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Analysis of ACE-inhibitors by CE using alkylsulfonic additives

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Abstract

Capillary electrophoresis (CE) was applied to the determination of angiotensin-converting enzyme (ACE) inhibitors in pharmaceuticals (tablets). Since a free solution CE system failed to reach a complete separation of closely related compounds (lisinopril, ramipril, benazepril, quinapril), alkylsulfonic additives (sodium heptansulfonate and (+)-10-camphorsulphonic acid) were added to the running buffer: improved separations were obtained suggesting a favourable effect of ion-pairing interactions between analytes and additives. The separations were carried out in acidic medium and a systematic investigation of electrophoretic parameters was made to evaluate the performance of the selected additives. Under the optimized conditions, ramipril and benazepril in their commercial dosage forms were determined confirming the applicability of the developed CE approach to the analysis of pharmaceutical samples; the results were also compared with those obtained applying a previously described and validated HPLC method. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Capillary electrophoresis; ACE inhibitors; Heptansulfonate; (+)-10-Camphorsulphonic acid

1. Introduction

Angiotensin-converting enzyme (ACE) inhibitors represent an important, structurally homogeneous and specific family of antihypertensive drugs also used for the treatment of heart failure [1,2]; their increasing use makes of interest analytical investigations as proved by established spectrophotometric [3] and chromatographic (HPLC) methods [3–8]. Free solution CE (CZE) [9] and micellar electrokinetic chromatography (MEKC) [10,11] systems have been also developed in order to evaluate active components and their degradates in ACE inhibitor containing pharmaceuticals.

The introduction of MEKC by Terabe et al. [12], allowed the application fields of capillary electrophoresis to be extended to neutral analytes and also to increase the selectivity in the separation of charged molecules. Compounds having the

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same charges and similar structures often migrate at a very close speed in CZE; interestingly, their differences in distribution constants to micellar phase lead to successfully separations [13].

In the present work, the separation of closely related compounds belonging to the class of ACE inhibitors (Fig. 1) has been emphasized following a different approach. High resolution separations of the positively charged solutes have been performed using ion-pairing reagents in acidic running buffers: both achiral (heptansulfonate) and chiral (camphorsulfonate) alkylsufonates were successfully employed in order to improve the resolution. High concentrations of heptansulfonate have been reported to be suitable for obtaining well resolved tryptic map from erythropoietin [14]; on the other hand, (+)-10-camphorsulfonic acid has been recently proposed as an additive improving the performance of cyclodextrins in chiral separations [15,16]. Actually the ability of alkylsulfonate in the obtaining baseline separations of basic compounds in RP-HPLC is well documented [17–20].

Therefore, in this paper, the usefulness of ion-pairing reagents such as sodium heptansulfonate and (+)-10-camphorsulfonic acid in the CE separation of ACE inhibitor drugs has been considered and the effects of ion-pairing reagent nature and concentration, running buffer pH and concentration were evaluated: baseline separation of four closely related drugs was obtained highlighting the system selectivity. The developed CE method was then applied to the analysis of ramipril and benazepril in commercial dosage forms (tablets) pointing out the suitability of the proposed approach for reliable quality control of ACE inhibitors.

2. Experimental

2.1. Materials

Ramipril (Ciba-Geigy, Italy), benazepril hydrochloride (Smith-Kline Beecham, Italy), lisinopril bihydrate (Sigma Tau, Italy) and quinapril (Malesci, Italy) were kindly supplied by

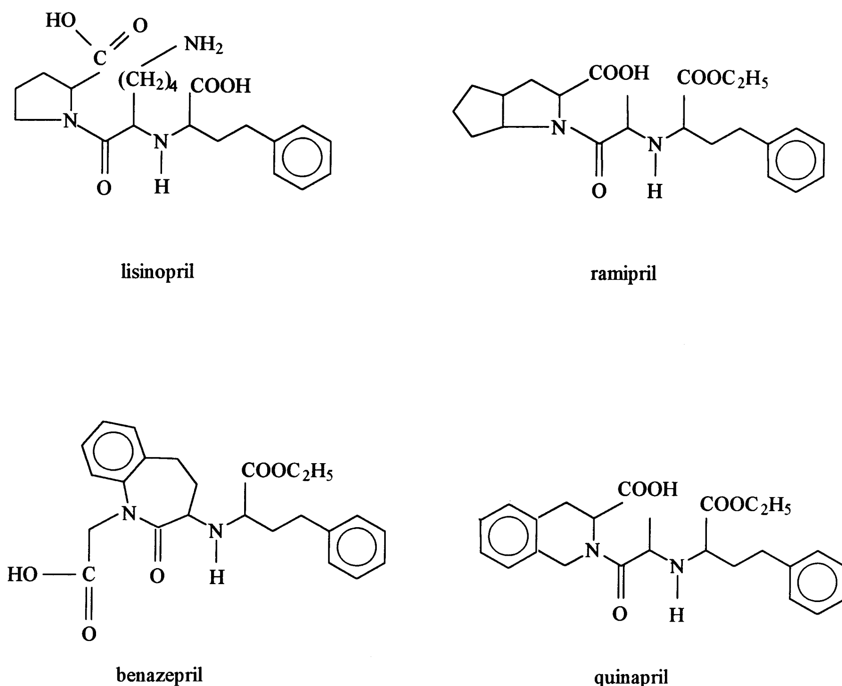

Fig. 1. Structures of the studied ACE inhibitors.

their manufactures. Sodium heptansulfonate (HS) was obtained from Romil (Cambridge, GB), (+)-10-camphorsulphonic (CSA) acid was from Fluka (Buchs, Switzerland) and pentansulfonic acid was from Sigma (St Louis, MO). Sodium phosphate, phosphoric acid, sodium hydroxide and all the other chemicals were obtained from Carlo Erba (Italy).

Running buffer solutions were prepared at different concentrations of sodium phosphate (10–40 mM) and of the ion-pairing reagents, HS and CSA, (50–100 mM); the solution pH was adjusted to the desired value (pH 2.5–4.5) using sodium hydroxide or phosphoric acid.

2.2. Apparatus

All separations were carried out using a ^{3D}CE Capillary Electrophoresis system (Hewlett-Packard, Waldbronn, Germany), equipped with a diode array detector. The data were collected on a HP Vectra 486 PC using the ^{3D}CE-ChemStation software. The electrophoretic runs were performed measuring the absorbance signal at 220 nm wavelength and applying a 25 kV voltage; the system was termostatted at different temperature in the range of 20–50°C. Fused-silica 'bubble' cell capillaries (Hewlett-Packard) 58.5 cm in length (50 cm effective length) × 50 μm I.D. were used. The capillary was conditioned prior each run for 3 min with the separation electrolyte. The samples were introduced hydrodynamically for 10 s (injection pressure 5 kPa); before the injection into the CE system, each solution (running buffer and sample solutions) was subjected to filtration through on membrane 0.2 μm GyroDisc (Orange Scientific, Waterloo, Belgium).

HPLC analyses were performed on a Waters pump and a Jasco Uvidec 100 V detector connected to a HP 3396 series integrator. Manual injections were carried out with a Rheodyne model 7125 injector equipped with a 20 μl sample loop; the detection wavelength was 215 nm. The chromatographic runs were performed under previously described and validated conditions [3]. Stationary phase: Hypersil ODS column 5 μm (250 mm × 4.5 mm i.d.). Mobile phase: mixture A:B (52:48), where A is 20 mM sodium heptansulfonate (pH 2.5) and B is acetonitrile–THF (95:5 v/v), at a flow rate of 1 ml/min.

2.3. Calibration graphs

Stock solutions of benazepril hydrochloride (0.5 mg/ml) and ramipril (2 mg/ml) were prepared in water dissolving the compounds with 2 ml phosphate buffer pH 2.5 (30 mM) and diluting to volume of 10 ml. Appropriate dilution in water were done in order to give benazepril hydrochloride solutions in the concentration range of 0.012–0.045 mg/ml and ramipril solutions of 0.06–0.16 mg/ml; each final solution contained 0.01 mg/ml of lisinopril bihydrate as the internal standard. The peak correct area (area/migration time) ratios (Y) of the analyte to internal standard were plotted against the corresponding analyte concentration (C) to obtain the calibration graphs.

2.4. Analysis of pharmaceutical formulations

A powdered sample of drug formulation (tablet) equivalent to about 0.3 mg of benazepril and 1.2 mg of ramipril was dispersed in 2 ml of phosphate buffer pH 2.5 (30 mM); after sonication (3 min) and stirring (3 min) 1 ml of internal standard solution (lisinopril 0.1 mg/ml) was added and the sample was diluted to volume (10 ml) with water to give a final concentration in the order of the mean value of the calibration range. The samples obtained after filtration through 0.2 μm membrane, were directly injected into the CE system.

When the HPLC method was applied, the extraction was carried out with the same solvent system used for the chromatographic runs.

3. Results and discussion

3.1. CZE separation

The zwitterionic nature of the four studied analytes (Fig. 1), offers the opportunity of choosing both acidic and basic running buffers for their electrophoretic separation. In a free solution CE

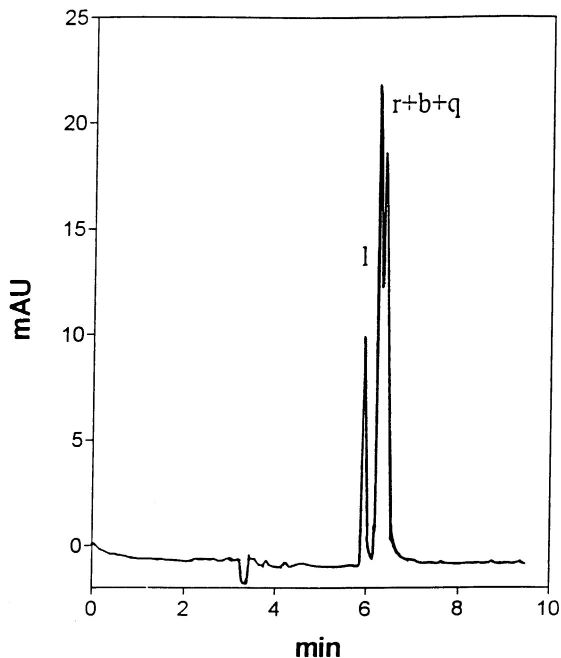

Fig. 2. CZE electropherogram of the ACE inhibitors lisinopril (l), ramipril (r), benazepril (b) and quinapril (q). Conditions: borate buffer (50 mM) pH 8.5; fused-silica 'bubble' capillary 58.5 cm (50 cm effective length) × 50 μm I.D.; applied voltage, 25 kV; detection 220 nm; temperature 50°C; injection time 10 s.

an alkalyne medium (borate buffer pH 8.5, 50 mM) was firstly chosen according to previous reports [9]. Because of the slow *cis–trans* isomerization, due to the hindered rotation around the *N*-substituted peptide bond [3–5], proline moiety bearing molecules (ramipril, lisinopril) showed better peak symmetry when analysed under relatively high temperature. Under these electrophoretic conditions, however, comigration of ramipril, benazepril and quinapril was observed making the method not suitable for the selective separation of the studied analytes (Fig. 2). Even in front of several attempts to improve the separation, through the adjustment of the nature, concentration and pH of the running buffer, poor resolution was reached. Nevertheless good linearity responses were obtained when the drugs were separately analysed: linear calibration graphs were obtained for both benazepril and ramipril in the presence of lisinopril as internal standard (Table 1); moreover the availability of an UV diode array detector allowed unambiguous identification of the drugs to be achieved by the spectra comparison.

3.2. Use of ion-pairing reagents

The use of ion-pairing reagents in RP-HPLC of basic compounds is well documented [17–20] and the combined effect of diamine and of alkylsulfonate as additive to the mobile phase enabled baseline separations otherwise not performable [18]. In CE the employment of alkylsulfonates (sodium heptansulfonate) is also described [14] as a mode to develop free solution separation of highly positive charged compounds. The role played by alkylsufonates aroused our interest in the evaluating the ability of these additives, and therefore experiments were performed in order to

Table 1
Calibration graphs of ramipril and benazepril: $y = mx + q$; 95% confidence interval for slope (m) and intercept (q), ($n = 5$)[a]

Analyte	m (SD)	q (SD)	r	Conc. range (mg/ml)
Ramipril[b]	9.754 (0.100)	0.008 (0.011)	0.9998	0.06–016
Benazepril[b]	13.834 (0.176)	0.002 (0.005)	0.9998	0.012–0.045
Ramipril[c]	10.355 (0.312)	0.037 (0.034)	0.9990	0.06–0.16
Benazepril[c]	15.606 (0.325)	−0.010 (0.010)	0.9993	0.012–0.045
Ramipril[d]	12.121 (0.170)	−0.055 (0.019)	0.9992	0.06–0.16
Benazepril[d]	14.948 (0.120)	0.0003 (0.004)	0.9990	0.012–0.045

[a] Conditions: fused-silica 'bubble' capillary (58.5 cm total length), temperature 50°C, voltage 25 kV, UV detection at 220 nm.
[b] Fifty millimolar borate running buffer, pH 8.5.
[c] Thirty millimolar phosphate running buffer pH 2.5 containing 100 mM CSA (camphorsulphonic acid).
[d] Twenty millimolar phosphate running buffer pH 4.0 containing 100 mM HS (sodium heptansulfonate).

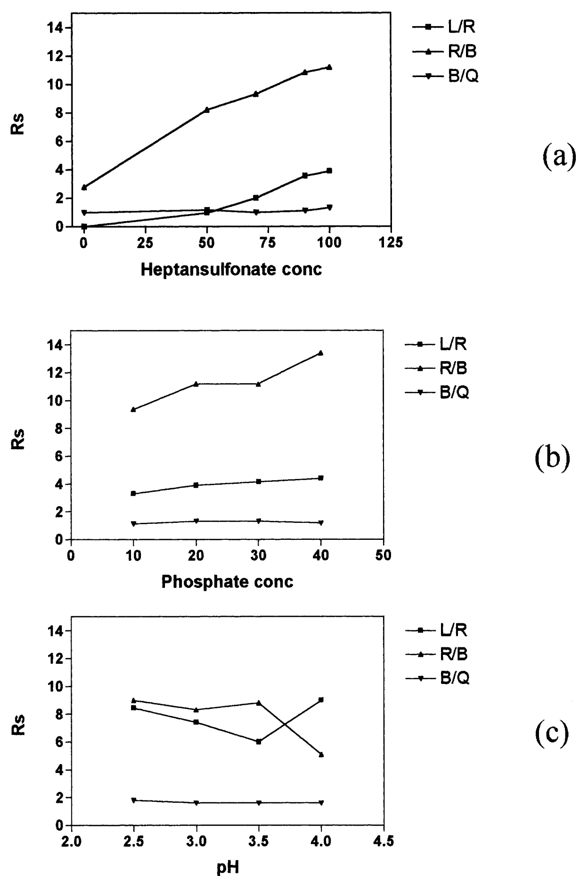

Fig. 3. Effect on the resolution of the couples lisinopril/ramipril (L/R), ramipril/benazepril (R/B) and benazepril/quinapril (B/Q) of the following parameters: (a) heptansulfonate concentration; (b) phosphate concentration; and (c) running buffer pH. The resolution values (R_s) are the mean of three replicate injections. Other conditions as in Fig. 2.

optimize their application in CE separation of ACE inhibitors.

In acidic solutions the examined drugs are present in the fully protonated form (p*K*a of lisinopril: 1.7, 3.3, 7.0, 11.1), thus exhibiting the best features to interact by electrostatic forces with alkylsulfonates. Under a constant voltage of 25 kV, and with the capillary column at 50°C, the effect of varying HS and CSA concentration on the resolution were investigated. The detection wavelength was set at 220 nm being the absorptivity of the alkylsulfonic additives not significant. Other parameters influencing the separation (running buffer pH and concentration) were studied and optimized by the evaluation of electrophoretic parameter resolution (R_s), calculated according to the well-known basic formula of liquid chromatography [8].

3.2.1. *Sodium heptansulfonate as ion-pairing agent*

With the aim to reach a baseline resolution of the four studied ACE inhibitors, HS was added to the running buffer consisting of pH 3.0 phosphate solution (20 mM). Using this additive in the range of 50–100 mM, resolution between lisinopril and ramipril (L/R), ramipril and benazepril (R/B), benazepril and quinapril (B/Q) was enhanced even at low concentration levels (Fig. 3a); however, to obtain a complete separation of all the analytical peaks a 100 mM concentration of HS was necessary. Under these conditions the recorded current was 120 μA, not so high to give detrimental effect on the separation process. The progressive general increase of resolution led us to evaluate higher additive levels, but a final concentration of 120 mM heptansulfonate did not significantly improve the results. Very small differences in the migration times of the studied analytes were observed for different level of added heptansulfonate and the electroosmotic flow was practically constant (4.3×10^{-5} cm ^{2} V^{-1} s^{-1}) over the used concentration range.

Due to the known influence of buffer concentration on the electroosmotic flow and analyte electrophoretic mobilities [13], the effect of varying phosphate concentration (10–40 mM) on the resolution was also considered. Under the chosen conditions (buffer pH 3.0, voltage of 25 kV and constant temperature of 50°C) a 100 mM HS concentration was employed. Actually just small differences in the behaviour of the analytes were evidenced under the applied conditions (Fig. 3b); anyway a 40 mM phosphate buffer provided too high current and the concentration of the background electrolyte was kept at 20 mM.

The pH of the buffer is of paramount importance in each electrophoretic separation: it influences the charge of the analyte (effective mobility) and the electroosmotic flow through the effect on the silanol dissociation on the capillary wall (apparent mobility) [13].

In the presence of ion-pairing reagents the different percentage of positive charge on the basic nitrogen of the studied solutes could influence the electrostatic interactions alkylsulfonate-protonated nitrogen. Increasing pH of the buffer lead reduction of R_s for all the couples of adiacent peaks (Fig. 3c) likely due to the increased electroosmotic flow (EOF pH $2.5 = 5.5 \times 10^{-5}$ cm^2 $V^{-1}s^{-1}$, EOF pH $4.0 = 13 \times 10^{-5}$ cm^2 V^{-1} s^{-1}); interestingly at pH 4.0, this effect should be still combined with the cationic character of the analytes explaining the reduced analysis time. Since a significant improving of the peak shape was shown for each tested analyte, the separation was considered, under the described conditions, optimised; higher pH values lead to a lost of resolution and comigration of the analytes was displayed. Strong acidic conditions promote good resolution especially on the peak couple ramipril/benazepril (Fig. 3c) nevertheless a significant peak tailing was observed. Using pH 2.5 phosphate buffer (20 mM) in order to reduce the described peak tailing, the addition of 10% of organic solvents (methanol, acetonitrile and propanol) in the running buffer was evaluated: increased migration times were displayed without positive effects on the peak shape and resolution. Interestingly, the presence of 1 and 2 M of urea, a well-known additive used in MEKC [21], provided good peak-symmetry likely due to a reduction of hydrogen bond between additive and analyte, probably responsible for the peak tailing [1].

In an attempt to evaluate the potentiality of other alkylsulfonate additives, sodium pentansulfonate and (+)-10-camphorsulfonic acid (CSA) were also assessed; under the conditions optimized for HS, pentansulfonate gave worst results (no B/Q resolution), while CSA showed interesting behaviour as ion-pairing reagent, mainly providing good peak shape.

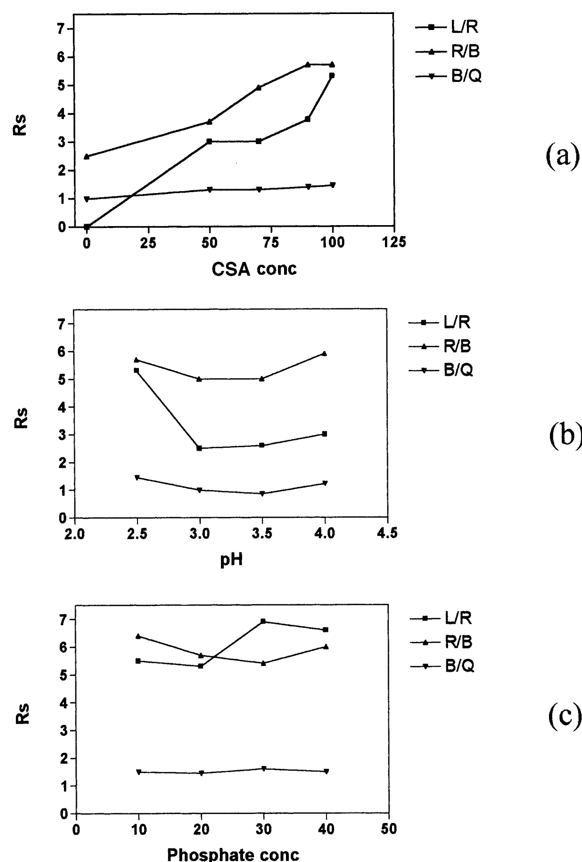

Fig. 4. Effect on the resolution of the couples lisinopril/ramipril (L/R), ramipril/benazepril (R/B) and benazepril/quinapril (B/Q) of the following parameters: (a) CSA concentration; (b) running buffer pH; and (c) phosphate concentration. The resolution values (R_s) are the mean of three replicate injections. Other conditions and symbols as in Fig. 2.

3.2.2. CSA as ion-pairing reagent

The optimization of the electrophoretic conditions employing CSA as additive to the running buffer followed the same pathway applied for the above described heptansulfonate (HS). Studies on the effect of CSA concentration over the range 50–100 mM demonstrated that high levels of additive are important in order to produce good separations. This effect was mainly observed for the resolution of lisinopril/ramipril and ramipril/benazepril (Fig. 4a). Investigations on the effect of the concentration of running buffer led to choose a 30 mM phosphate solution as a background electrolyte (Fig. 4b).

Concerning the buffer pH, even in the presence of CSA the choice of acid background electrolyte was driven by the needs to have strong electrostatic interactions between the protonated nitrogen and the additives' sulfonate group. Differently from the results obtained using heptansulfonate, CSA seems to provide a more robust CE system

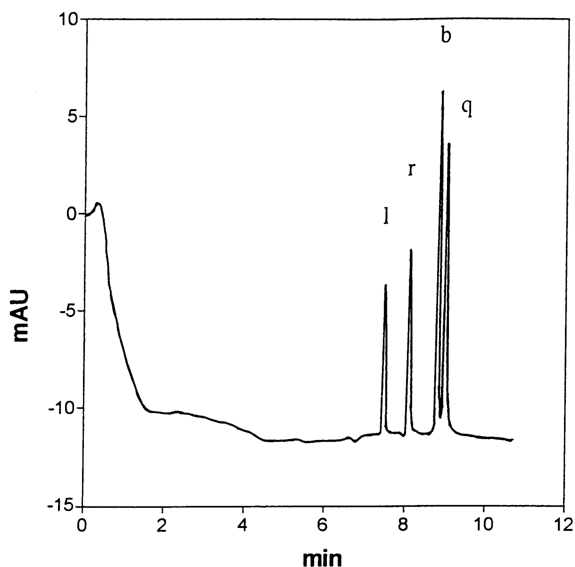

Fig. 5. Separation of the studied ACE inhibitors using CSA (100 mM) as ion-pairing reagent in a phosphate running buffer pH 2.5 (30 mM). Other conditions and symbols as in Fig. 2.

from the point of view of BGE pH values. Critical effects of the pH value are observed just for the couple lisinopril/ramipril, where anyway the resolution value is always kept higher than 2.5 (Fig. 4c); the effects of the different applied conditions on the migration times were negligible: in the presence of CSA the differences in the electroosmotic mobility over the pH range of 2.5–4 was $\Delta\mu_{eof} \approx 1.5 \times 10-^{5}$ cm^2 V^{-1} s^{-1}. Anyway, at higher pH values than 4.0 a significant loss in resolution was displayed. As a result, CSA in a strong acidic medium (pH 2.5) and HS in a pH 4.0 running buffer, seem to offer the best conditions to develop CE methods for the separation and analysis of ACE inhibitor drugs: short and stable analysis time (RSD% = 1.8 on the migration time of ramipril for five replicate runs when CSA was employed), good resolution and peak shape (Fig. 5) make these systems suitable for the application to real pharmaceutical samples.

3.3. Effect of run temperature

Peak splitting and band broadening were previously observed for ramipril in RP-HPLC [4] mainly at temperature below 50°C. The same behaviour was confirmed in the present study when an acidic running buffer (pH 2.5) was used without any additive. At 20°C a net splitting was displayed; with increasing temperature (> 50°C), the conversions between the two rotamers accelerate and singles peaks were obtained. In the presence of alkylsulfonic additives (100 mM of both HS and CSA), a worsening of the peak shape with the decreasing of temperature was found but in less extent compared to that in free solution. These observations support the hypothesis of real interactions (electrostatic forces) alkylsulfonate-analyte.

3.4. Analysis of pharmaceutical formulations

To verify the opportunities given by the developed CE method, two commercial pharmaceutical preparations (tablets) containing the ACE inhibitors benazepril hydrochloride and ramipril were analysed. Linearity of the response was evaluated in three different optimized electrophoretic conditions for benazepril and ramipril standard solutions (Table 1). The intra-day precision expressed as RSD% ($n = 5$) of benazepril versus internal standard correct peak area ratio was 1.2%, using a phosphate buffer pH 4.0 (20 mM) containing HS at 100 mM concentration; the inter-day precision evaluated under the above described electrophoretic conditions for the analysis of benazepril tablets ($n = 10$) was found to correspond to relative standard deviation (RSD%) of 2.4%. Stability of the analytes was determined by comparing the mean peak correct area of standard solutions (concentration corresponding approximately to the mean value of the calibration range) which have been in storage for 3 days at room temperature with the peak correct area of freshly prepared solutions. The evaluated mean peaks correct area of the stored solutions were within 99% of the freshly solutions suggesting the stability of the analyte during all the procedure. The limit of detection (LOD) evaluated by progressive dilution of standard solutions until S/N = 3 was reached, was found to be 10 μM for ramipril and 5 μM for benazepril (detection at λ 220 nm). Analyses of commercially available pharmaceutical samples were carried out under

Table 2
Results for the analyses ($n = 5$) of commercial formulations containing ramipril[a] and benazepril[b]

Analyte	Found % (RSD%) CE[c]	Found % (RSD%) CE[d]	Found % (RSD%) CE[e]	Found % (RSD%) HPLC[f]
Ramipril	96.3 (1.3)	95.2 (1.8)	97.0 (1.4)	96.8 (0.9)
Benazepril	99.0 (1.5)	97.8 (2.5)	102.0 (0.8)	99.5 (1.0)

[a] Composition: ramipril 5 mg, hydroxypropylmethylcellulose, starch, microcrystalline cellulose, sodium stearyl fumarate, iron oxide.
[b] Composition: benazepril hydrochloride 10 mg, microcrystalline cellulose, hydrogenated castor oil, lactose, starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose, iron oxide, polyethylene glicole 8000, titanium oxide. The data are expressed as a percentage of the claimed content.
[c] Fifty millimolar borate running buffer, pH 8.5.
[d] Thirty millimolar phosphate running buffer pH 2.5 containing 100 mM CSA (camphorsulphonic acid).
[e] Twenty millimolar phosphate running buffer pH 4.0 containing 100 mM HS (sodium heptansulfonate).
[f] High performance liquid chromatographic analysis (conditions described in the text).

each optimized electrophoretic condition and the results were compared with those obtained applying a previously described HPLC method [3]. The extraction of the active ingredients from these formulations was simple using water (benazepril hydrochloride) and pH 2.5 phosphate buffer (ramipril); after sonication and stirring, the samples were filtered and directly injected into the CE system. No interfering peaks were observed in the obtained electropherograms although several excipients were present in both formulations (see Table 2). The CE assay results (Table 2) were found to be in close agreement with the claimed content and with those determined by the application of the HPLC method. The results obtained under different CE conditions were compared by applying the F-test and t-test at the 95% confidence level; no significant difference were found. A representative electropherogram of a commercial formulation (benazepril tablets) obtained using 100 mM HS as running buffer additive (pH 4.0) is shown in Fig. 6.

3.4.1. Robustness and ruggedness

As above discussed, running buffer pH is one of the most important parameters influencing the electrophoretic separation; small variations of pH value can change the electrophoretic data. In the proposed applications to real samples, importance should be give to the pH value of the running buffer containing HS; a worsening of the peak shape is obtained at pH lower than 4.0, on the other hand, significant loss of resolution is showed for pH values higher than 4.0. On the contrary, variations of the alkylsulfonate additives (both HS and CSA) concentration (within 5 mM) as well as the BGE (phosphate) concentration around the optimized values were not found to give significative differences on the electrophoretic data (R_s, migration time).

Analytical results from two operators (10 determinations) on the analysis of benazepril tablets, performed using the same instrumentation and

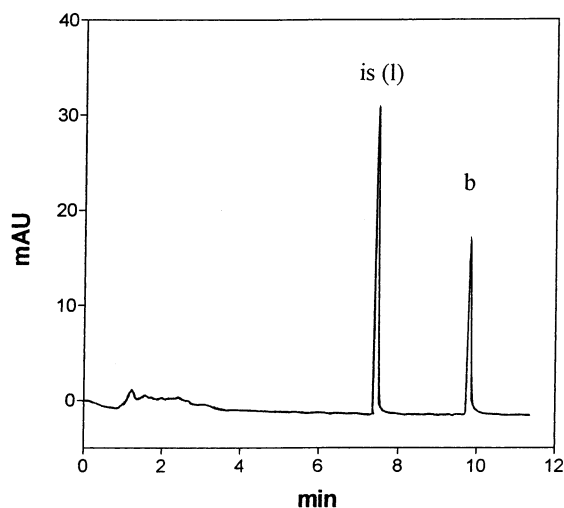

Fig. 6. Representative electropherogram of a benazepril commercial sample analysed under the following conditions: phosphate running buffer (30 mM) pH 4 in the presence of HS 100 mM is (1): internal standard lisinopril, b: benazepril. Other conditions as in Fig. 2.

applying the method based on the use of HS as additive, were in close agreement: 102.5% (found %), 1.8% (RSD%).

4. Conclusions

ACE inhibitor drugs can be analysed by CE system employing alkylsulfonic additives to improve the analyte resolutions. Heptansulfonate (HS) and camphorsulphonic acid (CSA) at relatively high concentration levels (100 mM) proved to be useful ion-pairing reagents for the protonated analytes. The comparison of the performances of these additives emphasizes differences related to the peaks shape: CSA in strong acidic medium provided sharper analytical peaks than HS and this evidence may suggest the existence of actual interaction analyte-alkylsulfonate. Investigations on the effect of running buffer pH and concentration allowed to find the best electrophoretic conditions and reliable quantitative analyses of ACE inhibitor drugs in pharmaceuticals were carried out.

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