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On-line micellar electrokinetic chromatography–mass spectrometry with a high-molecular-mass surfactant

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Abstract

On-line coupling of micellar electrokinetic chromatography and electrospray ionization mass spectrometry (MEKC–ESI-MS) using a high-molecular-mass surfactant was explored. Some standard mixtures, pharmaceuticals and industrial surfactants were separated and detected with 1% butyl acrylate–butyl methacrylate–methacrylic acid copolymer sodium salt (BBMA) in 20 m*M* ammonium formate (pH 7). The effect of the concentration of surfactants on sensitivity was studied with direct injection of caffeine to the ESI-MS. The partial filling technique in MEKC was studied with BBMA. Before the pseudo-stationary phase zone reached the detector, six non-ionic naphthalene derivatives were separated successfully by partial filling MEKC with a 5% BBMA zone introduced at 50 mbar for 20 s. The partial filling method was also applied to the on-line MS detection of caffeine and its metabolites. © 1998 Elsevier Science B.V.

Keywords: Partial filling micellar electrokinetic chromatography; Micellar electrokinetic chromatography–mass spectrometry; Detection, electrophoresis; Surfactants; Caffeine; Naphthalenes

1. Introduction

Micellar electrokinetic chromatography (MEKC) is a mode of capillary electrophoresis (CE), where ionic micelles are used as pseudo-stationary phases [1–5]. Almost all advantages of capillary zone electrophoresis (CZE) apply to MEKC as well, and many applications of MEKC separations have been reported. Coupling of CZE or MEKC with general spectroscopic detection methods must be useful. On-line coupling techniques for CE–MS have been studied by several groups [6–19]. Electrospray ionization (ESI) interfaces developed by Smith and co-workers [6–9] are useful for CE–MS. On the other hand, on-line coupling techniques for MEKC–MS have not yet been well developed, because of the presence of the surfactant in the running solution. Several methods have been reported for on-line MEKC–MS. Using a coupled capillary set-up and on-line heart-cutting of the MEKC separation zones was reported [20]. We reported an on-line MEKC–MS system with a high-molecular-mass surfactant, butyl acrylate–butyl methacrylate–methacrylic acid copolymer sodium salt (BBMA) [21]. A partial filling technique in MEKC for MS detection was reported [22,23]. Although Varghese and Cole used a cationic surfactant, cetyltrimethylammonium chloride [24], and a anionic surfactant, sodium dodecyl sulfate (SDS) [25], as an additive to the running solution for CE–ESI-MS, the separation mode described was not MEKC because the surfactant concentrations were below critical micelle concentration (CMC).

The advantage of using a high-molecular-mass

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surfactant is a direct coupling of conventional MEKC to the MS detector without any special interfacing devices and separation methods. We reported conventional MEKC with BBMA [26,27]. The molecular mass of the BBMA was measured to be about 40 000 by size-exclusion chromatography (SEC) using standard polyethylene glycol (PEG). BBMA showed high efficiency and significantly different selectivity in MEKC for naphthalene derivatives in comparison with SDS [26]. The CMC of BBMA was found to be effectively zero [26]. Thus, BBMA is suitable for MEKC–MS because of the formation of the micelle at low surfactant concentrations, a higher molecular mass beyond the hardware mass range, and high efficiency in separations. The mechanism of signal suppression by anionic surfactants including BBMA in ESI-MS detection was discussed elsewhere [28].

In this paper, we describe some applications of the on-line MEKC–ESI-MS system and study of the partial filling technique with BBMA. The partial filling technique in MEKC (PF-MEKC) was first presented by us [29].

2. Experimental

2.1. Apparatus

The experimental framework of the MEKC–ESI-MS system was the same as in a previous report [21]. MEKC was performed with laboratory-built instruments which consisted of a Matsusada Precision Devices HCZE30PN0.25-LDSW high-voltage power supply (Kusatsu, Shiga, Japan) and a fused-silica capillary 50 cm×50 μm I.D×150 μm O.D. obtained from Tokyo Kasei (Tokyo, Japan). The partial filling-MEKC was performed with a Jasco CE-910 CE system (Tokyo, Japan) and a fused-silica capillary of 1 m×50 μm I.D×150 μm O.D. An ESI interface was laboratory-built and consisted of a stainless steel tube of 190 μm I.D.×350 μm O.D. (G 28), inside which the fused-silica capillary was coaxially inserted, a polytetrafluoroethylene (PTFE) tee union, which held the stainless steel tube, the capillary and a PTFE tube for the delivery of a sheath flow. The MS system consisted of a modified Hitachi M-1000 LC-APCI-MS (Tokyo, Japan) which was constructed with a quadrupole mass spectrometer and a differential pumping region.

MEKC using UV detection was performed on a Hewlett-Packard HP3DCE system (Waldbronn, Germany).

2.2. Procedure

On-line MEKC–ESI-MS work was performed with the system described above using BBMA solutions in 10 m*M* ammonium formate buffer (pH 7) containing 10% methanol. Samples were injected by the hydrostatic injection method (10–30 s at 15 cm). The MEKC applied voltage was 10 kV (13 kV at the capillary inlet and 3 kV at the end of the capillary located in the ESI interface). The sheath liquid consisted of water, methanol and formic acid (50:50:1, v/v/v) and was delivered by a Hitachi HPLC pump L6300 at approximately 5 μl/min, or a Harvard Apparatus Model 44 syringe pump (Natick, MA, USA) at 1 μl/min. Electrospray was performed using a 3-kV gradient between the capillary end and the first MS sampling orifice. The MS system was operated in the positive ion mode. All MS detection was performed in the scanning mode, m/z 1–1000, at 4 s/scan. Drift voltage was 70 V, focusing voltage 140–150 V and resolution 50–55. The m/z value was not always accurate because the calibration was not performed frequently and the room temperature was not constant. And so, in order to see if the analyte ion is produced and also to find the m/z value for the major peaks, the mass spectra of all analytes were obtained by direct injection to the detector before the on-line MEKC–MS work.

Conventional MEKC using a UV detector was performed as described previously [26,27]. In partial filling-MEKC, the micellar zone was introduced in a part of the capillary by pressurization with the instruments described above.

2.3. Reagents

BBMA was supplied as a 23% aqueous solution by Dai-ichi Kogyo Seiyaku (Kyoto, Japan). Since BBMA contains a minor amount of low-molecular nass components, it was purified by the reprecipitation method with acetone [26,27]. SDS was purchased from Nacalai Tesque (Kyoto, Japan). All

other reagents were of analytical grade and water was purified with a Milli-Q system.

Sample compounds, pyridoxine, nicotinamide, octyltrimethylammonium bromide, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, cetyltrimethylammonium bromide and PEG 1000 were obtained from Nacalai Tesque, caffeine, phenyltrimethylammonium chloride, tetraphenylphosphonium chloride, and octaoxyethylene dodecanol were obtained from Wako Pure Chemical (Osaka, Japan), 1,7-dimethylxanthine, 1-methylxanthine, 7-methylxanthine, 1-methyluric acid and 7-methyluric acid were from Aldrich (St. Louis, MO, USA); all were of analytical grade and used as received. Other pharmaceuticals were supplied commercially and used as received. Sample solutes were dissolved in about 50% aqueous methanol.

3. Results and discussion

3.1. MEKC–ESI-MS with BBMA

For the pseudo-stationary phase in on-line MEKC–ESI-MS, BBMA is expected to be suitable because of the formation of the micelle at low surfactant concentrations. This advantage was verified by the separation of non-ionic naphthalene derivatives, 1-naphthalenemethanol, 1-naphthol and 2-naphthol, with 0.025% BBMA using UV detection. This BBMA concentration is practically lower than the CMC of SDS expressed by % (w/w). BBMA has not been frequently employed in applications of MEKC, compared with SDS. BBMA showed significantly different selectivity in contrast to SDS [26]. Therefore, it is important to investigate characteristics of separation and selectivity in the BBMA system. Sulfamides, sulfamethazine, sulfisomidine, sulfadiadine and sulfisoxazole, were separated and detected by ESI-MS with 2% BBMA previously [21].

Fig. 1 shows single-ion chromatograms of some pharmaceuticals by MEKC–ESI-MS with BBMA. All the solutes were used as hydrochloride. The mass spectra were scanned from m/z 5–800 for 4 s/scan. All the solutes were successfully detected both by single-ion chromatograms and by total-ion chromatograms under the conditions of 1% BBMA. However,

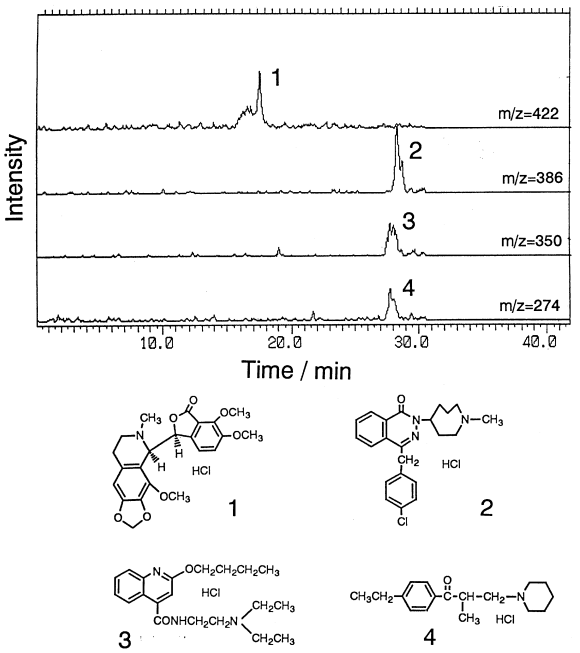

Fig. 1. MEKC–ESI-MS of pharmaceuticals and their molecular structures. Solute: 1, noscapine; 2, azelastine; 3, dibucaine; 4, eperisone. MEKC conditions: capillary, 50 cm×50 μm I.D., fused-silica; separation solution, 1% BBMA in 10 m*M* ammonium formate (pH 7); applied voltage, 13 kV. ESI-MS conditions: electrospray voltage, 3 kV; MS scanning, from m/z 1 to 800 at 4/scan; mode, positive; drift voltage, 70 V; focusing voltage, 140 V; resolution, 55; sheath liquid flow, water–methanol–formic acid (50:50:1, v/v/v) at ca. 5 μl/min.

azelastine, dibucaine and eperisone were not separated. Significantly broad peaks were probably ascribed to the ESI interface, because MEKC–UV gave much narrower peaks. Poor S/N ratios were also due to the poor transfer efficiency of our ESI system and poor sensitivity of our MS system. If a modern MS system is employed, the S/N ratio will be much higher.

Fig. 2 shows single-ion chromatograms of another pharmaceuticals with 1% BBMA. Isopropylantipyrine was well detected. Some other cold medicines, acetaminophen, ethenzamide and guaifenesin, were not detected under the same conditions as in Fig. 2. Water soluble vitamins, caffeine, pyridoxine and nicotinamide, were detected, but all of them migrated fast and were not separated enough under the same conditions. MEKC is suitable for analyses of pharmaceuticals involving cationic,

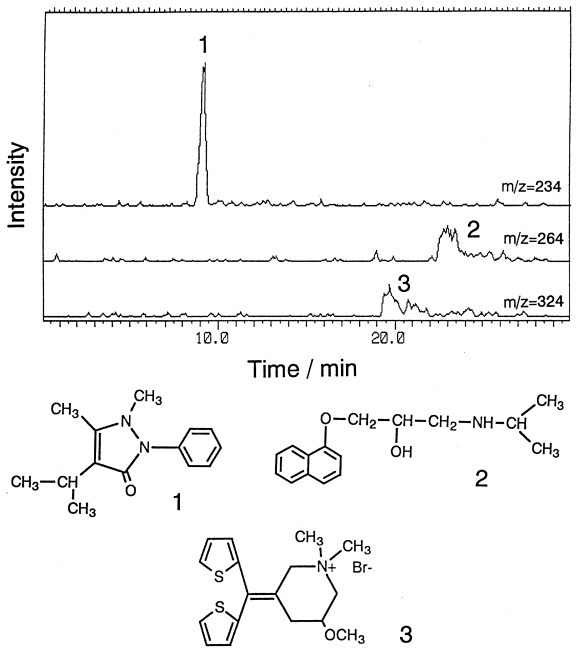

Fig. 2. MEKC–ESI-MS of pharmaceuticals and their molecular structures. Solutes: 1, isopropylantipyrine; 2, propranolol; 3, timepidium bromide. Conditions as in Fig. 1.

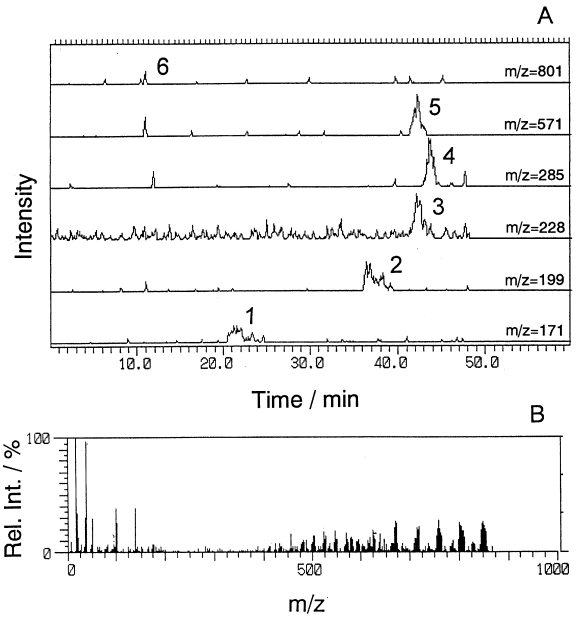

Fig. 3. MEKC–ESI-MS of cationic and non-ionic surfactants (A) and mass spectrum of the peak 6 (B). Solutes: 1, octyltrimethylammonium bromide; 2, decyltrimethylammonium bromide; 3, dodecyltrimethylammonium bromide; 4, cetyltrimethylammonium bromide; 5, octaoxyethylenedocecanol; 6, PEG 1000. Separation solution; 2% BBMA in 10% methanol and 10 m*M* ammonium formate (pH 7). Other conditions as in Fig. 1.

anionic and neutral analytes, but it is important to optimize the MEKC separation conditions for the on-line ESI-MS detection of pharmaceuticals. In this work, however, no optimization was tried because the purpose of the study was to investigate the possibility of MEKC–MS using a high-molecular-mass surfactant. The MEKC separation with BBMA may be improved by the addition of organic solvent, organic modifiers and changing the pH. The effect of the addition of methanol to the BBMA system has been studied previously [27], and methanol will not cause a problem in ESI-MS detection. The effect of pH with the BBMA system has also been studied [26]. Although the lower pH condition was suitable to ESI-MS detection in positive ion mode, BBMA precipitated below pH 4 [26].

Fig. 3A shows the single-ion chromatograms of cationic (1–4) and non-ionic surfactants (5–6) with 2% BBMA. PEG 1000 was the mixture and the molecular masses were widely distributed. The single-ion chromatogram of PEG 1000 was detected by the strongest peak below m/z 1000. Although the intensity of the peak 6 in Fig. 3A was weak, the mass spectrum of this peak was the same as that of PEG 1000 observed by the direct injection, as shown in Fig. 3B. It should be noted that PEG 1000 migrated close to t_0 owing to the weak interaction with BBMA micelle. All the cationic surfactants were successfully separated and the migration order was the same as the carbon numbers of the alkyl chain. An increase of the spectrum background caused by separation solution was observed in the chromatogram of peak 3. Under the same conditions as in Fig. 3, non-ionic surfactants having polyoxyethylene groups, octa-, penta-, and di-oxyethylenedodecanol, were well detected, but not separated. With 0.5% BBMA, all the cationic surfactants showed significant tailing owing to the strong interaction with the negatively charged capillary wall.

3.2. Dependence of ESI signal intensities on the concentration of surfactant

Dependence of ESI signal intensities of caffeine

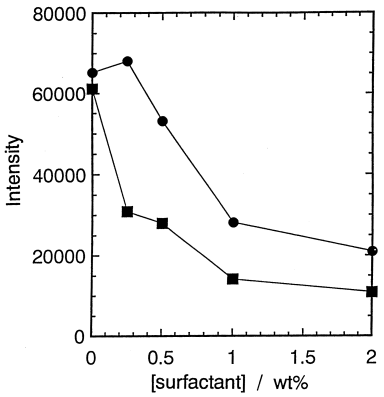

Fig. 4. Dependence of the ESI-MS intensities of caffeine on the concentration of surfactants by liquid injection. ●, BBMA; ■, SDS.

on the concentrations of surfactants, BBMA and SDS, were studied with direct introduction of the sample solution to the ESI system. The direct introduction of the caffeine solution containing BBMA or SDS was performed with the same sheath liquid flow as the on-line work. The concentration of caffeine was 10 m*M* and the solution was introduced by pressurization. Fig. 4 shows that the signal intensity of the proton-attached ion of caffeine decreased with the increase of either BBMA or SDS concentration. A rapid and steady decrease was observed with SDS rather than with BBMA. It should be noted that the decrease in signal intensity was slight with an increase in BBMA concentration from 0 to 0.5% compared with SDS. Fig. 5 shows examples of ESI-MS spectra of caffeine in the presence of BBMA (A and B) or SDS (C and D). In Fig. 5C Fig. 5D, the molecular ion of SDS due to sodium attachment (marked as $[SDS+Na]^+$) and the singly charged dimer ion (marked as $[2SDS+Na]^+$) were observed. Weak sodium attached ions of caffeine (marked as $[M+Na]^+$) were observed with either BBMA or SDS system. The sodium-attached ions of caffeine increased with increases of the concentrations of BBMA or SDS. When the drift voltage was reduced down to 30 V, the sodium-attached ion of caffeine was observed to be stronger than the proton-attached ion in the presence of 0.5% BBMA. Cole and co-workers [25] studied the decrease of the ESI-MS signal of tamoxifen and its metabolites with the SDS system in methanol media.

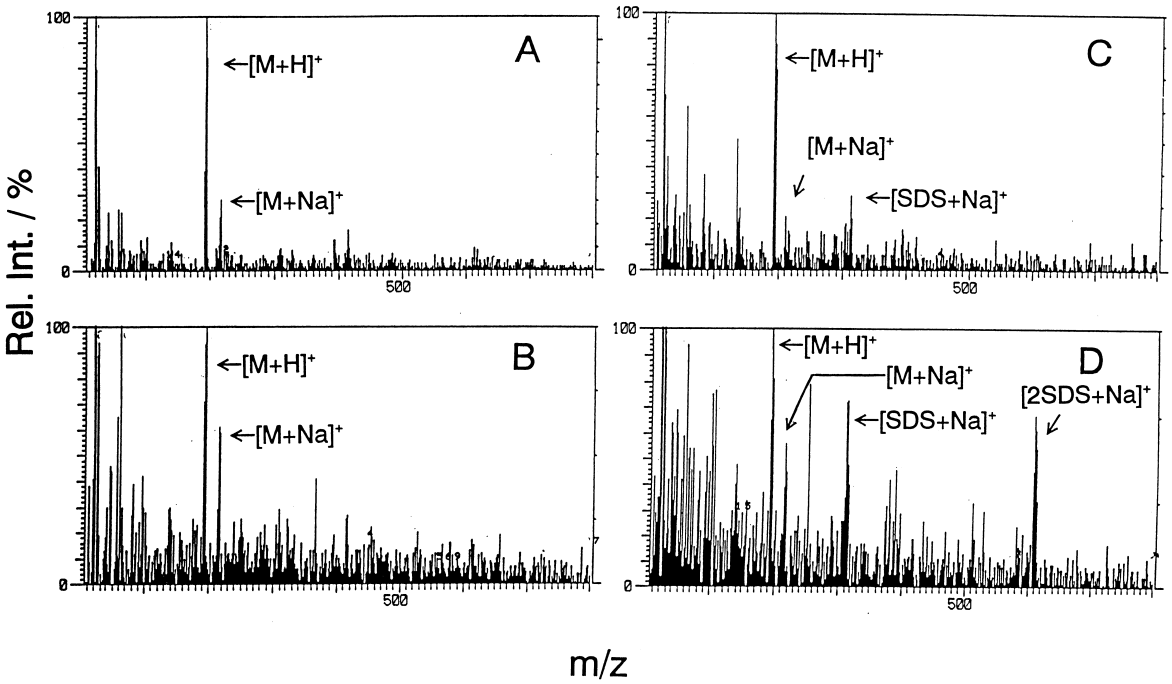

Fig. 5. ESI mass spectra of caffeine with BBMA (A,B) and SDS (C,D). Surfactant concentration; 0.5% (A,C) and 2% (B,D).

In this case, the abundance of the protonated tamoxifen analogs decreased steadily as the SDS concentration increased from 0 to 10 m*M* (from 0 to 0.29%) and leveled off between 10 and 30 m*M* (between 0.29 and 0.87%). In Fig. 4, it can be seen that the intensity leveled off over 1% SDS.

The detailed mechanism of the signal suppression by the surfactants in MEKC–ESI-MS should be complex because there are two main steps, the production of charged droplets and the production of gas-phase ions from the charged droplets, in the generation of gas-phase ions of the analyte by ESI and both steps should be affected by the pH, buffer ions and surfactant ions of the MEKC separation solution. Rundlett and Armstrong [28] presented a mechanism of the signal suppression by anionic surfactants in ESI-MS. They proposed the ESI-produced offspring droplets model caused by Coulombic interaction between oppositely charged solute and surfactant ions. For the detailed study of the mechanism in ESI-MS with surfactants, it is interesting that the relatively strong signal of the SDS dimer ion was observed as shown in Fig. 5. Furthermore, the observation of sodium-attached caffeine ions, as shown in Fig. 5, indicate that the presence of sodium, the counter ion of the anionic surfactant, should cause the signal suppression of proton-attached ions of analyte in MEKC–ESI-MS.

On the basis of the study with direct introduction of the caffeine to the ESI-MS, the on-line MEKC–ESI-MS of caffeine with BBMA was performed under the conditions of relatively slight signal suppression. Fig. 6 shows the single-ion chromatogram (A) and spectrum of the peak (B) of caffeine by MEKC–ESI-MS with 0.5% BBMA. Sheath liquid flow-rate was 1 μl/min. Other conditions were the same as in Fig. 1. The amount of the injected sample was 180 ng (concentration was 5 mg/ml and 37 nl injected). The detectability in MEKC–ESI-MS was far less than that in conventional LC–MS. The lower

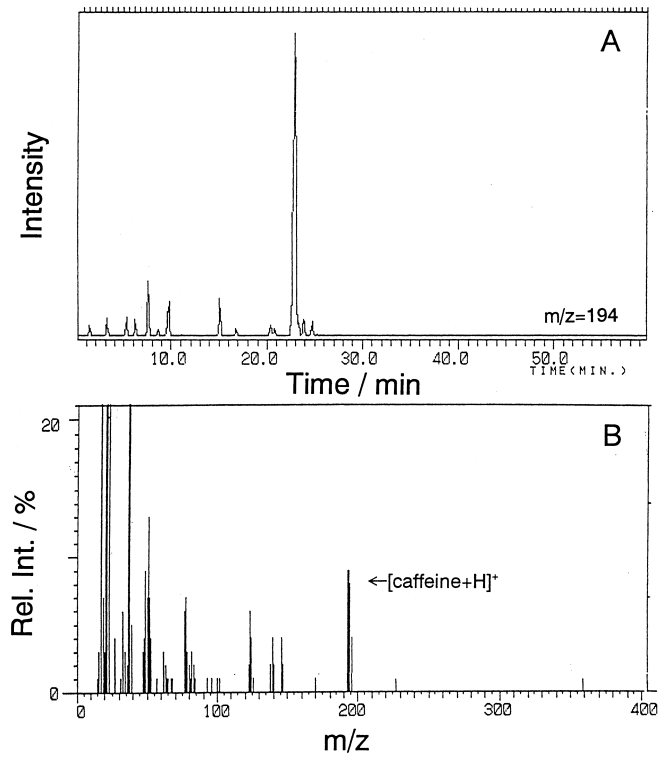

Fig. 6. MEKC–ESI-MS of caffeine (A) and mass spectrum of the peak (B). Conditions: capillary, 100 cm×50 μm I.D. fused-silica; separation solution, 0.5% BBMA in 20 m*M* ammonium formate (pH 7); sheath liquid flow, water–methanol–formic acid (50:50:1, v/v/v) at 1 μl/min; amount of injected sample, 180 ng. Other conditions as in Fig. 1.

detectability was probably caused by the ESI-interface which was laboratory-built and not fully optimized.

3.3. Partial filling technique with BBMA

The study described above indicates that the intensity of analyte ion decreases with the increase of the BBMA concentration. The partial filling technique (PF) of the pseudo-stationary phase is expected to solve the problem of signal suppression in ESI-MS detection on-line coupled with MEKC [22,23,29]. Fig. 7 shows the separation of naphthalene derivatives by the PF-MEKC with UV. Before the BBMA zone (marked with mc in Fig. 7A) reached the detector, six naphthalene derivatives were separated successfully and detected, with 5% BBMA zone introduced at 50 mbar for 30 s as shown in Fig. 7B. The effect of the buffer system on the PF-MEKC was studied. Borate, which is a nonvolatile buffer component, and formic acid, acetic acid, and propionic acid ammonium salts, which are volatile components, were compared. In the borate buffer, the BBMA zone was relatively sharp as shown in Fig. 7. With other buffers, however, the BBMA zone became broader. The BBMA zone showed remarkable fronting and overlapped with analyte peaks in the ammonium formate, acetate and propionate buffers. It was clearly shown that choice of the buffer system is critical for on-line coupling of PF-MEKC with ESI-MS, and more work is needed. BBMA should be useful to study PF-MEKC because the surfactant zone peak is directly detected by UV. In the study with SDS [22], a micellar marker, quinine, was used to detect the SDS zone.

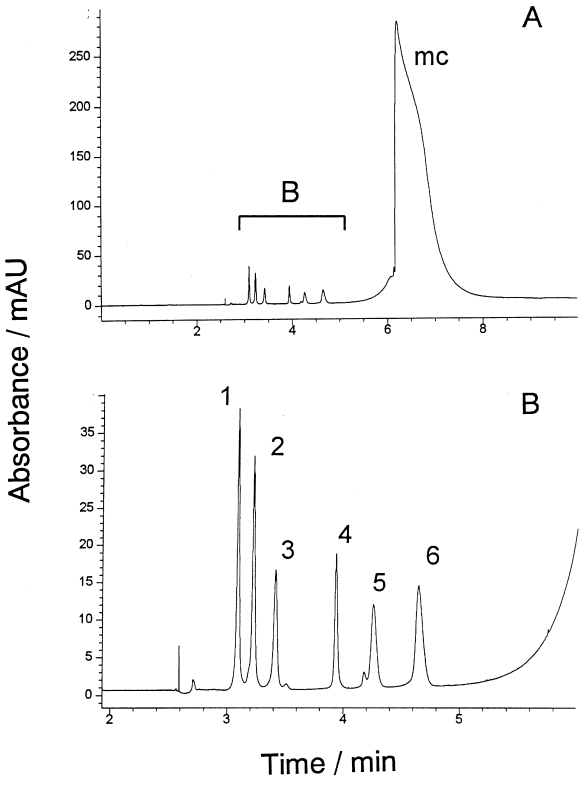

Fig. 7. PF-MEKC separation of naphthalene derivatives using BBMA. Solutes: 1, 1-naphthalenemethanol; 2, 1,6-dihydroxynaphthalene; 3, 1-naphthylamine; 4, 1-naphthaleneethanol; 5, 2-naphthol; 6, 1-naphthol. BBMA zone peak marked with mc. Conditions: capillary, 48 cm (40 cm to the detector)×50 μm I.D., fused-silica; separation solution, 5% BBMA zone introduced at 50 mbar for 20 s in 100 m*M* borate buffer (pH 9); applied voltage, 20 kV; detection wavelength, 210 nm.

Fig. 8 shows the PF-MEKC separation of caffeine and its metabolite compounds in the borate buffer system. Before the BBMA zone passed through the detector, five analytes were separated successfully with a 5% BBMA zone introduced at 50 mbar for 20 s. Migration order was the same as by conventional MEKC with BBMA.

Fig. 9A shows the total-ion and single-ion chromatograms of the same analytes as in Fig. 8 by PF-MEKC–ESI-MS in the ammonium formate system. Fig. 9B shows the mass spectra acquired from the peaks in Fig. 9A. Peaks of caffeine, 1,7-dimethylxanthine, 1-methylxanthine and 7-methylxanthine were detected both by the single-ion chromatograms and total-ion chromatogram. 1-Methyluric acid was not detected owing to the decrease of detectability brought about by the overlap of the partially filled BBMA zone in the ammonium formate buffer system.

4. Conclusions

On-line MEKC–ESI-MS using diluted BBMA solutions was explored. Although the resolution was not high enough, some standard mixtures, the pharmaceuticals and industrial surfactants, were sepa-

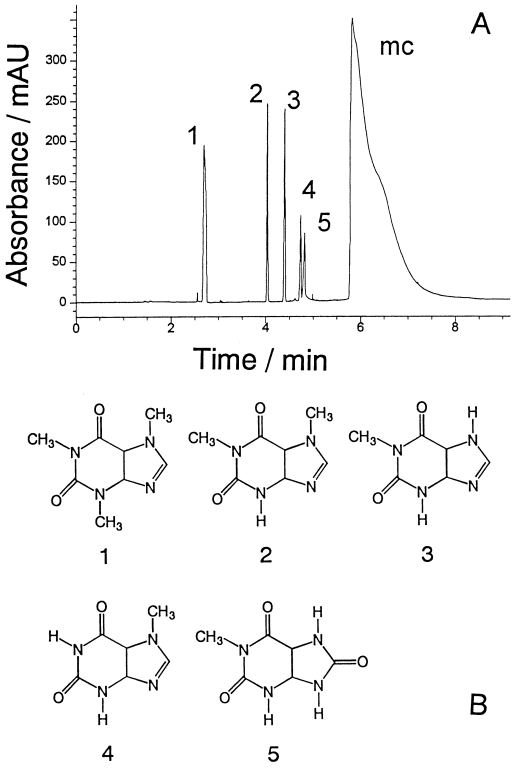

Fig. 8. PF-MEKC separation of caffeiene and its metabolites using BBMA (A) and molecular structure of them (B). Solutes: 1, caffeine; 2, 1,7-dimethylxanthine; 3, 1-methylxanthine; 4, 7-methylxanthine; 5, 1-methyluric acid. BBMA zone peak marked with mc. Conditions as in Fig. 7.

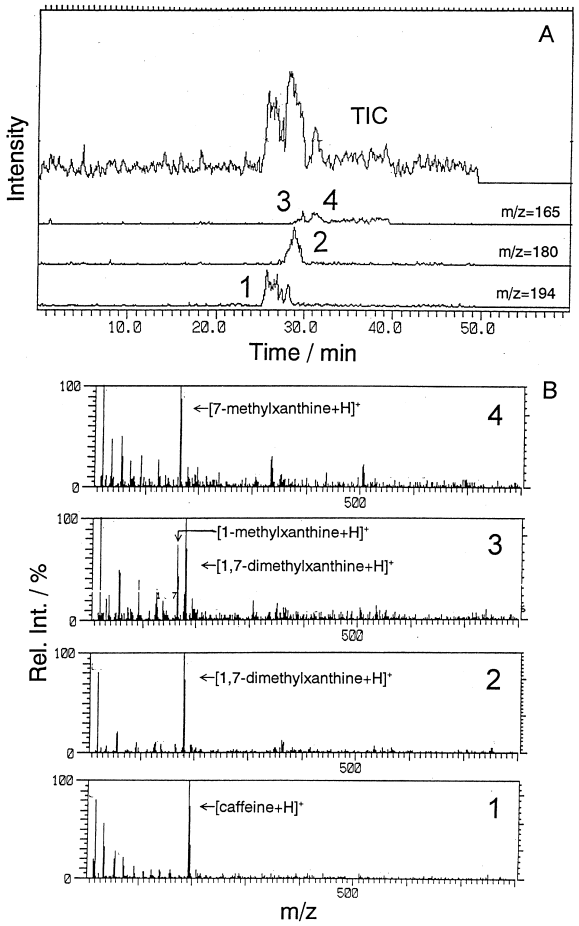

Fig. 9. MEKC–ESI-MS of caffeine and its metabolites using BBMA (A) and mass spectra of the peaks (B). Solutes as in Fig. 8. Conditions: capillary, 100 cm×50 μm I.D., fused-silica; separation solution, 2% BBMA introduced at 100 mbar for 120 s in 20 m*M* ammonium formate (pH 7); applied voltage, 20 kV. Other conditions as in Fig. 1.

rated and detected successfully by the direct coupling of the conventional MEKC to the ESI-MS detector. In order to improve the resolution, higher BBMA concentrations were required. However, by direct injection study, the high BBMA concentration significantly degraded ESI-MS intensity. Therefore, PF-MEKC with BBMA was investigated and applied to the on-line MS detection of caffeine and its metabolites. The performance of the on-line MS detection system in this work was not yet very high. A more detailed study of the signal suppression by surfactants in MEKC–ESI-MS will be necessary for further development.

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