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Cationic vesicles as chiral selector for enantioseparations of nonsteroidal antiinflammatory drugs by micellar electrokinetic chromatography

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Abstract

A vesicle-forming chiral cationic surfactant (1*R*,2*S*)-(−)-*N*-dodecyl-*N*-methyl-ephedrinium bromide was evaluated as a pseudo-stationary phase in micellar electrokinetic chromatography (MEKC) for enantioseparation of eight non-steroidal anti-inflammatory drugs e.g., carprofen, flurbiprofen, fenoprofen, ibuprofen, indoprofen, ketoprofen, naproxen and suprofen by capillary electrophoresis. The effects of varying experimental conditions such as pH and concentration of surfactant in the running buffer on the enantiomer separation of the drugs are reported. A mixture of five of the above drugs was separated and each enantiomeric pair was also separated simultaneously in a single run by use of the surfactant. The strong electrostatic interactions between the analytes and the vesicles seemed to have a major role in the enantiomeric separation of the profens.
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Keywords: Vesicles; Cationic surfactant; MEKC; Enantioseparation; Anti-inflammatory drugs

1. Introduction

One of the important objectives of chromatography is separation of enantiomers from their racemic mixture. This is because of the growing need for enantiomerically pure drugs in the pharmaceutical industries. In recent years, enantiomer separations by micellar electrokinetic chromatography (MEKC) have become a popular technique in capillary electrophoresis (CE). In MEKC, a variety of chiral micelle-forming surfactants [1–5] have been used for enantiomeric separations. The MEKC technique, first introduced by Terabe et al. [6] for separation of organic molecules uses a micellar pseudostationary phase as a buffer additive in capillary zone electrophoresis that separates charged as well as neutral analytes. The MEKC usually utilizes negatively charged micelles formed from anionic surfactants such as sodium dodecyl sulfate (SDS), which constitutes the pseudostationary phase. The separation is achieved by differential partitioning of analytes between the pseudostationary phase and the bulk aqueous phase. After Dobashi et al. [7,8] first reported the use of amino acid derivatized surfactants as chiral selectors in enantioseparation, there have been many reports on enantiomer separations by MEKC [1–5]. Recently, it has been demonstrated that the use of polymeric surfactants as chiral selectors in MEKC improves peak resolution as compared to monomeric surfactants [9–12]. However, one of the disadvantages of MEKC using micelle-forming surfactants is low migration range, which affects separation. One approach to increase migration range is use of vesicle-forming surfactants as chiral selectors in MEKC. Hong et al. [13] have used vesicles formed from SDS and dodecyltrimethylammonium bromide as pseudostationary phase in MEKC to separate *n*-alkylphenones and found that the vesicular system provides about two times wider migration window, and higher polar group selectivity, migration time and efficiency as compared to the pure SDS micellar system. Delgado-Zamarreño et al. [14] have also separated food antioxidants using sulfosuccinate vesicles. Pascoe et al. [15] as well as Agbodjan and Khaledi [16] have studied partitioning of surfactant and

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alkylphenones, respectively, in vesicular systems in CE. Recently, we have demonstrated the use of vesicle-forming amino acid derivatized surfactants as chiral selectors in MEKC [17]. However, in most of the works reported so far, the anionic surfactants have been the preferred chiral selectors for enantiomer separations. Although cationic surfactants such as cetyltrimethylammonium bromide (CTAB) have been widely used for either slowing down or reversing the electroosmotic flow (EOF) [18,19], the use of cationic surfactants has been avoided because they adsorb on the capillary wall surface by dynamic electrostatic interactions between the negatively charged Si–O^- groups and the positively charged quaternary ammonium ions and thereby affect resolution. However, the use of D-(+)-tubocurarine chloride a cationic macrocycle for the enantiomeric separations of dansylated α-aminoacids has been reported by Nair et al. [20]. O'Keeffe et al. have demonstrated the use of cationic cyclodextrin derivatives for the enantioseparation of some 2-arylpropionic acids (APA) [21]. Rundlett and Armstrong have also reported enantiomer separations of some profens using vancomycin, a positively charged macrocyclic antibiotic as chiral selector in MEKC [22].

The profens are APAs and are an important class of non-steroidal anti-inflammatory drugs. These drugs are characterized by low solubility in water. Some of these have similar charge densities, which makes their separation difficult in aqueous system. However, there are several reports on the separation of profen enantiomers using different operating modes of CE [21–37]. The chiral selectors used includes linear oligo- or polysachharides [23,24], β-CD and hydroxypropyl β-CD [35,36], vancomycin [32] and ristocetin A [33].

In the present work, we introduce (1*R*,2*S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB), a cationic surfactant for enantioseparations of carprofen (CRP), flurbiprofen (FLP), fenoprofen (FNP), ibuprofen (IBP), indoprofen (INP), ketoprofen (KTP), naproxen (NPX) and suprofen (SUP) by MEKC. The structures of the chiral selector and the drug molecules are shown in Fig. 1. It is believed that electrostatic, hydrophobic, hydrogen-bonding and π–π interactions between analyte molecules and the chiral selector are responsible for enantiomeric separation. Since there are two stereogenic centers, one hydroxyl group and a phenyl ring on the surfactant head group, DMEB is expected to be a good chiral selector for polar as well as nonpolar molecules. Further, our recent studies on the aggregation behavior of DMEB in aqueous solution have shown that the surfactant molecules self-assemble to form vesicular structures [38]. Therefore, to find an application of this surfactant, we have chosen DMEB for use as chiral selector in enantiomeric separation of the profens by MEKC. There is no report on enantiomer separation by CE using DMEB, except the one by Bunke et al. [39] who obtained enantiomeric separation of atropisomeric methaqualone. The DMEB has previously been used also as a phase transfer catalyst in asymmetric syntheses [40]. The selection of the APAs as a general class

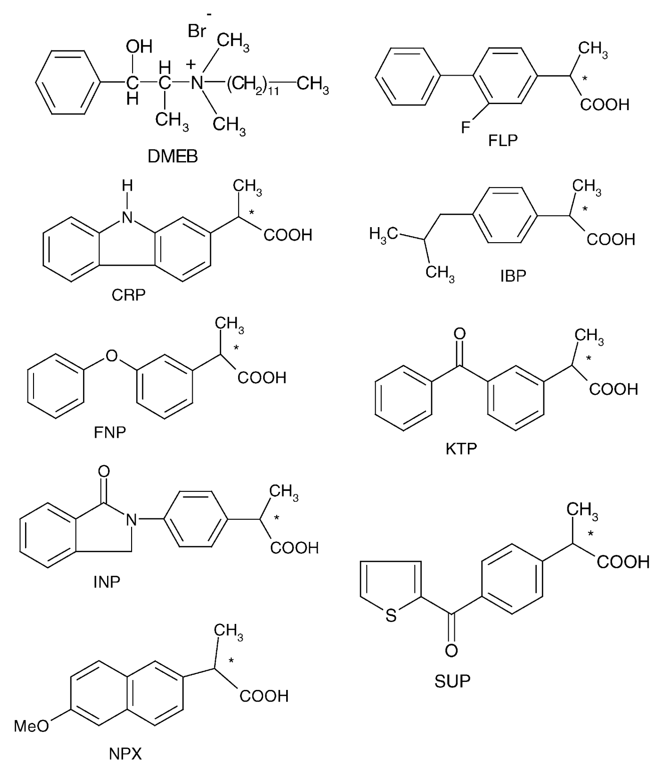

Fig. 1. Molecular structures of DMEB, CRP, FLP, FNP, IBP, INP, KTP, NPX and SUP.

of analytes was based on the results previously reported in the literature [21–37]. The aim of this work is to study the effects of varying experimental conditions such as pH and concentration of DMEB in the running buffer on the enantioseparation of the selected profens by MEKC.

2. Experimental

2.1. Materials

The DMEB and dodecanophenone were obtained from Aldrich (Milwaukee, WI, USA) and used without further purification. The racemic mixtures of carprofen, flurbiprofen, fenoprofen, ibuprofen, indoprofen, ketoprofen, naproxen and suprofen were procured from Sigma (St. Louis, MO, USA) and were used as received. Sodium borate, sodium dihydrogenphosphate and disodium hydrogenphosphate were obtained from Fisher Scientific (Fair Lawn, NJ, USA) and were used directly from the bottle.

2.2. Methods

Buffer solutions in the pH range 6–8 were prepared by mixing appropriate volume of the stock solutions (0.2 M) of sodium dihydrogenphosphate and disodium hydrogenphosphate in distilled doubly deionized water obtained from UV/UF water system (US Filter Corp., Rockford, IL, USA).

The total buffer concentrations were maintained at 20 mM. Borate buffer of pH 9.1 was prepared by dissolving sodium borate in water. The ionic strengths of all the buffer solutions were adjusted to 0.05 by adding appropriate amount of 0.5 M NaCl solution. Aliquots of surfactant stock solution were diluted appropriately with the corresponding buffer and the pH of the final solution was noted. Sample solutions were prepared by dissolving racemic mixtures in methanol–water 1:1 (v/v). The concentrations of the samples were in the range of 0.1–0.2 mg mL^{-1}.

2.3. Capillary electrophoresis procedure

The buffer solutions were filtered through a 0.45 μm Nalgene (Rochester, NY, USA) syringe filters. The buffer solutions were then degassed in an ultrasonic bath for 10 min. An untreated fused silica tube (effective length, 55.5 cm; 50 μm i.d.) purchased from Polymicro Technologies (Phoenix, AZ, USA) was used as separation capillary. Before first use, each new capillary was conditioned for 30 min with 1 M NaOH and then for another 10 min with 0.1 M NaOH. Finally, the capillary was rinsed with deionized water for 20 min. Prior to each run, the capillary was flushed first with deionized water for 5 min and then with the MEKC buffer for 5 min to ensure reproducibility of the EOF velocities and migration times. The separations were performed at constant voltage of −20 kV. Direct UV detection was employed using a detector wavelength of 254 nm. The EOF velocity was measured by injecting methanol. Dodecanophenone was used as micelle mobility marker and was detected at 245 nm in separate experiments. The injection of the samples was done at 0.5 psi pressure for 2 s. The temperature of the capillary was maintained at 25 °C.

2.4. Calculations

The capacity factors (k) and selectivity factors (α) were calculated by use of the equations [41]:

$$k = \frac{[t_R(1 + \mu_r) - t_{o,mc}]}{[t_{o,mc}(1 - t_R/t_{mc})]} \quad (1)$$

$$\alpha = \frac{k_1}{k_2} \quad (2)$$

where t_o and $t_{o,mc}$ are, respectively, the migration times of the EOF marker in the absence and presence of surfactant; t_{mc} and t_R are the migration time of the micelles and analyte, respectively, and μ_r is the relative electrophoretic mobility. μ_r is given by the equation [41]:

$$\mu_r = \frac{t_{mc}}{t_o} - \frac{t_{mc}}{t} \quad (3)$$

where t is the migration time of the analyte in absence of surfactant; k_1 and k_2 are the capacity factors of the two enantiomers.

2.5. Instrumentation

A Biofocus 3000 automated CE apparatus (Bio-Rad, Hercules, CA, USA) equipped with a multi-wavelength UV–vis detector and a thermostating liquid system was used. The UV–vis spectra were recorded on a Shimadzu UV-1601 spectrophotometer. Surface tension measurements were performed with a torsion balance (S.D. Hurdson & Co., Kolkata) by use of Du Nuoy ring method. The pH measurements were carried out on a model PH5652 pH meter (Electronic Corporation of India, Kolkata) using combined glass electrode. All measurements were carried out at ambient room temperature (∼25 °C).

3. Results and discussion

3.1. Aggregation behavior of DMEB

The molecular self-assembly of DMEB have been recently studied in our laboratory. It was found that in aqueous solution, DMEB self-assembles to form vesicular structures above a concentration called critical vesicle concentration (cvc). The detailed studies of the solution behavior of DMEB will be reported elsewhere [38]. To examine if similar microstructures also exist in the electrophoretic buffer used for the present study, we have investigated aggregation behavior of DMEB in phosphate buffer (results not shown here). Surface tension measurements have resulted a cvc value of 1.8 mM in 20 mM phosphate buffer (pH 7.0, μ = 0.05). At a constant ionic strength of the solution, the cvc value was found to be independent of pH. The electron microscopic studies have shown the formation of spherical vesicles in the buffered solution of DMEB above cvc value. In the presence of organic counter ions such as salicylate, the size of the vesicles is enhanced which suggests strong electrostatic interactions of DMEB vesicles with salicylate ions.

3.2. Enantioseparation of profens

The DMEB molecule contains two stereogenic centers (Fig. 1). The C-2 carbon of the molecule has a hydroxyl group and a phenyl ring attached to it. The UV spectrum (not shown) of a buffered aqueous solution (pH 7, μ = 0.05) of DMEB shows a weak band with λ_{max} = 257 nm. The molar absorptivity (135 L mol^{-1} cm^{-1}) at this wavelength is very small. At 254 nm, the molar absorptivity (104 L mol^{-1} cm^{-1}) of DMEB was further lower. There was no change in the UV spectrum upon change in pH. All these and the low cvc value make DMEB a good chiral selector in MEKC. However, like other quaternary ammonium-containing species such as CTAB surfactant reported in the literature, when DMEB is used in the running buffer, the positively charged DMEB molecules adsorb on the fused silica walls, resulting in formation of a positively charged surface. As a consequence, the bulk running buffer solution is electroosmotically driven

toward the positive electrode. Therefore, the CE runs were all conducted in the reversed-polarity mode. The influence of experimental parameters such as pH and surfactant concentration on the enantiomer separation was examined as described below.

3.3. Effects of pH

The profens have dissociable carboxylic acid groups. Their pK_a values are in the range of 4.03–4.50 [28,35]. Therefore, the effect of pH on the enantio-separation of the eight APAs were investigated using 20 mM phosphate and borate buffer ($\mu = 0.05$) containing 10 mM DMEB in the pH range of 6–9. Since in MEKC, enantiomer separation usually occurs at surfactant concentration greater than five times its critical micelle concentration (cmc) value, we arbitrarily chose 10 mM to investigate the pH effect. The APAs could not be enantiomerically separated at pH $\leq$ 6.4. Although the separations were good at pH $\geq$ 7, some tailing which is typical of amine selectors was observed in the chromatograms. This was observed in case of all the APAs. The peak separations suggested that best enantioseparation was achieved at pH 7.4 for FLP, FNP, KTP, NPX and at pH 7.9 for CRP, IBP, INP and SUP. O'Keeffe et al. have also reported similar results by using positively charged cyclodextrin derivatives [21]. However, these authors demonstrated that the optimum resolution for the APAs occurred at pH 5–6. This might be due to the difference in the abilities of cyclodextrins and DMEB vesicles to alter the acidities of the analytes. Indeed, several authors have reported the change of pK_a of organic acids in the presence of cyclodextrins [42–44] and micelles [45,46]. The absence of any separation of enantiomers below pH 6.4 suggests that the electrostatic interactions between the APAs and the positively charged vesicles are the controlling factors for the enantioseparations. In solutions of pH less than pK_a value, the profens are either partially ionized or remain in uncharged form. Consequently, in this pH range, the electrostatic interactions between the analyte and the chiral selector is not favourable, and therefore, no enantiomeric separation was observed below pH 6.4. On the other hand, at alkaline pH, the analyte–vesicle and analyte–capillary wall electrostatic interactions are so strong that peak tailing results with loss of separation. The shorter height of the second peak suggests that the corresponding enantiomer interacts more strongly than the one that corresponds to the first peak.

3.4. Effects of surfactant concentration

To determine the concentration of DMEB at which optimum enantioseparation was obtained, the separations were carried out using 20 mM phosphate buffer at pH 7.4 for FLP, FNP, KTP and NPX, and at pH 7.9 for CRP, IBP, INP and SUP containing varying surfactant concentration in the range of 5–20 mM. There was no separation of enantiomers at or below the surfactant concentration of 7 mM. It appeared that the maximum separation could be achieved at ∼10 mM DMEB.

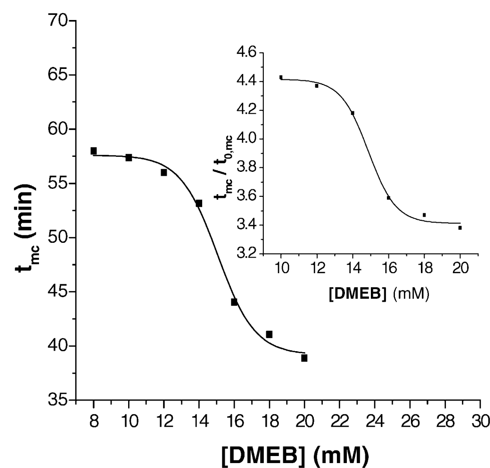

Fig. 2. Plot of t_{mc} vs. surfactant concentration; (inset) plot of $t_{mc}/t_{o,mc}$ vs. surfactant concentration.

Above this concentration, the separation either deteriorated or remained unaltered upon increase in surfactant concentration. The loss of enantiomer separation at higher surfactant concentrations could be due to some structural changes of the vesicles. In the absence of any phase change, molecular self-assemblies usually grow bigger with increase in surfactant concentration. As a result, the migration time of the analytes increases with surfactant concentration. However, in the present study, we have observed a decrease of migration time. In fact, the measured t_{mc} values at different surfactant concentrations at pH 7.4 also showed a deceasing trend. The data have been plotted in Fig. 2. The plot of $t_{mc}/t_{o,mc}$ is also shown as an insert to Fig. 2. As can be seen, there is a sigmoidal decrease in t_{mc} as well as in $t_{mc}/t_{o,mc}$ value with the increase in surfactant concentration. This suggests structural change, for example from vesicles to disc- or thread-like micelles. However, if thread-like micelles were formed, then the migration time would have increased as a result of increased solution viscosity. This implies that the microstructures formed at higher surfactant concentrations have disc-like shape. Such structural transitions have been reported for many surfactants in the literature [47,48]. The loss of peak separation at higher surfactant concentration is due to structural transition of the vesicles to micelles.

The optimized chromatograms are shown in Fig. 3. The separation parameters such as capacity factors (k) and selectivity factors (α) along with the migration times at the optimum conditions are listed in Table 1. The α value of the profens are in the order KTP > NPX > SUP > INP > CRP > IBP > FNP ≈ FLP. The results suggest that the chiral selectivity of DMEB for one of the isomers over the other varies between 5 and 21%. These values are comparable to those obtained by others using cyclodextrins [21,23,24]. The enantiomeric separation (R_S) of the profens could not be estimated because of the complexity in calculation when the effect of ion-pair formation between DMEB molecules and the oppositely charged APAs was incorporated. However, a comparison of the peak separations (Δt_R) of the APAs ob-

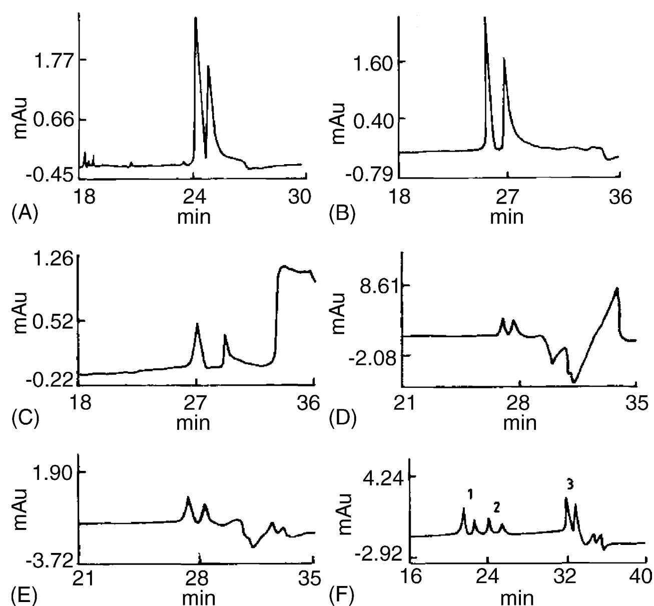

Fig. 3. Chromatograms of chiral MEKC separations of (A) FLP; (B) KTP; (C) NPX; (D) FNP; (E) IBP and (F) INP (1), SUP (2) and CRP (3); 20 mM phosphate buffer (μ = 0.05), pH 7.4 (A, B, C and D), pH 7.9 (E and F) containing 10 mM DMEB; separation capillary: total length = 60 cm, effective length = 55.5 cm × 50 μm i.d.; total applied voltage, −20 kV; detection wavelength, 254 nm; temperature, 25 °C.

tained by use of 10 mM DMEB suggest that the separations are in the order KTP > NPX > SUP > INP > CRP > IBP > FNP ≈ FLP, which is same as that for α value. The difference in the selectivities of the profens is probably due to differences in hydrophobic interactions with the DMEB vesicles. This is indicated by the migration order of the analytes. Since KTP, INP and SUP have hydrogen-bond donor/acceptor groups (C=O and N–H), they are less hydrophobic than the other APAs. This suggests that these drugs interact weakly with the vesicles and consequently migrates faster. The other compounds being more hydrophobic interact strongly with the vesicles, and therefore, are retained longer resulting in peak tailing. It seems that the enantioseparation of the profens is also partly influenced by the strength of hydrogen-bonding between the analyte and DMEB following entanglement with the vesicles. However, the π–π interaction between the aromatic rings of the analytes and that of the DMEB molecule cannot be ruled out. The strong electrostatic interactions of the negatively charged analytes with the positively charged vesicles and capillary wall surface as discussed above can be associated with the deterioration of peak shapes as evidenced in the chromatograms.

Table 1
Migration times of enantiomers (t_{R1}, t_{R2}), peak separations (Δt_R), capacity factors (k) and selectivity factors (α) of the different profens in 20 mM phosphate buffers (μ = 0.05) containing 10 mM DMEB

Name	pH	t_{R1} (min)	t_{R2} (min)	Δt_R (min)	k_1	k_2	α
CRP	7.9	31.92	33.08	1.16	12.10	13.40	1.10
FLP	7.4	24.88	25.51	0.63	5.52	5.82	1.05
FNP	7.4	26.89	27.53	0.64	6.50	6.84	1.05
IBP	7.9	27.74	28.72	0.98	8.43	9.14	1.08
INP	7.9	21.83	23.32	1.49	5.40	6.17	1.14
KTP	7.4	25.30	27.62	2.32	5.56	6.73	1.21
NPX	7.4	27.35	29.49	2.14	7.02	8.30	1.18
SUP	7.9	23.82	25.35	1.53	5.17	5.91	1.14

3.5. Simultaneous separation and enantioseparation of profens

We have tried to separate all the APAs from each other as well as each pair of enantiomers in a single run by employing their mixture. Owing to similar pK_a values the migration time of the profens are close to each other resulting in co-migration of some of the profens in the chromatogram causing the loss of peak separation. However, it was possible to separate five of the drugs from a mixture of six selected profens. Fig. 4 shows the chromatogram of a mixture of CRP, NPX, FNP, KTP, SUP and INP. When IBP and FLP were included in the mixture or the pH of the separation buffer was raised, the separation deteriorated. As can be seen all the APAs were separated from each other and enantioseparations were achieved for each of them, except for CRP. Similarly, when the mixture of CRP, INP and SUP were employed, they separated from each other and peaks of the individual enantiomers for each profen were also well resolved (Fig. 3F) at pH 7.9. Simultaneous separation and enantiomeric separations (not shown) could also be achieved for the mixture of FNP, KTP and NPX at pH 7.4. The migration times of the analytes in the chromatogram shown in Fig. 4 are in the order CRP > NPX > FNP > KTP > SUP > INP. The same migration order can also be observed for enantioseparation of individual compounds (see Table 1). If charge to mass ratio of the analytes is considered, then the migration times are expected to be in the order INP > CRP > SUP > KTP > FLP > FNP > NPX > IBP. As explained in the preceding paragraph, the observed migration order is due to the difference in hydrophobic interactions of these analytes with the DMEB vesicles.

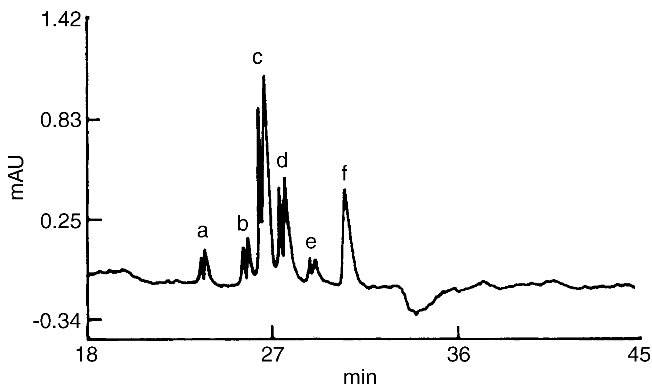

Fig. 4. Enantiomeric separation of a mixture of six profens: (a) INP; (b) SUP; (c) KTP; (d) FNP; (e) NPX and (f) CRP by MEKC with 20 mM phosphate buffer (pH 7.4, μ = 0.05) containing 10 mM DMEB; other conditions are same as in Fig. 3.

4. Conclusions

This is the first demonstration of enantiomer separation by use of a vesicle-forming cationic surfactant as chiral selector in MEKC. The results suggest that DMEB can function as an effective chiral additive for the CE separation of the optical isomers of compounds containing a carboxylate group in the vicinity of the chiral center. The separation of a mixture of five or three profens and each pair of enantiomers was achieved in a single run. The enantiomer separations of the profens were found to be dependent on pH. Best enantiomeric separation was achieved at pH 7.4 for all the profens, except CRP, IBP, INP and SUP. Optimum enantioseparation of the latter compounds was obtained at pH 7.9. The concentration of DMEB required for optimum separation is about 10 mM. The loss of peak separation of the profens at higher surfactant concentrations is due to structural transition of the vesicles to disc-like micelles. The electrostatic interactions between the cationic vesicles and the analytes play a major role in the enantioseparation of the profens. On the other hand, the hydrophobic as well as hydrogen-bonding interactions determine the migration order of the drugs.

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