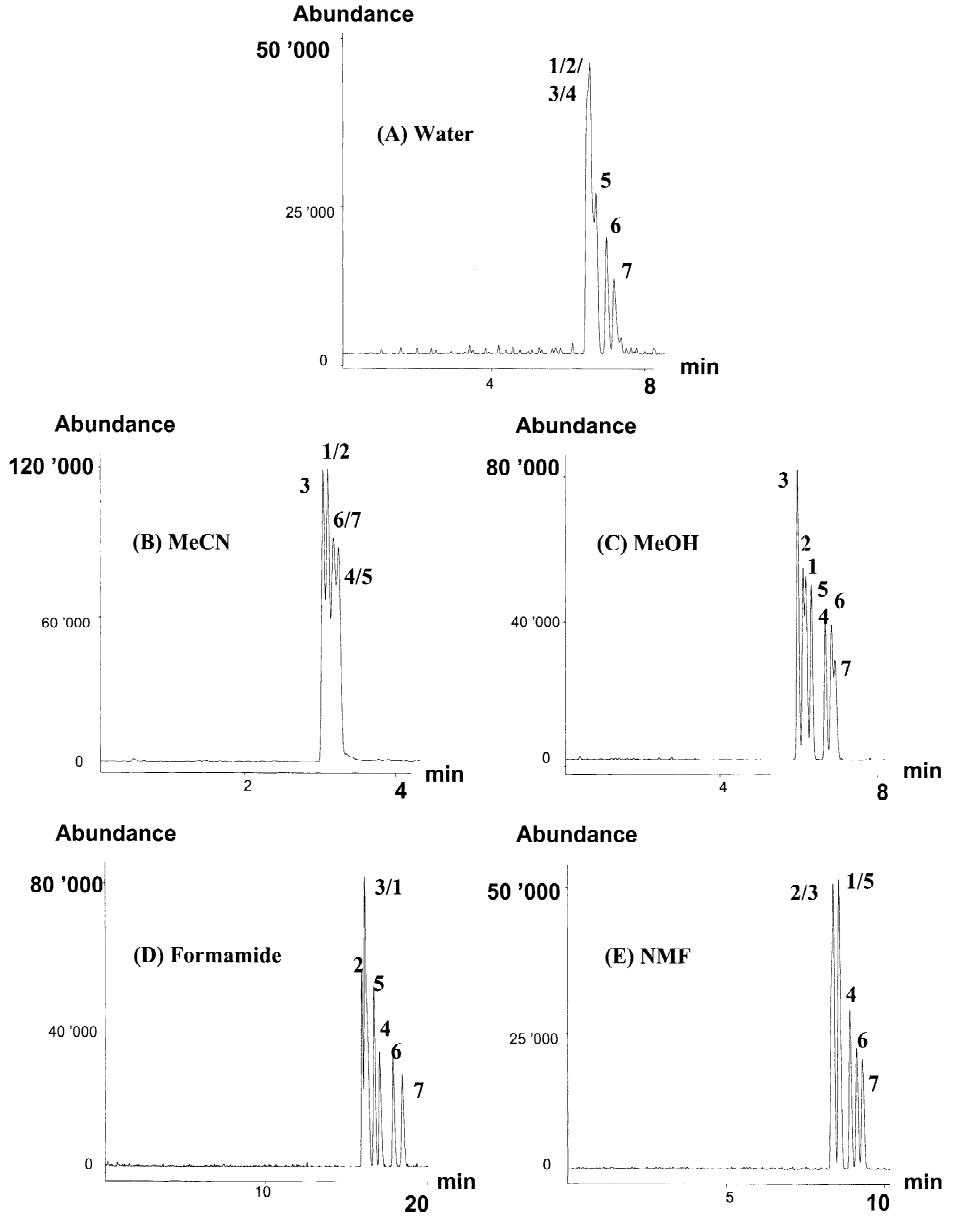

Fig. 4. Reconstituted ion current (RIC) of standard β-blockers mixture. Experimental conditions: fused-silica capillary of 58 cm×50 μm I.D., 25 °C, 25 kV, injection by pressure, 1% effective length according to electrolyte viscosity. (A) Formic acid (100 m*M*) in water. (B–E) 25 m*M* ammonium formate and 1 *M* formic acid in (B) MeCN, (C) MeOH, (D) Formamide, (E) NMF. β-Blocker concentration: 1 mg l^{-1} for (A–C); 10 mg l^{-1} for (D,E). Peak numbers correspond to β-blockers, according to Fig. 1.

of resolution. This behavior was attributed to higher electric fields applied in NACE–MS (431 V cm^{-1}) versus NACE–UV (388 V cm^{-1}) and to a siphoning effect caused by the presence of a nebulizing gas. This gas flow is generally added, in combination with applied high voltage, to assist droplets gene-

ration and solvent evaporation during the electrospray.

Although peak overlapping was observed with all investigated solvents, the use of MS detection in the single ion monitoring mode allowed the determination of each compound with a very high confidence. Under the selected ESI-MS conditions, the predominant ion was the protonated molecular ion ($[M+H]^+$) which was monitored for the identification of each β-blocker. However, in order to avoid misinterpretation and bad quantitative results for compounds which possess a close molecular mass (i.e., pindolol–alprenolol and oxprenolol–atenolol–metoprolol), electrophoretic selectivity was highly required with a single quadrupole instrument. As shown in Fig. 4, while peaks 249 (pindolol) and 250 (alprenolol) co-eluted with water, MeCN and MeOH, those peaks were baseline separated in the presence of NMF. Furthermore and, as shown in Fig. 5, peaks of oxprenolol, atenolol and metoprolol which possess close molecular masses were clearly separated with all investigated solvent, except water and MeCN. The small peaks shown in SIM electropherograms (Fig. 5) for m/z ratios 250, 267 and 268 correspond to isotopes ions $[M+H+1]^+$ of pindolol, oxprenolol and atenolol, respectively. This result indicated the utmost importance of selectivity in CE before MS detection and therefore the great interest to have different organic solvents to modify selectivity.

4. Conclusion

In this study, it was demonstrated that NACE–UV and NACE–ESI-MS were well adapted for the separation of β-blockers with different solvents, such as FA and NMF. These solvents showed several interesting electrophoretic characteristics. They exhibited different selectivity compared to water, MeCN and MeOH, as well as higher efficiency, especially NMF. Moreover, the basic characters of

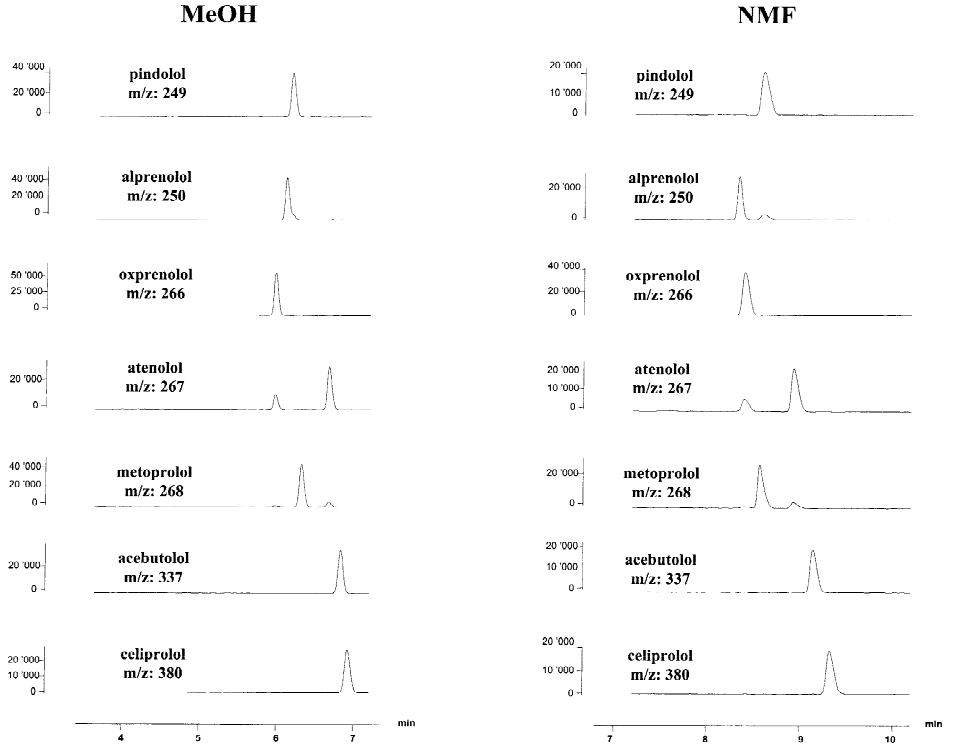

Fig. 5. Extracted ion current for each mass monitored in MeOH (A) and NMF (B). Experimental conditions as in Fig. 4.

FA and NMF as amphiprotic solvents, as well as their high cohesion energy densities may extend their solubilizing capacity to other additives (e.g., chiral selectors). However, UV detection with FA and NMF is restricted to the analysis of compounds absorbing at wavelengths higher than 250 nm, such as β-blockers. This is why coupling CE with ESI-MS is of particular interest, since it should allow the use of FA and NMF for the analysis of other drugs. Nevertheless, due to their low volatility, FA and NMF showed a loss in sensitivity compared to MeOH and MeCN. On the other hand, FA and NMF allowed to obtain very stable electrophoretic and electrospray currents.

This study demonstrated the utmost importance to have at disposal different solvents in order to modify selectivity in CE, since a single quadrupole mass spectrometer cannot distinguish isobaric compounds or compound with close mass to charge ratio (e.g., for pindolol and alprenolol). While only pure organic solvents were investigated in this study, mixtures of FA or NMF with MeCN or MeOH should be a promising alternative to extend the application range of NACE by adding new separation performances. Therefore, the use of formamide and its derivatives in conjunction with MS detection will certainly open new possibilities in NACE separation, without any restrictions due to their optical properties. These solvents are also very useful for labile compounds, substances with low aqueous solubility and for electrophoretic separation that cannot be achieved in aqueous buffer. Subsequently, the use of these solvents to achieve separation based on solvophobic interaction will constitute an area of particular interest.

References

[1] I.E. Valko, H. Siren, M.L. Riekkola, LC·GC Int. 3 (1997) 190.
[2] I. Bjornsdottir, J. Tjornelund, S.H. Hansen, Electrophoresis 19 (1998) 2179.
[3] S.H. Hansen, J. Tjornelund, I. Bjornsdottir, Trends Anal. Chem. 15 (1996) 175.
[4] F. Steiner, M. Hassel, Electrophoresis 21 (2000) 3994.
[5] M.L. Riekkola, M. Jussila, S.P. Porras, I.E. Valko, H. Siren, J. Chromatogr. A 892 (2000) 155.
[6] M.T. Bowser, A.R. Kranack, D.D.Y. Chen, Trends Anal. Chem. 17 (1998) 424.
[7] F. Wang, M.G. Khaledi, Anal. Chem. 68 (1996) 3460.
[8] I.E. Valko, H. Siren, M.L. Riekkola, Chromatographia 43 (1996) 242.
[9] I.E. Valko, H. Siren, M.L. Riekkola, Electrophoresis 18 (1997) 919.
[10] A. Tivesten, S. Folestad, V. Schönbacher, K. Svensson, Chromatographia 49 (1999) S7.
[11] Y. Marcus, in: Ion Solvation, Wiley, Chichester, 1985.
[12] C. Reichardt, in: Solvents and Solvent Effects in Organic Chemistry, VCH, Weinheim, 1990.
[13] H. Salimi-Mossavi, R.M. Cassidy, Anal. Chem. 67 (1995) 1067.
[14] N. Suzuki, Y. Ishihama, T. Kajima, N. Asakawa, J. Chromatogr. A 829 (1998) 411.
[15] H. Salimi-Mossavi, R.M. Cassidy, J. Chromatogr. A 790 (1997) 185.
[16] K. Heinig, C. Vogt, G. Werner, J. Cap. Electrophoresis 3 (1996) 261.
[17] E. Drange, E. Lundanes, J. Chromatogr. A 771 (1997) 301.
[18] J. Tjornelund, S.H. Hansen, J. Chromatogr. A 779 (1997) 235.
[19] V.L. Ward, M.G. Khaledi, J. Chromatogr. B 718 (1998) 15.
[20] J. Muzikar, T. Van de Goor, B. Gas, E. Kenndler, J. Chromatogr. A 924 (2001) 147.
[21] J.H.T. Luong, A. Hilmi, A.L. Mguyen, J. Chromatogr. A 864 (1999) 323.
[22] S. Cherkaoui, Clinical and forensic applications of capillary electrophoresis, in: J.R. Petersen, A. Mohammad (Eds.), Pathology and Laboratory Medicine Series, Humana Press, Clifton, NJ, 2001.
[23] K. Raith, R. Wolf, J. Wagner, R.H.H. Neubert, J. Chromatogr. A 802 (1998) 185.
[24] W. Ahrer, W. Buchberger, Fresenius J. Anal. Chem. 365 (1999) 604.
[25] L. Geiser, S. Cherkaoui, J.-L. Veuthey, J. Chromatogr. A 895 (2000) 111.
[26] S. Cherkaoui, J.L. Veuthey, Electrophoresis 23 (2002) 442.
[27] S. Cherkaoui, S. Rudaz, J.L. Veuthey, Electrophoresis 22 (2001) 491.
[28] W. Lu, G.K. Poon, P.L. Garmichael, R.B. Cole, Anal. Chem. 68 (1996) 668.
[29] C.S. Liu, X.F. Li, D. Pinto, E.B. Hansen, C.E. Cerniglia, N.J. Dovichi, Electrophoresis 19 (1998) 3183.
[30] Q. Yang, L.M. Benson, K.L. Johnson, S. Naylor, J. Biochem. Biophys. Methods 38 (1999) 103.
[31] J. Schwartz, in: M. Schorderet et al. (Ed.), Pharmacologie, 3rd ed., Frison-Roche, Stalakine, 1998.
[32] J.A. Franciosa, Coron. Art. Dis. 10 (1999) 369.
[33] K. Burger, in: Solvation, Ionic and Complex Formation Reactions in Non-Aqueous Solvents: Experimental Methods for Their Investigation, Elsevier, New York, 1983.
[34] A.S. Lister, J.G. Dorsey, J. High Resolut. Chromatogr. 20 (1997) 523.