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Technical Note

SUB-MINUTE CAPILLARY ZONE ELECTROPHORESIS METHOD FOR DETERMINATION OF HYDROCHLOROTHIAZIDE IN COMBINATION WITH OTHER ACTIVE INGREDIENTS IN NINE DIFFERENT PHARMACEUTICAL SAMPLES

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Capillary electrophoresis (CE) methods have unique potential for applications in quality control of pharmaceutical formulations. Here, we show that a single and ultra-fast CE method can be used for the determination of hydrochlorothiazide (HCT) in combination with nine other active ingredients in a single run in different pharmaceutical samples: atenolol (ATE), metoprolol (MET), propranolol (PRO), benazepril (BEN), captopril (CAP), enalapril (ENA), lisinopril (LIS), ramipril (RAM), and valsartan (VAL). This goal was achieved using a single and simple background electrolyte (BGE) composed of 10 mmol L^{-1} of boric acid with pH adjusted to 9.0 with sodium hydroxide. All samples can be analyzed in less than 1 min with the attainment of good analytical performance, such as high-resolution separation (r > 1.3), low sample and reagents consumption (environmentally friendly method), low relative standard deviation (RSD) values for peak area (< 4.0%) and migration times (< 1.7%), and linear relationships with good correlation coefficients (> 0.995). Furthermore, recovery tests showed good results (100 ± 5%) for all evaluated compounds.

Keywords: contactless detection; drugs; environmentally friendly; simultaneous quantification; ultra-fast analysis.

INTRODUCTION

Capillary electrophoresis (CE) is a powerful technique for the separation and quantification of compounds in samples of different areas of interest such as clinical, environmental, industrial, pharmaceutical, and food industry.[1] The attractiveness of the technique is due to unique characteristics such as high separation efficiency, short analysis time using conventional equipment (separation of many compounds in minutes or even in seconds), low-cost, wide applicability (different kinds of compounds can be separated using the same column) and low reagent/sample demand (environmentally friendly methods).[2]

Capillary electrophoresis with capacitively coupled contactless conductivity detection (CE-C^4D) is an excellent alternative for the determination of active ingredients in pharmaceutical formulations. The C^4D mode detects compounds with different physical-chemical characteristics (organic/inorganic ions or with and without chromophore group) and with very different concentrations (wide linear ranges for most compounds) in a single run. According to the literature, a considerable number of pharmaceutical samples have in their composition active ingredients with different physical-chemical properties.[3]

Hydrochlorothiazide (HCT) is a first-line drug for the control of hypertension in the world.[4] It can be used as a single active ingredient or often in combination with many other antihypertensive drugs such as atenolol (ATE), metoprolol (MET), propranolol (PRO), benazepril (BEN), captopril (CAP), enalapril (ENA), lisinopril (LIS), ramipril (RAM), valsartan (VAL), losartan (LOS), and others. Since different mechanisms are responsible for the elevation of blood pressure, the use of a combination therapy gives an antihypertensive effect two to five times stronger than the action of monotherapy, which affects only one or two of these mechanisms. ATE, MET, PRO, BEN, CAP, ENA, LIS, RAM, and VAL are drugs that potentiate the hypotensive action of HCT, allowing dose reduction and avoiding possible side effects. However, an overdose of these drugs can result in severe hypotension, which can lead to a level of unconsciousness, circulatory collapse, and/or shock. In this context, it is essential to monitor these pharmaceutical samples and ensure access to good-quality drugs. A summary of the physicochemical properties of HCT and other active ingredients under study is shown in Table 1S (Supplementary Material).[5]

The literature describes the use of analytical techniques such as chromatographic, spectrophotometry, and electrochemistry for the determination of HCT in the presence of other active ingredients. However, to the best of our knowledge, no analytical technique has provided the simultaneous analysis of HCT, and active ingredients commonly found in the same sample. It is possible to find a great number of methods, using different techniques, for the determination of HCT in the presence of some of these compounds such as HCT and ATE,[6] HCT and MET,[7] HCT and PRO,[8] HCT and BEN,[9] HCT and CAP,[10] HCT and ENA,[11] HCT and RAM,[12] and, HCT and VAL.[13] Moreover, most of the reported methods or techniques have one or more limitations, including great consumption of organic solvents, high acquisition and/or operation cost, and/or time-consuming. Therefore, the development of a simple, rapid, and low-cost analytical method for quality control of most samples with the presence of both HCT and another active ingredient is highly desirable.

In the present work, we show the potential of the CE-C^4D system for rapid quality control of nine pharmaceutical samples containing HCT and another active ingredient (ATE or MET or PRO or BEN or CAP or ENA or LIS or RAM, or VAL). The composition of each sample can be evaluated in a single run (less than 1 min) using the single CE-C^4D method here proposed.

EXPERIMENTAL

Reagents and samples

All reagents were analytical grade (purity ≥ 98%) and were used without further purification. Boric acid, histidine and

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methanol were purchased from Vetec (Duque de Caxias, Brazil), *N*-tris(hydroxymethyl)-methyl]-3-aminopropanesulfonic acid (TAPS), tris(hydroxymethyl) aminomethane (TRIS), 2-(cyclohexylamine) ethanesulfonic acid (CHES) and ramipril from Sigma-Aldrich (St. Louis, USA), atenolol, captopril, hydrochlorothiazide and propranolol from Attivos Magistrais (São Paulo, Brazil), enalapril, lisinopril, metoprolol and valsartan from Infinity Pharma (São Paulo, Brazil), benazepril from Copermed (Pouso Alegre, Brazil), and sodium hydroxide from Panreac (Castellar del Vallès, Spain).

All solutions were prepared by using ultrapure deionized water (ρ ≥ 18 MΩ cm) from a Millipore Direct-Q3 system (Bedford, MA, USA). Pharmaceutical samples were purchased from local drugstores. Stock and sample solutions were prepared before the experiments by simple dissolution in methanol. In the sample preparation process, ten pharmaceutical samples (tablets) were weighed and carefully mixed. Then, some portions were weighed and dissolved in methanol and finally diluted in water to achieve a concentration within the linear range of the calibration curve. Before injection in the CE system, all solutions were filtered using a membrane filter (pore size of 0.45 µm) purchased from Merck (Darmstadt, Germany).

Capillary electrophoresis measurements

Electropherograms were obtained using a lab-made CE system with two C^4D detectors that are fixedly located around the capillary at 10 cm from each end.[14] The separation column used in this work was a polyimide-coated fused-silica capillary 50 cm long (effective length of 10 and 40 cm for both detectors), 50 µm and 375 µm of inner (id) and outer (od) diameters, respectively. Before analysis (each workday), the capillary was flushed with aqueous solutions in the following order: (*i*) 10 min of deionized water; (*ii*) 10 min of 0.1 mol L^{-1} NaOH; (*iii*) 10 min of deionized water; (*iv*) and 10 min with the BGE. This procedure was repeated once every day before starting the analysis. The instrumental parameters were the following – BGE composition: 10 mmol L^{-1} boric acid with pH adjusted to 9 with NaOH; hydrodynamic injection: 25 kPa for 1.0 s (anodic side); separation potential: + 20 kV (injection side); total capillary length: 50 cm; effective capillary lengths: 10 and 40 cm; EOF: normal (unmodified fused-silica capillary).

RESULTS AND DISCUSSION

Recently, our research group showed that losartan, HCT, and potassium, ingredients of a pharmaceutical sample, can be separated and quantified in a single run in less than 40 s using a CE-C^4D method.[8] As stated in the Introduction section, HCT can be found combined with other active ingredients in nine different pharmaceutical samples. Considering this, we decided to evaluate whether the same CE-C^4D method could also be used for the quality control of all these samples. As can be observed in Table 1S (physicochemical properties of all compounds under study), at the pH value of the BGE used in the previous work (10 mmol L^{-1} boric acid with pH adjusted to 9 with NaOH), all target analytes are charged species (ATE, MET, and PROP are cations and BEN, CAP, ENA, LIS, RAM, and VAL are anions).[10] Therefore, the separation of these compounds may be enabled by capillary zone electrophoresis (CZE).

Initially, standard solutions containing similar composition to commercial pharmaceutical samples (A: HCT + ATE; B: HCT + MET; C: HCT + PRO; D: HCT + BEN; E: HCT + CAP; F: HCT + ENA; G: HCT + LIS; H: HCT + RAM; I: HCT + VAL) were injected into the CE-C^4D system using the same optimized conditions previously used for the determination of losartan, HCT, and potassium (hydrodynamic injection: 25 kPa for 1.0 s; separation potential + 20 kV - injection side; total capillary length: 50 cm; EOF normal).[8] In these studies, the amounts of both compounds were selected according to the difference in concentration that exists in real samples (Table 2S). Figure 1S shows the electropherograms obtained at both conductometric detectors (10 and 40 cm of effective capillary length) of the CE-C^4D system. In all cases, the mobility of the BGE was higher than that of the analytes ("negative peaks") and the separation of HCT and all target active ingredients was possible in the nine evaluated samples (A-I) using only 10 cm of effective capillary length (resolution ≥ 1.3). It is also possible to observe that the separation efficiency at the second detector is better (resolution ≥ 3.3), however, the analysis time is three times longer. As described in the literature, resolution values above 1.25 are acceptable[15] and high-throughput methods are always welcome.

Figure 1 shows a comparison between electropherograms obtained with standard and pharmaceutical sample solutions containing HCT + ATE (A), HCT + MET (B), HCT + PRO (C), HCT + BEN (D), HCT + CAP (E), HCT + ENA (F), HCT + LIS (G), HCT + RAM (H) and HCT + VAL (I). As can be seen, electropherograms with a similar profile (peak shape and migration time) were obtained for all standard and sample solutions. Overlapping or additional peaks from interfering species (inactive ingredients) were almost non-existent, which is probably due to the presence of sodium (high mobility) in the BGE composition. The results in Figure 1 also show that the separation of all compounds in a single run is not possible. ATE, MET, and PROP (Figures 1A, 1B, and 1C) and BEN, ENA, LIS, and RAM (Figures 1D, 1F, 1G, and 1H) exhibited similar migration times and the complete separation between these peaks was not possible.

To evaluate the precision of the CE-C^4D method, repeatability studies were carried out through ten successive injections of standard solutions with a similar composition of all samples under study (Figure 2S). The proposed CE method exhibited excellent precision for the detection of HCT and the nine other active ingredients with relative standard deviations less than 1.7% and 4.0% of the migration time and peak area, respectively. Additional studies showed that this stability was maintained up to twenty successive injections. After this, greater variations were observed in the migration times, however, the initial conditions were easily restored using a simple cleaning procedure: flushing with BGE for 3 min (25 kPa).

Next, the linear response ranges of all analytes under study were evaluated. Usually, a conductometric detector shows linear behavior in wide concentration ranges and this was confirmed for HCT (r = 0.996; 20-800 µmol L^{-1}), the compound found in all samples. The linear ranges of other compounds were obtained by the injection (n = 3) of standard solutions containing increasing concentrations of both HCT and the respective active ingredient from each sample (Figure 3S). In these studies, the difference in concentration between the active ingredients in each sample (Table 2S) was considered and maintained in all solutions. The results obtained in these studies are presented in Table 1.

As can be seen in Table 1 and Figure 3S, adequate correlation coefficients (r > 0.995) and linear ranges were obtained for all compounds under study. In addition, excellent reproducibility (inter-day precision) was observed for slope values of HCT (0.0704 ± 0.0037; RSD = 5.2%) since the nine calibration curves were obtained on different days. These results also indicate that peak areas of HCT are not influenced by the presence of other compounds in the samples. The LODs (Table 1) were estimated experimentally as being the concentration of each compound with peak height three times greater than the standard deviation of the mean of the background signal. It should be noted that the LOD values obtained with the CE-C^4D method for these compounds are slightly higher than those obtained by other techniques (*e.g.*, HPLC),

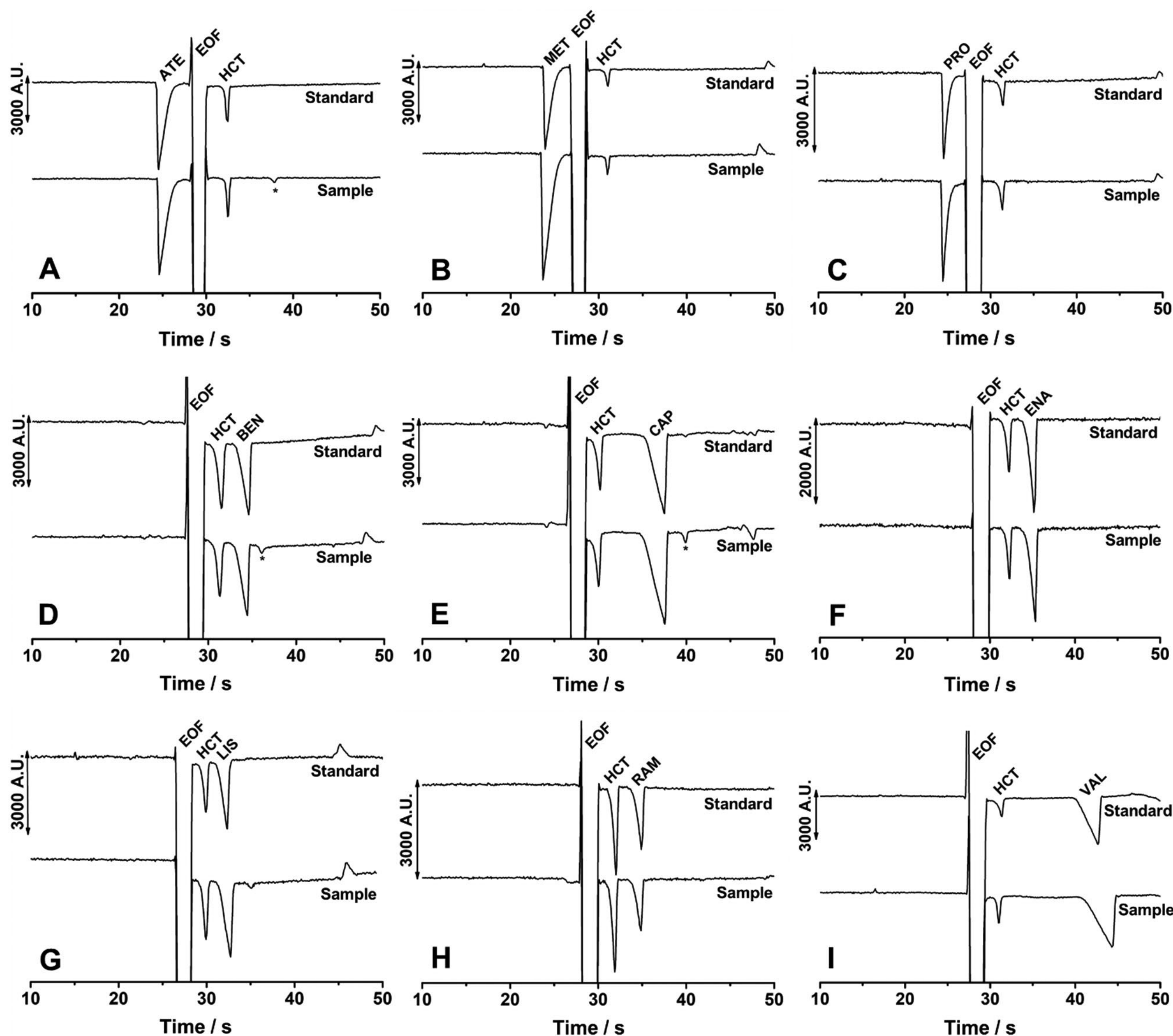

Figure 1. *Comparison between electropherograms obtained with standard: (A) HCT + ATE (200 + 400 µmol L⁻¹); (B) HCT + MET (75 + 131 µmol L⁻¹); (C) HCT + PRO (100 + 200 µmol L⁻¹); (D) HCT + BEN (450 + 300 µmol L⁻¹); (E): HCT + CAP (300 + 600 µmol L⁻¹); (F) HCT + ENA (150 + 188 µmol L⁻¹); (G) HCT + LIS (150 + 150 µmol L⁻¹); (H) HCT + RAM (350 + 117 µmol L⁻¹); (I) HCT + VAL (100 + 870 µmol L⁻¹) and pharmaceutical sample solutions. BGE: 10 mmol L⁻¹ boric acid with pH adjusted to 9.0 with NaOH; hydrodynamic injection: 25 kPa for 1.0 s; separation potential: + 20 kV (injection side); total capillary length: 50 cm; effective capillary length: 10 cm; EOF: normal*

however, for pharmaceutical samples, features like the speed of analysis (≥ 85 injections h^{-1}), low-operation cost, and minimal waste production are more relevant.

Next, the performance of the proposed CE-C^4D method was evaluated by the analysis of nine pharmaceutical formulations containing HCT and one of the active ingredients under study. The results obtained are shown in Table 2.

It can be observed that the results obtained by the proposed method (CE-C^4D) indicate that the amounts of active ingredients in the samples are close to the values indicated in the medication package inserts. Only the amount obtained for LIS can be considered an exception since the analyzed concentration was much lower (66%) than the value reported in the package insert. The accuracy of the method was evaluated through the analysis of pharmaceutical samples before and after spiked with known concentrations of each active ingredient (recovery studies). The results obtained in these studies were included in Table 2 and more detailed information (value found in the unspiked sample, value found in spiked sample, and spiked value) can be found in Table 3S. The mean recovery value obtained in these studies was 100 ± 5% (n = 18), which indicates the absence of matrix effects and adequate accuracy of the proposed CE method.

Table 4S shows a comparison of the results obtained for simultaneous determination of HCT and other analytes by the proposed and other methods (HPLC) previously published. As can be observed, the limits of detection of HPLC methods are better than that obtained with the proposed CE method, however, for pharmaceutical sample analysis, low limits of detection are usually not required. Moreover, the CE method is faster, less expensive, and consumes less samples and reagents (greener analytical method) than HPLC. Finally, it is important to emphasize that only the CE-C^4D method here proposed has the capacity to carry out quality control of nine pharmaceutical samples with different compositions.

CONCLUSIONS

The results presented here clearly show that the capillary electrophoresis technique has great potential for quality control of pharmaceutical samples containing HCT in combination with other

Table 1. Analytical characteristics of the proposed CE method (value ± SD)

	LOD (μmol L^{-1})	r	Slope (b)	Linear range (μmol L^{-1})	RSD (%; n = 10)	Resolution*	Migration time (s)	Analytical frequency (injection h^{-1})
HCT	10	0.999	0.0783	50-300	2.5	2.1 ± 0.1	32.4 ± 0.2	111
ATE	3	0.999	0.2229	100-600	2.6	2.2 ± 0.1	24.4 ± 0.2	
HCT	10	0.998	0.0678	50-200	4.0	2.2 ± 0.1	30.8 ± 0.4	117
MET	4	0.999	0.1627	230-910	2.7	1.8 ± 0.1	23.7 ± 0.4	
HCT	10	0.999	0.0707	50-250	3.6	2.0 ± 0.1	31.3 ± 0.1	115
PRO	5	0.996	0.1935	100-500	2.2	1.8 ± 0.1	24.4 ± 0.1	
HCT	10	0.999	0.0720	75-750	2.5	1.3 ± 0.1	30.2 ± 0.1	109
BEN	5	0.996	0.1795	50-500	2.2	1.5 ± 0.1	33.1 ± 0.1	
HCT	10	0.999	0.0670	100-500	3.2	1.3 ± 0.1	31.3 ± 0.1	95
CAP	7	0.998	0.1341	200-1000	2.1	4.0 ± 0.2	37.9 ± 0.1	
HCT	10	0.999	0.0682	50-500	2.5	1.8 ± 0.1	32.3 ± 0.1	102
ENA	5	0.998	0.1765	63-625	2.7	2.5 ± 0.1	35.3 ± 0.2	
HCT	10	0.996	0.0687	50-500	3.7	1.8 ± 0.1	30.5 ± 0.1	108
LIS	5	0.995	0.2090	50-500	2.4	1.7 ± 0.1	33.3 ± 0.1	
HCT	10	0.999	0.0732	150-800	3.8	1.7 ± 0.1	32.1 ± 0.1	102
RAM	6	0.997	0.2147	50-267	3.4	2.3 ± 0.1	35.2 ± 0.1	
HCT	10	0.998	0.0611	50-400	2.9	1.4 ± 0.1	31.3 ± 0.1	85
VAL	14	0.998	0.0673	218-1740	2.2	3.3 ± 0.1	42.2 ± 0.1	

HCT: hydrochlorothiazide. ATE: atenolol. MET: metoprolol. PRO: propranolol. BEN: benazepril. CAP: captopril. ENA: enalapril. LIS: lisinopril. RAM: ramipril. VAL: valsartan. *Calculated between analyte peak and previous peak. Except for ATE, MET, and PRO (calculated between analyte peak and EOF signal). SD: standard deviation. RSD: relative standard deviation.

Table 2. Results obtained in the analysis of pharmaceutical samples and recovery experiments (value ± SD)

Sample	Analyte	Label value (mg $tablet^{-1}$)	CE-C^4D (mg $tablet^{-1}$)	Recovery (%)
A	HCT	12.5	12.0 ± 0.4	106 ± 3
	ATE	100	99.3 ± 1.0	93 ± 2
B	HCT	12.5	11.8 ± 0.2	92 ± 2
	MET	100	99.3 ± 0.4	104 ± 3
C	HCT	25	25.6 ± 1.6	101 ± 4
	PRO	40	42.5 ± 0.4	98 ± 3
D	HCT	6.3	5.8 ± 0.1	95 ± 3
	BEN	5	5.2 ± 0.1	94 ± 2
E	HCT	25	24.1 ± 0.1	98 ± 3
	CAP	50	47.6 ± 0.3	96 ± 4
F	HCT	12.5	12.5 ± 0.4	97 ± 2
	ENA	20	19.3 ± 0.7	101 ± 5
G	HCT	12.5	13.3 ± 0.3	105 ± 2
	LIS	20	13.1 ± 0.3	105 ± 3
H	HCT	12.5	13.2 ± 0.1	106 ± 3
	RAM	5	4.6 ± 0.1	100 ± 4
I	HCT	12.5	11.8 ± 0.1	105 ± 2
	VAL	160	175.6 ± 2.2	104 ± 3

HCT: hydrochlorothiazide. ATE: atenolol. MET: metoprolol. PRO: propranolol. BEN: benazepril. CAP: captopril. ENA: enalapril. LIS: lisinopril. RAM: ramipril. VAL: valsartan. SD: standard deviation.

target species. The proposed CE method is rapid (> 85 injections h^{-1}), requires minimal amount of sample and/or reagents by analysis (attributes of green analytical chemistry), and presented good separation efficiency (resolution > 1.3), stability (RSD < 4.0% and < 1.7% for peak area and migration time, respectively), and accuracy (recovery of 100 ± 5%).

SUPPLEMENTARY MATERIAL

The supplementary material is available at http://quimicanova.sbq.org.br in pdf format, with free access.

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