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Journal of Pharmaceutical and Biomedical Analysis
31 (2003) 329–339
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Simultaneous determination of hydrochlorothiazide and several angiotensin-II-receptor antagonists by capillary electrophoresis

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Received 23 September 2002; received in revised form 21 November 2002; accepted 21 November 2002

Abstract

We have investigated the capability of the capillary zone electrophoretic (CZE) and micellar electrokinetic capillary chromatographic (MEKC) methods to simultaneously separate hydrochlorothiazide and six angiotensin-II-receptor antagonists (ARA-IIs): candesartan, eprosartan mesylate, irbesartan, losartan potassium, telmisartan, and valsartan. The CZE and MEKC methods are suitable for the qualitative and quantitative determination of combined HCT/ARA-IIs in pharmaceutical formulations. Depending on the ARA-II, at least one of the two methods can be used for each combination. The two methods have been validated in terms of their linearity of response, reproducibility, and accuracy.

Keywords: Capillary electrophoresis; Angiotensin-II-receptor antagonists; Hydrochlorothiazide

1. Introduction

Angiotensin-II-receptor antagonists (ARA-IIs) are safe and effective agents for the treatment of hypertension and heart failure, either alone, or in conjunction with hydrochlorothiazide (HCT), a thiazide diuretic ([1]). They have been proposed as an alternative to the more traditional angiotensin-converting enzyme inhibitors, because they selectively block the angiotensin type 1 (AT_1) receptor, which is responsible for vasoconstriction, and they prevent salt and water retention. The angiotensin type 2 (AT_2) receptor, which is thought to have cardioprotective effects and inhibitory effects on growth, is unaffected by ARA-IIs [2–5]. HCT increases the rate of urine excretion by the kidney, primarily through decreased tubular reabsorption of sodium and chloride, and by increased osmotic transport of water to the renal tubules. Thiazide diuretics are extremely useful in the treatment of oedema associated with mild to moderate congestive heart failure. Moreover, these diuretics are also the primary agents used in the control of hypertension, either alone, or in combination with

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0731-7085/03/$ - see front matter
PII: S0731-7085(02)00643-X

other drugs, such as ARA-IIs. Their hypotensive effect is believed to initially arise from the reduction of blood volume by Na^+ depletion, and later on, by direct relaxation of arteriolar smooth muscle [6,7].

Until now, high performance liquid chromatography has been the major technique used for the simultaneous determination of the concentration and presence of HCT, losartan potassium [8–12], and valsartan [13,14]. Capillary electrophoresis (CE) is an alternative technique. Although analysis by means of CE has been carried out for both HCT [15–19] and ARA-IIs [20], only one study has reported the simultaneous determination of HCT and losartan by CE [21].

In previous investigations, a capillary zone electrophoretic (CZE) method [22], and a micellar electrokinetic capillary chromatographic (MEKC) method [23] were optimized for the separation of six ARA-IIs. Each method could be used to identify the six ARA-IIs, but for quantification of the ARA-IIs, a combination of two systems was necessary (Table 1).

The aim of the present study was to investigate the capability of the CZE and the MEKC methods to identify simultaneously HCT and several ARA-IIs. The usefulness of the above systems for the quantitative determination of these compounds in their pharmaceutical formulations was investigated, and the most important parameters for quantitative analysis were validated. The chemical structures of the HCT and ARA-II compounds studied are shown in Fig. 1.

Table 1
Overview of the two identifying methods and their usefulness to quantify the ARA-IIs

	CZE method[a]	MEKC method[b]
Candesartan	−	+
Eprosartan mesylate	+	+
Irbesartan	+	−
Losartan potassium	+	+
Telmisartan	+	−
Valsartan	−	+

[a] 60 mM sodium phosphate buffer (pH 2.5).
[b] 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS.

2. Experimental

2.1. Instrumentation and electrophoresis procedure

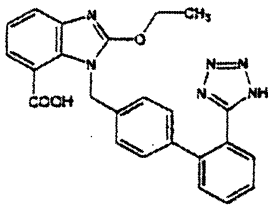
Experiments were performed on a Crystal CE (Thermo Capillary Electrophoresis, Franklin), equipped with PC 1000 software installed on a Dell computer with an OS/2 operating system. A fused-silica capillary was used, 85 cm in total length (33 cm to the detector), and 50 μm internal diameter (I.D.). The Crystal CE was temperature controlled at 25 °C for the tray, and at 30 °C for the capillary. The sample solutions were injected by pressure (50 mbar) for 5 s. A constant voltage of 25 kV was applied, and UV absorbance at 214 nm was employed for detection by means of a variable-wavelength UV detector (Spectra FOCUS detector, Spectra-Physics, San Jose, CA). The pH measurements were performed on a calibrated Metrohm 744 pH Meter (Herisau, Switzerland).

2.2. Reagents

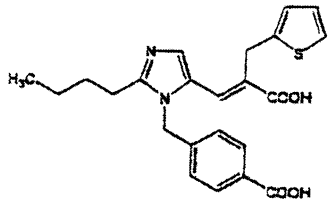
Sodium dihydrogen phosphate monohydrate (p.a.) and disodium hydrogen phosphate dihydrate (p.a.) were obtained from Merck (Darmstadt, Germany), sodium dodecyl sulfate (SDS) from Sigma (St. Louis), phosphoric acid (85%, w/w) and sodium hydroxide from UCB (Leuven, Belgium), and hydrochloric acid (37%, w/w) from Panreac (Barcelona, Spain). HCT was purchased from Profarma (Belgium). Candesartan was obtained from AstraZeneca (Mölndal, Sweden), eprosartan mesylate from Solvay (Weesp, The Netherlands), irbesartan from Sanofi-Synthelabo (Gentilly Cedex, France), losartan potassium from Merck Sharp & Dohme (Rahway, NJ), telmisartan from Boehringer Ingelheim (Ingelheim, Germany) and valsartan from Novartis (Basel, Switzerland).

The commercially available drugs Co-Aprovel® (Sanofi-Synthelabo), Cozaar Plus® (MSD), and Co-Diovane® (Novartis) were used for quantitative determinations.

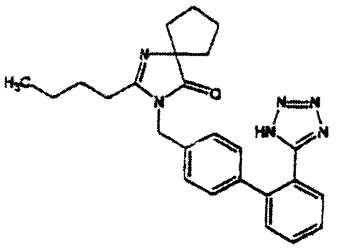
All solutions were prepared with distilled water obtained from deionized water.



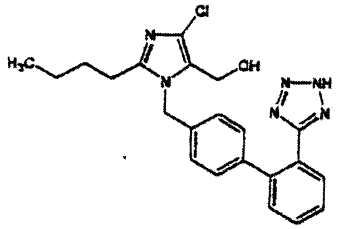
Candesartan (C)



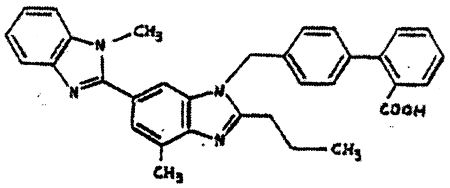
Eprosartan (E)



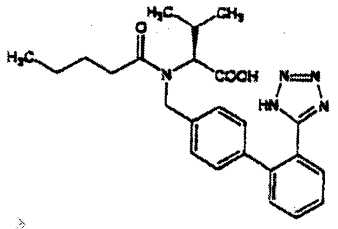
Irbesartan (I)



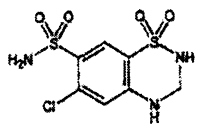
Losartan (L)



Telmisartan (T)



Valsartan (V)



Hydrochlorothiazide (HCT)

Fig. 1. Chemical structures of the ARA-IIs and HCT.

2.3. Running buffers

In the CZE method, a 60 mM sodium phosphate buffer (pH 2.5) was used as the running buffer. The solution was prepared by adjusting the pH of a 60 mM sodium dihydrogen phosphate solution to pH 2.5 by the addition of 60 mM phosphoric acid solution.

In the MEKC method, the separation of the ARA-IIs was achieved using a 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS. The sodium phosphate buffer was prepared by adjusting the pH of a 55 mM sodium dihydrogen phosphate solution to pH 6.5 by the addition of 55 mM disodium hydrogen phosphate solution. A running buffer solution was prepared by dissolving an appropriate amount of SDS in the sodium phosphate buffer to obtain a SDS concentration of 15 mM.

2.4. Internal standard solutions

Depending on the method employed, two different internal standards were used: sulfanilamide or eprosartan mesylate.

For quantitative determination using the CZE mode, sulfanilamide was used as the internal standard, because it migrates to the middle of the ARA-II and HCT compounds. Although other ARA-IIs can be used, these compounds are less suitable because their migration times are more favourable for determining the ARA-II than the HCT. An appropriate mass of sulfanilamide (Table 2a) was dissolved in 10 ml of 1 M HCl, and the solution was diluted to a volume of 100 ml using water.

For quantitative determination performed using the MEKC mode, another ARA-II compound was used as the internal standard. The selection was made based on the substance to be examined. Although each ARA-II can be combined with another, eprosartan mesylate was chosen as the most frequent internal standard, because of its high solubility. An appropriate mass of the compound (Table 2b) was dissolved in 10 ml of 0.1 M NaOH, and the solution was diluted to a volume of 100 ml using water.

2.5. Choice of solvent

The choice of solvent depended on the pH of the medium. For the assay of irbesartan, losartan potassium, and HCT in an acidic medium (for the CZE method), the running buffer could not be used as a solvent for the preparation of the reference and sample solutions, because of the poor solubility of the ARA-IIs and HCT compounds. Therefore, methanol was added to dissolve the active substances, and the solutions were then diluted with water.

Losartan potassium and valsartan concentrations were determined using the MEKC method, but the same problems with solubility were encountered, because the running buffer could not be used as the solvent in the preparation of the reference and the sample. Therefore, 0.1 M NaOH was added to dissolve the active substances, and the solutions were then diluted with water. This medium is suitable for dissolving HCT, and so no addition of methanol was required.

The use of different solvents according to the method employed, led to various preparations of reference and sample solutions. Therefore, a distinction was made between the two methods employed. Depending on the ratio of ARA-II and HCT in the pharmaceutical formulation, the determination was performed either simultaneously or as separate determinations.

2.6. Reference solutions for qualitative determination

2.6.1. CZE method

A stock solution of HCT in methanol was prepared at a concentration of 3 mg/ml. The reference solutions were prepared by dissolving approximately 3 mg of the corresponding ARA-II reference compound in 1 ml of 1 M HCl, and then mixing the solution with 1 ml stock solution of HCT, which was then diluted with water to a volume of 10 ml.

2.6.2. MEKC method

The ARA-II and HCT reference solutions were prepared by dissolving approximately 3 mg of the corresponding reference compound in 1 ml of 0.1

Table 2a
Sample preparation for the quantitative determination using the CZE method

	Determination	Sample solution (mg powder)	Internal standard solution (mg/ ml)	Diluted sample solution (mg active substance/ml)
Irbesartan 150 mg				
HCT 12.5 mg	Separated	±100 mg	Sulfanilamide:	I: ±0.25
[Co-Aprovel 150/12.5®]		±300 mg	2.2 mg	HCT: ±0.125
Irbesartan 300 mg				
HCT 12.5 mg	Separated	±100 mg	Sulfanilamide:	I: ±0.25
[Co-Aprovel 300/12.5®]		±600 mg	2.2 mg	HCT: ±0.125
Losartan potassium 50 mg				
HCT 12.5 mg	Simultaneously	±200 mg	Sulfanilamide:	L: ±0.40
[Cozaar Plus®]			2.2 mg	HCT: ±0.10

M NaOH solution, and diluting this to a volume of 10 ml with water.

2.7. Reference solutions for quantitative determination

2.7.1. CZE method

The irbesartan reference solution for determination in Co-Aprovel® was prepared by dissolving approximately 50 mg of the reference compound in 50 ml of methanol, and then diluting the solution to a volume of 100.0 ml with water. A volume of 10.0 ml of the solution was then mixed with 10.0 ml of the internal standard solution.

The HCT reference solution for determination in Co-Aprovel® was prepared by dissolving approximately 100 mg of the corresponding reference substance in methanol, and then diluting the solution to a volume of 100.0 ml with the same solvent. Twenty-five ml of this stock solution was mixed with 25.0 ml of methanol, and this solution was diluted to a volume of 100.0 ml with water. A volume of 10.0 ml of the solution was then mixed with 10.0 ml of the internal standard solution.

The losartan potassium and HCT reference solution for simultaneous determination in Cozaar Plus® was prepared by mixing approximately 8 mg of losartan potassium with 5.0 ml of HCT stock solution ($\approx$ 40 mg HCT in 100.0 ml methanol) and 10.0 ml of the internal standard solution, and diluting the solution to a volume of 20 ml with water.

2.7.2. MEKC method

The valsartan reference solution for determination in Co-Diovane® was prepared by dissolving approximately 40 mg of the reference compound in 10 ml of 0.1 M NaOH, and diluting the solution to a volume of 100.0 ml with water. Ten millilitres

Table 2b
Sample preparation for the quantitative determination using the MEKC method

	Determination	Sample solution (mg powder)	Internal standard solution (mg/ ml)	Diluted sample solution (mg active substance/ml)
Losartan potassium 50 mg				
HCT 12.5 mg	Simultaneously	±130 mg	Eprosartan:	L: ±0.25
[Cozaar Plus®]			0.5 mg	HCT: ±0.06
Valsartan 80 mg				
HCT 12.5 mg	Separated	±80 mg	Eprosartan:	V: ±0.20
[Co-Diovane®]		±80 mg	1.0 mg	HCT: ±0.15

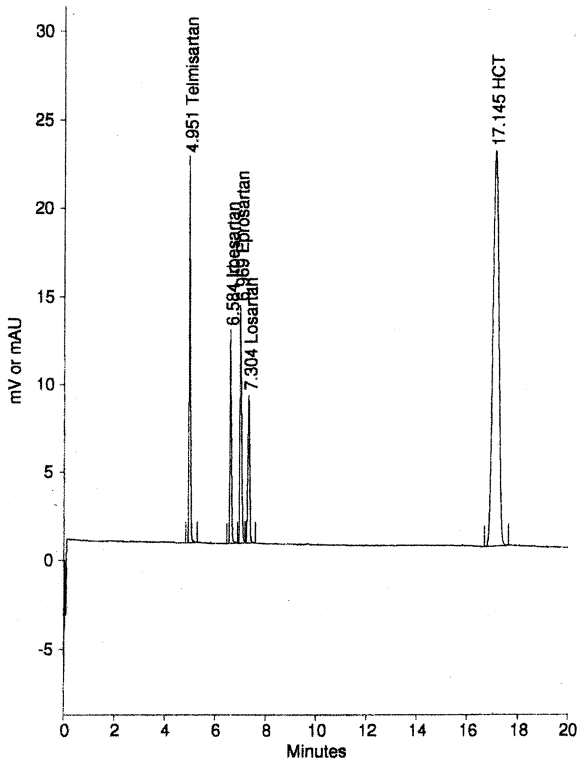


Fig. 2. Electropherogram of a mixture of HCT and several ARA-IIs using a fused-silica capillary 85 cm (33 cm to the detector) × 50 μm I.D., and 60 mM sodium phosphate buffer (pH 2.5) as the running buffer. The applied voltage is 25 kV and detection is at 214 nm.

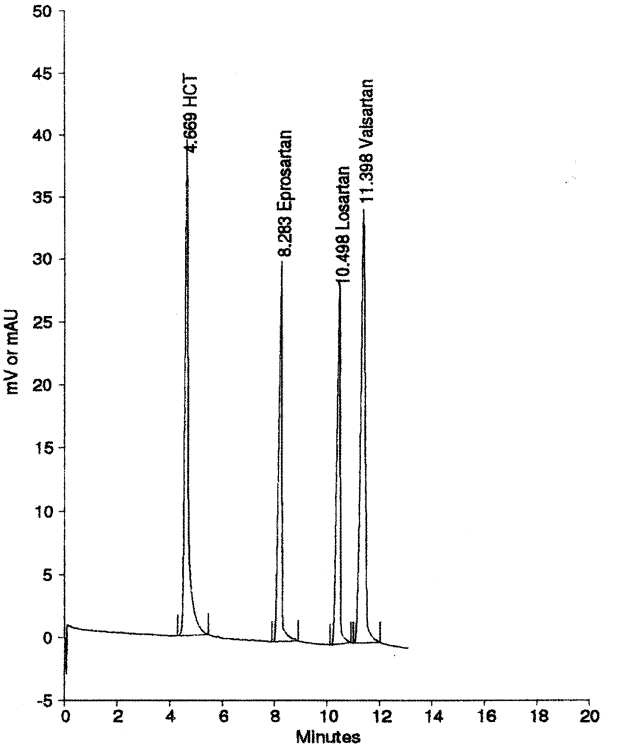


Fig. 3. Electropherogram of a mixture of HCT and several ARA-IIs using a fused-silica capillary 85 cm (33 cm to the detector) × 50 μm I.D., and 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS as the running buffer. The applied voltage is 20 kV and detection is at 214 nm.

of the solution was then mixed with 10.0 ml of the internal standard solution.

The HCT reference solution for determination in Co-Diovane® was prepared by dissolving approximately 60 mg of the corresponding reference compound in 0.1 M NaOH, and then diluting the solution to a volume of 50.0 ml using the same solvent. Twenty-five millilitres of this stock solution was diluted to a volume of 100.0 ml with water. A volume of 10.0 ml of the solution was then mixed with 10.0 ml of the internal standard solution.

The losartan potassium and HCT reference solution for simultaneous determination in Cozaar Plus® was prepared by mixing 5.0 ml of a stock solution of losartan potassium (made by dissolving ≈25 mg losartan potassium in 5 ml of 0.1 M NaOH solution and diluting to a volume of 25.0 ml with water), 5.0 ml of a stock solution of HCT (≈25 mg of HCT in 100.0 ml of methanol), and 10.0 ml of the internal standard solution.

2.8. Sample preparations for quantitative determination

A minimum of 20 tablets of each compound were weighed, ground, and mixed.

2.8.1. CZE method

To prepare the irbesartan sample solution for determination in Co-Aprovel®, the required mass of powder was sonicated with 50 ml of methanol, diluted to a volume of 100.0 ml with water, and then filtered. Ten millilitres of the filtrate was then mixed with 10.0 ml of the appropriate internal standard solution (Table 2a).

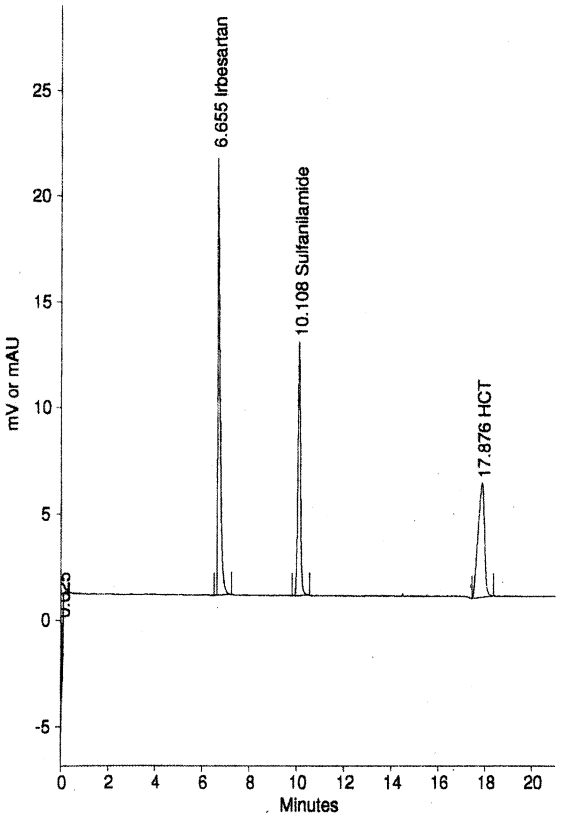


Fig. 4. Electropherogram of the quantitative determination of HCT and irbesartan [Co-Aprovel 300/12.5®] on a fused-silica capillary 85 cm in total length (33 cm to the detector) × 50 μm I.D. *Conditions:* 60 mM sodium phosphate buffer (pH 2.5) as the running buffer; applied voltage, 25 kV; detection at 214 nm.

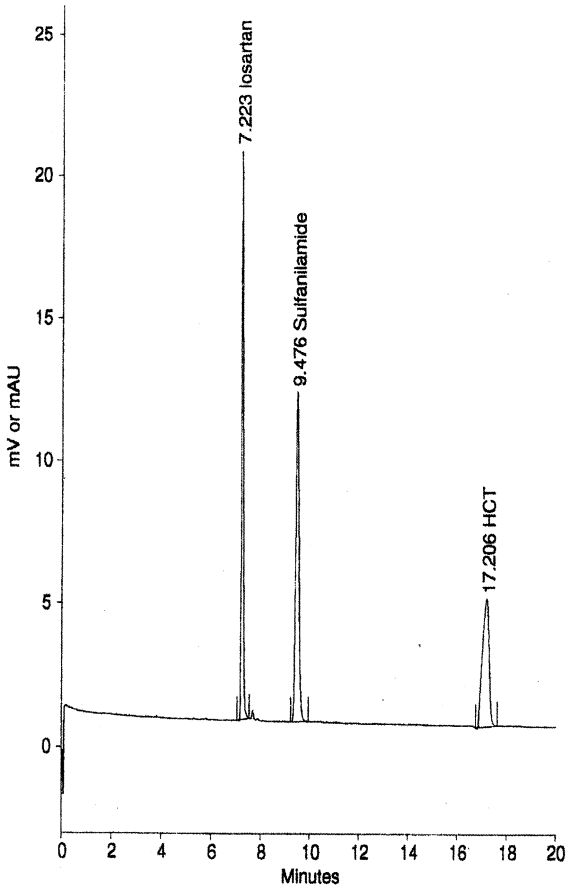


Fig. 5. Electropherogram of the quantitative determination of HCT and losartan potassium (Cozaar Plus®) on a fused-silica capillary 85 cm in total length (33 cm to the detector) × 50 μm I.D. *Conditions:* 60 mM sodium phosphate buffer (pH 2.5) as the running buffer; applied voltage, 25 kV; detection at 214 nm.

To prepare the HCT sample solution for determination in Co-Aprovel®, the required mass of powder was sonicated with 25 ml of methanol, diluted to a volume of 50.0 ml with water, and then filtered. Ten millilitres of the filtrate was then mixed with 10.0 ml of the appropriate internal standard solution (Table 2a).

To prepare the losartan potassium and HCT sample solution for simultaneous determination in Cozaar Plus®, the required mass of powder was sonicated with 25 ml of methanol, diluted to a volume of 50.0 ml with water, and then filtered. Ten millilitres of the filtrate was then mixed with 10.0 ml of the appropriate internal standard solution (Table 2a).

2.8.2. MEKC method

To prepare the valsartan sample solution for determination in Co-Diovane®, the required mass of powder was sonicated with 10 ml of 0.1 M NaOH, diluted to a volume of 100.0 ml with water, and then filtered. Ten millilitres of the filtrate was then mixed with 10.0 ml of the appropriate internal standard solution (Table 2b).

To prepare the HCT sample solution for determination in Co-Diovane®, the required mass of powder was sonicated with 5 ml of 0.1 M NaOH, diluted to a volume of 20.0 ml with water, and then filtered. Ten millilitres of the filtrate was then

Table 3
Linearity

	Method	Concentration range (mg/ml)	Correlation coefficient (r^2)
Irbesartan	CZE[a]	0.08–0.40	0.9999
HCT		0.04–0.20	1
Losartan potassium	CZE[a]	0.12–0.60	0.9995
HCT		0.03–0.15	0.9998
Losartan potassium	MEKC[b]	0.08–0.40	0.9995
HCT		0.02–0.10	0.9998
Valsartan	MEKC[b]	0.05–0.25	0.9997
HCT		0.05–0.25	0.9997

[a] 60 mM sodium phosphate buffer (pH 2.5).
[b] 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS.

mixed with 10.0 ml of the appropriate internal standard solution (Table 2b).

To prepare the losartan potassium and HCT sample solution for simultaneous determination in Cozaar Plus®, the required mass of powder was sonicated with 25 ml of methanol, diluted to a volume of 50.0 ml with water, and then filtered. Ten millilitres of the filtrate was mixed with 10.0 ml of the appropriate internal standard solution (Table 2b).

All the samples and buffers were filtered by passing them through a 0.45-μm membrane filter (Millipore, Bedford, USA).

3. Results and discussion

In previous investigations, the CZE method [22] and the MEKC method [23] were optimized for the separation of six ARA-II compounds: cande-

Table 4
Precision (repetability) of the total analysis of 10 replicate samples

Substance to be examined	Method	Theoretical amount (mg/tablet)	Amount found	Relative standard deviation ($n = 10$) (%)
Irbesartan				
HCT	CZE[a]	150 mg	150.7 mg±0.72 mg or 100.5%	0.48
[Co-Aprovel 150/12.5®]		12.5 mg	12.77 mg±0.06 mg or 102.2%	0.47
Irbesartan				
HCT	CZE[a]	300 mg	298.6 mg±1.47 mg or 99.5%	0.49
[Co-Aprovel 300/12.5®]		12.5 mg	12.81 mg±0.10 mg or 102.5%	0.78
Losartan potassium				
HCT 12.5 mg	CZE[a]	50 mg	50.21 mg±0.58 mg or 100.4%	1.15
[Cozaar plus®]		12.5 mg	12.38 mg±0.16 mg or 99.0%	1.29
Losartan potassium				
HCT 12.5 mg	MEKC[b]	50 mg	49.48 mg±0.26 mg or 99.0%	0.53
[Cozaar plus®]		12.5 mg	12.46 mg±0.08 mg or 99.7%	0.61
Valsartan 80 mg				
HCT 12.5 mg	MEKC[b]	80 mg	79.74 mg±0.35 mg or 99.7%	0.43
[Co-Diovane®]		12.5 mg	12.54 mg±0.13 mg or 100.3%	1.04

[a] 60 mM sodium phosphate buffer (pH 2.5).
[b] 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS.

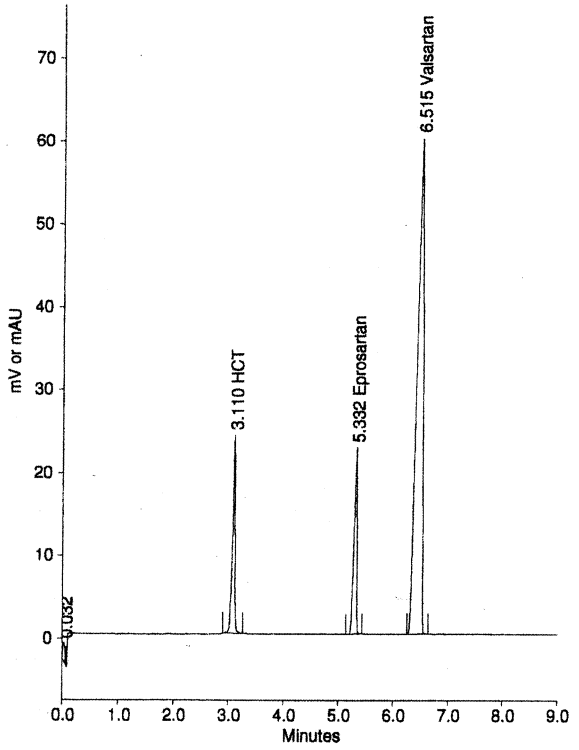


Fig. 6. Electropherogram of the quantitative determination of HCT and valsartan (Co-Diovane®) on a fused-silica capillary 85 cm in total length (33 cm to the detector) × 50 μm I.D. *Conditions:* 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS as the running buffer; applied voltage, 25 kV; detection at 214 nm.

sartan, eprosartan mesylate, irbesartan, losartan potassium, telmisartan, and valsartan. Each method could be used to identify the six ARA-IIs, but to quantify the ARA-IIs, a combination of the two systems was required (Table 1). The CZE method is suitable for the quantitative determination of the more soluble ARA-IIs: eprosartan mesylate, losartan potassium, irbesartan, and telmisartan, whereas the MEKC method can quantify the more stable ARA-IIs: candesartan, eprosartan mesylate, losartan potassium, and valsartan [22,23].

The capability of these two methods to determine HCT and the ARA-IIs simultaneously was investigated. To maintain selectivity in the separation of the ARA-IIs, the same buffer as was previously used in the two optimized methods was employed. With the CZE method (using 60 mM of sodium phosphate buffer (pH 2.5)), HCT is baseline separated from the ARA-IIs. Moreover, this separation gives no problems, because the compounds have different charges: the ARA-IIs are positively charged and migrate from the beginning, whereas HCT is uncharged, and migrates with the marker (Fig. 2). Consequently, the separation and determination of HCT is non-selective. Despite this, the simultaneous identification and quantification of ARA-IIs and HCT can have the advantage of reducing the analytical work.

Table 5
Repetability of 10 consecutive injections of the same sample

Sample solution	Method	Relative standard deviation ($n = 10$) (%)
Irbesartan	CZE[a]	0.28
HCT		0.53
Losartan potassium	CZE[a]	1.00
HCT		1.54
Losartan potassium	MEKC[b]	0.81
HCT		2.21
Valsartan	MEKC[b]	0.10
HCT		0.45

[a] 60 mM sodium phosphate buffer (pH 2.5).
[b] 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS.

With the MEKC method, the separation of the ARA-IIs can be achieved using a 55 mM sodium phosphate buffer solution (pH 6.5) containing 15 mM SDS. This running buffer is also appropriate for the separation of HCT and the ARA-IIs. However, the separation is more selective than the separation achieved by the CZE method: no co-elution of the marker and HCT occurs. HCT is negatively charged and migrates immediately after the marker, whereas while the ARA-IIs are also negatively charged, they elute soon after HCT (Fig. 3).

3.1. Quantitative determination in pharmaceutical formulations

The CZE and MEKC methods may be applied in the quantitative determination of the combina-

tion of HCT/ARA-IIs in tablets (Figs. 4–6). Depending on the ARA-II, at least one of the two methods discussed can be used. As already mentioned, the CZE method can be applied for the quantitative determination of eprosartan mesylate, losartan potassium, irbesartan, and telmisartan, whereas the MEKC method can quantify candesartan, eprosartan mesylate, losartan potassium, and valsartan. Consequently, there are no problems for determining the concentration of HCT and the combined ARA-IIs, namely irbesartan (Co-Aprovel®), losartan potassium (Cozaar Plus®), and valsartan (Co-Diovane®). Subject to the ratio of ARA-II and HCT in the pharmaceutical formulation, the determination can be performed simultaneously or as a separate determination (Tables 2a and 2b).

Using different placebo mixtures, it has been demonstrated that the following excipients do not adversely affect the results: microcrystalline cellulose, sodium carboxymethylcellulose, pregelatinized starch, pregelatinized maize starch, lactose, magnesium stearate, hydroxypropylcellulose, hydroxypropylmethylcellulose, crospovidone, silicon dioxide, talc, titanium dioxide, and poloxamer 188.

3.2. Validation of the method

3.2.1. Linearity

The detector responses were found to be linear for the different components in the concentration range used, as described in Table 3. The amount of the internal standard was adjusted according to the concentration range used. Regression analysis data for the calibration curves were calculated using the peak areas.

3.2.2. Precision

The precision (repeatability) was determined from analysis of 10 replicate samples under the same operating conditions, performed by the same analyst, and on the same day. The mean value of the concentration and the relative standard deviation are summarized in Table 4.

The error in the equipment and the relative standard deviation of the estimations were determined by performing 10 consecutive injections of the same sample (Table 5).

3.2.3. Accuracy

The accuracy of the method was determined by investigating the recovery of each component at three levels ranging from 80 to 120% of the theoretical concentration from placebo mixtures spiked with the active substance (Table 6).

4. Conclusions

The above results demonstrate that CE separation of HCT and one of the six nominated ARA-IIs can be achieved using a 60 mM sodium phosphate buffer solution at pH 2.5, or by using

Table 6
Accuracy

	Method	Recovery placebo + 80% ($n = 3$)	Recovery placebo + 100% ($n = 3$)	Recovery placebo + 120% ($n = 3$)
Irbesartan	CZE[a]	101.8% ± 0.5%	101.0% ± 0.0%	102.3% ± 0.2%
HCT		96.8% ± 0.9%	96.1% ± 0.2%	96.5% ± 0.6%
Losartan potassium	CZE[a]	102.2% ± 1.0%	101.2% ± 0.1%	102.8% ± 0.3%
HCT		100.7% ± 0.7%	99.0% ± 0.8%	99.9% ± 0.7%
Losartan potassium	MEKC[b]	102.2% ± 0.9%	102.0% ± 0.5%	98.5% ± 0.3%
HCT		102.7% ± 0.3%	97.3% ± 0.8%	100.1% ± 0.9%
Valsartan	MEKC[b]	100.0% ± 0.1%	102.2% ± 0.2%	98.6% ± 0.2%
HCT		100.9% ± 0.4%	100.1% ± 0.0%	99.2% ± 0.2%

[a] 60 mM sodium phosphate buffer (pH 2.5).
[b] 55 mM sodium phosphate buffer (pH 6.5) containing 15 mM SDS.

a 55 mM sodium phosphate buffer solution at pH 6.5 containing 15 mM SDS, according to the combined ARA-II. Both the CZE and the MEKC methods can be applied successfully to the qualitative and the quantitative determination of the above compounds in pharmaceutical formulations. The possibility of simultaneous identification and quantification of the active ingredients in the finished product is very attractive from the analytical viewpoint.

Acknowledgements

The following firms are kindly acknowledged for having supplied their products: AstraZeneca, Solvay, Sanofi-Synthelabo, Merck Sharp & Dohme, Boehringer Ingelheim, and Novartis.

References

[1] G.H. Cocolas, in: J.N. Delgado, W.A. Remers (Eds.), Textbook of Organic Medicinal and Pharmaceutical Chemistry, tenth ed., Lippincott-Raven, Philadelphia, New York, 1998, p. 603.
[2] B. Pitt, M.A. Konstam, Am. J. Cardiol. 82 (1998) 47S–49S.
[3] R. Willenheimer, B. Dahlof, E. Rydberg, L. Erhardt, Eur. Heart J. 20 (1999) 997–1008.
[4] I.C. Johnston, M. Naitoh, L.M. Burrell, J. Hypertens. (Suppl. 15) (1997) S3–S6.
[5] T. Unger, Am. J. Cardiol. 84 (1999) 9S–15S.
[6] W.O. Foye, Principles of Medicinal Chemistry, second ed., Henry Kimpton Publishers, London, Great Britain, 1981.
[7] D.A. Koechel, in: J.N. Delgado, W.A. Remers (Eds.), Textbook of Organic Medicinal and Pharmaceutical Chemistry, Lippincott-Raven, Philadelphia, New York, 1998, p. 553.
[8] S.A. Ozkan, J. Liquid Chromatogr. Relat. Technol. 24 (2001) 2237–2346.
[9] N. Erk, J. Pharm. Biomed. Anal. 24 (2001) 603–611.
[10] G. Carlucci, G. Palumbo, P. Mazzeo, M.G. Quaglia, J. Pharm. Biomed. Anal. 23 (2000) 185–189.
[11] A.P. Argekar, J.G. Sawant, Anal. Lett. 33 (2000) 869–880.
[12] G.V. Kanumula, B. Raman, Indian Drugs 37 (2000) 38–41.
[13] E. Satana, S. Altinay, N.G. Goger, S.A. Ozkan, Z. Senturk, J. Pharm. Biomed. Anal. 25 (2001) 1009–1013.
[14] G. Carlucci, V. di Carlo, P. Mazzeo, Anal. Lett. 33 (2000) 2491–2500.
[15] S. Hillaert, K. De Grauwe, W. Van den Bossche, J. Chromatogr. A 924 (2001) 439–449.
[16] M.I. Maguregui, R.M. Jimenez, R.M. Alonso, J.Chromatogr. Sci. 36 (1998) 516–522.
[17] H.F. Chen, J. Wang, Yaowu Fenxi Zazhi 18 (1998) 245–248.
[18] H.F. Yang, Y.F. Liu, Z.H. Wang, T.H. Ding, Sepu 16 (1998) 158–160.
[19] B.R. Thomas, X.G. Fang, X. Chen, R.J. Tyrrell, S. Ghodbane, J. Chromatogr. B, Biomed. Appl. 657 (1994) 383–394.
[20] R.C. Williams, M.S. Alasandro, V.L. Fasone, R.J. Boucher, J.F. Edwards, J. Pharm. Biomed. Anal. 14 (1996) 1539–1546.
[21] M.G. Quaglia, E. Donati, G. Carlucci, P. Mazzeo, S. Fanali, J. Pharm. Biomed. Anal. 29 (2002) 981–987.
[22] S. Hillaert, W. Van den Bossche, J. Chromatogr. A 979 (2002) 323–333.
[23] S. Hillaert, T.R.M. De Beer, J.O. De Beer, W. Van den Bossche, J. Chromatogr. A 984 (2003) 135–146.