ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
27 (2002) 901–912

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

www.elsevier.com/locate/jpba

Simultaneous determination of fosinopril and hydrochlorothiazide in pharmaceutical formulations by spectrophotometric methods

Nevin Erk *

Department of Analytical Chemistry, Faculty of Pharmacy, University of Ankara, 06100 Ankara, Turkey

Received 24 April 2001; received in revised form 12 July 2001; accepted 20 July 2001

Abstract

Three new spectrophotometric procedures for the simultaneous determination of fosinopril and hydrochlorothiazide are described. The first method, derivative-differential spectrophotometry, comprised of measurement of the difference absorptivities derivatized in the first-order (ΔD_1) of a tablet extract in 0.1 N NaOH relative to that of an equimolar solution in methanol at wavelengths of 227.6 and 276.4 nm, respectively. The second method, depends on the application ratio spectra derivative spectrophotometric method to resolve the interferance due to spectral overlapping. The analytical signals were measured at 237.9, 243.8 nm for fosinopril and 262.4, 269.3 and 278.6 nm for hydrochlorothiazide in the binary mixture, in the first derivative of the ratio spectra of the mixture solutions in methanol. Calibration graphs were established for 4.0–50.0 μg ml^{-1} fosinopril and 2.0–14.0 μg ml^{-1} hydrochlorothiazide in binary mixture. The third method, absorbance ratio method, the determination of fosinopril and hydrochlorothiazide was performed by using the absorbances read at 210.0, 219.5 and 271.7 nm in the zero-order spectra of their mixture. The developed methods were compared with absorbance ratio method. Application of the suggested procedures were successfully applied to the determination of this compound in synthetic mixtures and in pharmaceutical preparations, with high percentage of recovery, good accuracy and precision. © 2002 Published by Elsevier Science B.V.

Keywords: Fosinopril; Hydrochlorothiazide; Simultaneous determination; Derivative differential spectrophotometry; Ratio spectra derivative spectrophotometry; Absorbance ratio method

1. Introduction

Tablets containing fosinopril, a new chemical class of angiotensin-converting enzyme (ACE) inhibitors in combination with a diuretic drug were found to provide therapeutic effects. Hydrochlorothiazide, is shown to possess diuretic actions. More recently a new combination dosage form of fosinopril and hydrochlorothiazide is indicated in the treatment and management of edema and hypertension.

The simultaneous determination of fosinopril and hydrochlorothiazide has been carried out in

* Fax: +90-312-230-5000.
E-mail address: erk@pharmacy.ankara.edu.tr (N. Erk).

0731-7085/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0731-7085(01)00628-8

pharmaceutical formulation using a computational program by spectrophotometry [1] and high performance liquid chromatography [2]. Many analytical procedures have been described for the individual determination of hydrochlorothiazide, jointly with other pharmaceuical substances, including high performance liquid chromatography (HPLC) [3–9], polarography [10], capillary zone electrophoresis [11], and spectrophotometry [12–21] procedures.

Spectrophotometry is a common technique in the field of pharmaceutical and biomedical analysis. Direct UV absorbance measurement is subject to interference from coformulated drugs, excipients and degradation products. Derivative spectrophotometry offers greater selectivity than does normal spectrophotometry in the simultaneous determination of two or more compounds without previous chemical separation [22,23]. Difference spectrophotometry based on pH changes has also been reported to be useful in the determination of binary mixtures [24]. There are few reports on utilization of the above two combined techniques for the estimation of individual drug substances [25] and for combined preparations [26,27].

Recently, Salinas et al. [28,29] developed a new spectrophotometric method, which is based on the use of the first derivative of the ratio spectra for resolving binary mixtures. This method permits the use of the wavelength of greatest sensitivity (a maximum or a minimum) as the signal of measurement. Moreover, the presence of a lot of maxima and minima is another advantage by the fact that these wavelengths give an opportunity for the determination of active compounds in the presence of other compounds and excipients which possibly interfere the assay.

The fosinopril–hydrochlorothiazide mixture is not yet offical in any pharmacopoeia. I was desirable to develop a simple and fast procedure that could be applied in quality control laboratories for the simultaneous determination of fosinopril and hydrochlorothiazide in the presence of each other.

In this report, three new methods, differential derivative spectrophotometry, ratio first derivative spectrophotometry and absorbance ratio method are reported and the optimum experimental parameters for each method are described. These proposed methods were especially chosen since these are used for the determination of both analytes in synthetic mixtures and pharmaceutical preparations reported in pharmacopoeias.

2. Experimental

2.1. Apparatus

A double beam, Shimadzu 1601 spectrophotometer model with a fixed slit width (2 nm) connected to an IBM-PC computer loaded with an HP laserjet 1100 printer was used for all the absorbance signals and treatment of data.

2.2. Chemicals used

Fosinopril and hydrochlorothiazide were kindly donated by Bristol-Mayers Squibb Pharm. Ind. All other chemicals were of analytical-reagent grade.

2.3. Pharmaceutical preparation

A commercial pharmaceutical preparation (Monopril® plus tablet Bristol Mayers Squibb Pharm. Ind., Turkey) was assayed. Its declared content was as follows: fosinopril—20.0 mg; hydrochlorothiazide—12.5 mg/tablet.

2.4. Reagents

Stock solutions of 1.0 mg ml^{-1} of fosinopril and hydrochlorothiazide were prepared in methanol. These solutions were used in the preparation of calibration graphs and for spectra. All solutions were protected from light and were analysed on the day of preparation.

2.5. Calibration for differential derivative spectrophotometry

Standard solutions of fosinopril and hydrochlorothiazide were prepared, by dissolving approximately 25 mg, accurately weighed, in 250 ml methanol. Appropriate volume aliquots of the

stock solution were transferred to 25 ml calibrated flasks. Accurate volumes were transferred into two sets of 25-ml calibrated flasks. One set was diluted to volume with 0.1 N NaOH and the other set was diluted to volume with methanol. The first series contained a constant concentration of fosinopril (10.0 μg ml^{-1}) and a varying concentration of hydrochlorothiazide (2.0–14.0 μg ml^{-1}). The second contained a constant concentration of hydrochlorothiazide (6.25 μg ml^{-1}) and a varying concentration of fosinopril (4.0–50.0 μg ml^{-1}).

2.6. Sample preparation for differential derivative spectrophotometry

Twenty tablets was accurately weighed and powdered in a mortar. An accurately weighed amount equivalent to one tablet was dissolved in methanol in 100-ml calibrated flask. After 30 min of mechanical shaking, the solution was filtered in a 100 ml calibrated flask through Whatman no 42 filter paper. The residue was washed three times with 10 ml of solvent and then the volume was completed to 100 ml with the same solvent. The solution was diluted 1:10 with 0.1 N NaOH and methanol, separately

2.7. Calibration for ratio spectra first derivative spectrophotometry

Samples were prepared in 100 ml calibrated flasks containing 4.0–50.0 μg ml^{-1} of fosinopril and 2.0–14.0 μg ml^{-1} of hydrochlorothiazide in methanol.

2.8. Sample preparation for ratio spectra first derivative spectrophotometry and absorbance ratio method

An accurately weighed amount of the well powdered tablets (equivalent to 20.0 mg of fosinopril and 12.5 mg hydrochlorothiazide) was dissolved in 100 ml in methanol. After 20 min of mechanically shaking, the solution was filtrated in a 100 ml calibrated flask through Whatman no 42 filter paper. The residue was washed three times with 10 ml of solvent then the volume was completed to 100 ml with methanol. The solution was diluted 1:10 with methanol. The ratio spectra first derivative spectrophotometry and absorbance ratio method described above were applied to the prepared solutions.

3. Spectrophotometric measurements

3.1. Differential-derivative spectrophotometry

The difference spectra between the methanolic solution and equimolar 0.1 N NaOH solution of pure drugs and sample were recorded from 200.0 to 300.0 nm by placing the methanolic solution in the reference compartment and the 0.1 N NaOH solutions in the sample compartment. A first derivative spectrum of each of the differential curves was subsequently recorded. The solutions were measured at 227.6 and 276.4 nm for fosinopril and hydrochlorothiazide, respectively.

3.2. Ratio spectra first derivative spectrophotometry

By this method, fosinopril and hydrochlorothiazide mixtures were analysed by measuring the signals at $^{1}DD_{237.9}$,[1] $^{1}DD_{243.8}$, $^{1}DD_{262.4}$, $^{1}DD_{269.3}$ and $^{1}DD_{278.6}$ on the derivatives of the ratio spectrum of the mixture using fosinopril and hydrochlorothiazide, respectively, as divisor.

3.3. Absorbance ratio method

Such a method of analysis is based on the linear relationship between the absorbancy ratio value of a binary mixture and the relative concentration of such a mixture. The quantification analysis of fosinopril and hydrochlorothiazide and in binary mixture are performed by using the following equations:

$$C_1 = (Q_1 - b_1/a_1)(A_{iso}/a_{iso}) \times 10^3,$$

$$C_2 = (Q_2 - b_2/a_2)(A_{iso}/a_{iso}) \times 10^3$$

where $Q_1 = A_1/A_{iso}$ for fosinopril, $Q_2 = A_2/A_{iso}$ for hydrochlorothiazide, C_1 and C_2 = concentrations

[1] order derivative Derivative Divided wavelength measure

of the fosinopril and hydrochlorothiazide, respectively, A_{iso} = absorbance at isoabsorptive point (λ_{iso} = 219.5 nm), a_{iso} = absorptivity at isoabsorptive point = $A_{iso}/C_1 + C_2$, a_1 = slope of regression equation (Q_1 vs. $C_1/C_1 + C_2$), a_2 = slope of regression equation (Q_2 vs. $C_2/C_1 + C_2$), $b_{1,2}$ = intercept values of these regression equations, A_1 and A_2 denotes the absorbances of the mixture solution measured at λ_1 and λ_2 (210.8 and 271.7 nm).

4. Results and discussion

4.1. Differential derivative spectrophotometry

The absorption (zero-order) UV spectra of fosinopril and hydrochlorothiazide in 0.1 N NaOH and methanol are shown in Fig. 1. Conventional UV spectrophotometry cannot be used for the simultaneous determination of both drugs in the presence of each other. The difference absorption spectra of fosinopril and hydrochlorothiazide and binary mixture showed in Fig. 2a. The first derivative differential spectra of both the drugs. Fig. 2b offered an advantage for their simultaneous determination by having zero-crossing points. The ΔD_1 amplitudes at 227.6 nm (zero crossing of hydrochlorothiazide) and at 276.4 nm (zero crossing of fosinopril) were chosen for the simultaneous determination of fosinopril and hydrochlorothiazide, respectively,in a binary mixture. The differential-derivative spectra showed the best linear response to analyte concentrations used at these wavelengths. Under the experimental conditions described,standard calibration curves fosinopril and hydrochlorothiazide were constructed by plotting first derivative value of the differential versus concentration, respectively. Conformity with with Beer' s law was evident in the concentration range from 4.0 to 50.0 μg ml^{-1} of fosinopril and from 2.0 to 14.0 μg ml^{-1} of hydrochlorothiazide Table 1. The regression curve was calculated by the least-squares method. The correlation coefficients were 0.9992 for fosinopril and −0.9999 for hydrochlorothiazide, indicating good linearity. Results of this method analysis of laboratory-prepared mixtures with different proportions of the drug is given in Table 2. The excipients (corn starch, magnesium stearete, lactose and talc) were added to the drug for recovery

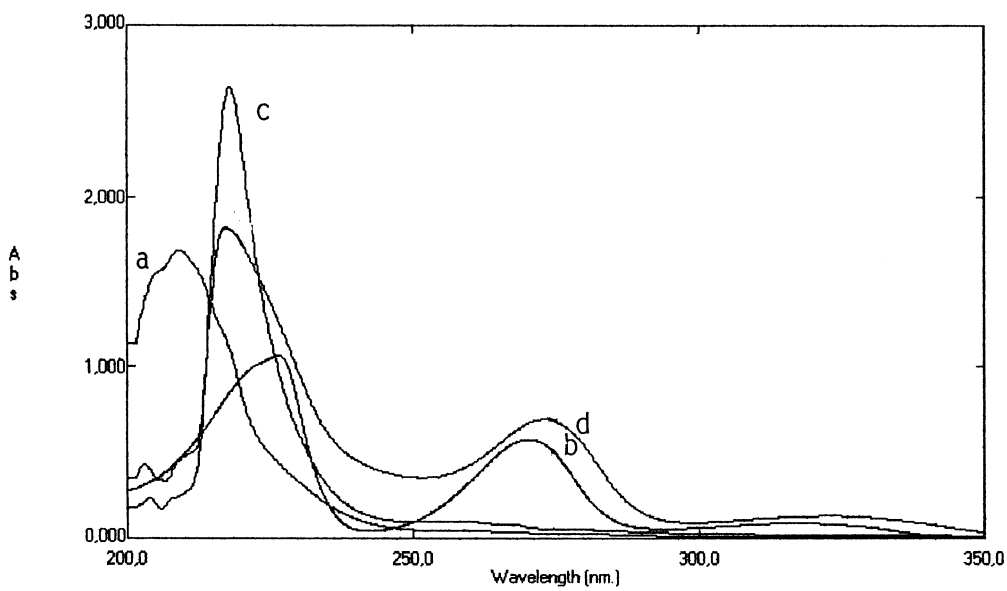

Fig. 1. Zero-order spectra of (a) 40.0 μg ml^{-1} fosinopril, (b) 12.5 μg ml^{-1} hydrochlorothiazide in methanol and, (c) 40.0 μg ml^{-1} fosinopril, (d) 12.5 μg ml^{-1} hydrochlorothiazide in 0.1 N NaOH.

Table 1
Statistical analysis for the calibration graphs of fosinopril and hydrochlorothiazide by use of differential derivative and ratio derivative spectrophotometry

Method	Analyte	Wavelength (nm)	Linearity range (μg ml^{-1})	Regression equation	Correlation coefficient	RSD of slope	RSD of intercept
Diff. Der. Spc.	Fos.	227.6	4.0–50.0	$Y = 4.3 \times 10^{-3} C_F + 5.7 \times 10^{-3}$	0.9992	0.115	0.208
	Hyd.	276.4	2.0–14.0	$Y = -2.3 \times 10^{-3} C_H - 2.8 \times 10^{-3}$	−0.9999	0.566	0.632
Rat. Der. Spc.	Fos.	237.9	4.0–50.0	$Y = 2.1 \times 10^{-3} C_F + 5.5 \times 10^{-3}$	0.9949	0.905	1.02
		243.8	4.0–50.0	$Y = 2.1 \times 10^{-3} C_F + 5.5 \times 10^{-3}$	0.9939	0.264	0.488
	Hyd.	262.4	2.0–14.0	$Y = 5.6 \times 10^{-2} C_H - 1.8 \times 10^{-3}$	0.9846	0.897	0.598
		269.3	2.0–14.0	$Y = 6.2 \times 10^{-2} C_H + 9.8 \times 10^{-3}$	0.9866	0.922	0.786
		278.6	2.0–14.0	$Y = -1.1 \times 10^{-2} C_H - 4.5 \times 10^{-2}$	−0.9856	0.645	0.596

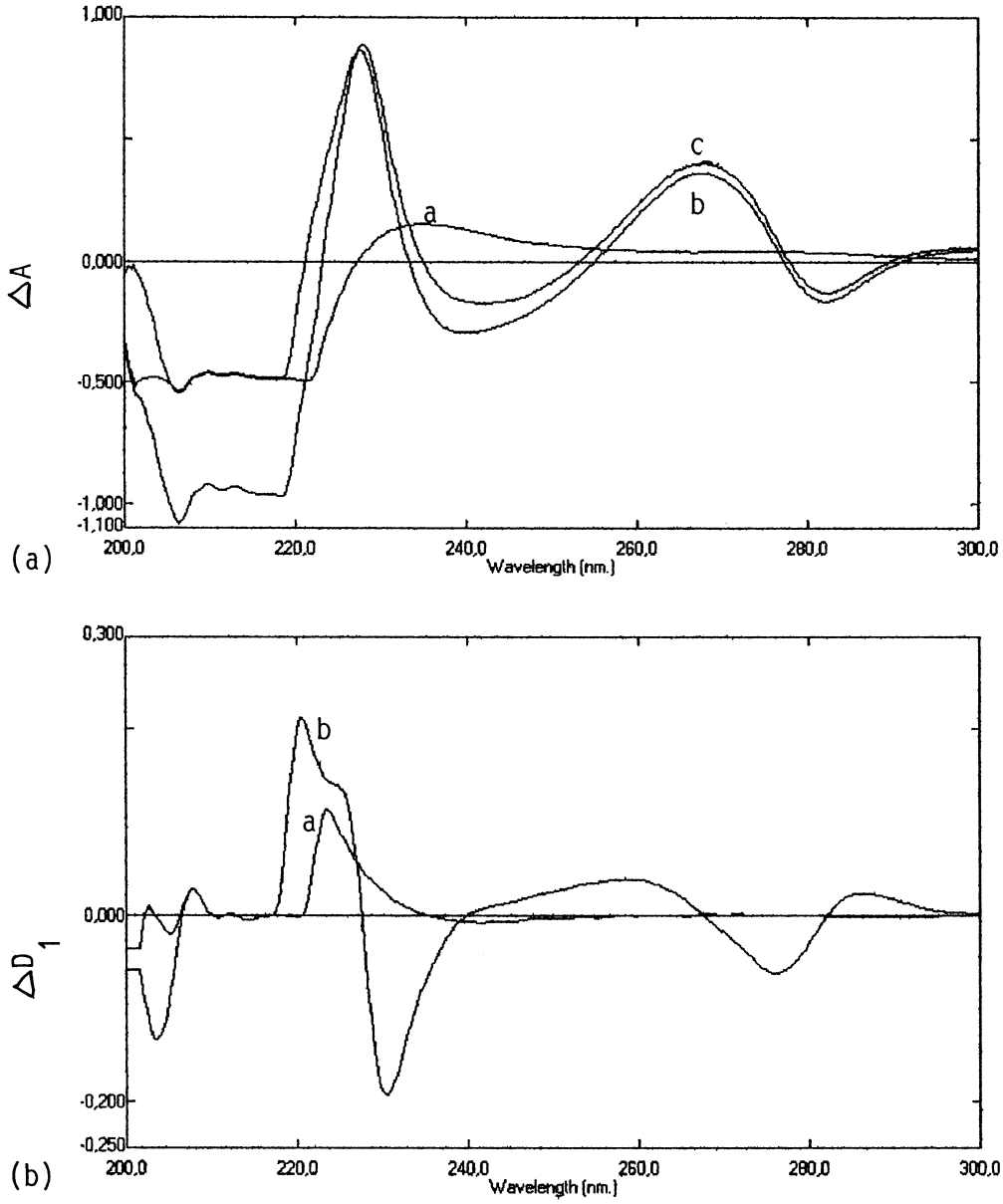

Fig. 2. (A) Differential spectra of (a) 40.0 μg ml^{-1} fosinopril, (b) 12.5 μg ml^{-1} hydrochlorothiazide and, (c) mixture of (40.0 μg ml^{-1} fosinopril and 12.5 μg ml^{-1} hydrochlorothiazide) in methanol vs. 0.1 N NaOH. (B) Differential derivative spectra of (a) 40.0 μg ml^{-1} fosinopril, (b) 12.5 μg ml^{-1} hydrochlorothiazide in methanol vs. 0.1 N NaOH.

studies according to manufacturer's batch formula for per tablets. The data shown in Table 3 indicate good accuracy and precision of the proposed procedure. The relative standard deviations were found to be less than 1.45% indicating reasonable repeatability of the method. The detection limits (LOD) [30] were 0.068 μg ml^{-1} for fosinopril, and 0.120 μg ml^{-1} for hydrochlorothiazide while the quantification limits (LOQ) [31] were 0.226 μg ml^{-1} for fosinopril, 0.893 μg ml^{-1} for hydrochlorothiazide (Table 4).

Table 2
Beer's law data and statistical analysis for the calibration graphs of fosinopril and hydrochlorothiazide using absorbance ratio method

	Fosinopril	Hydrochlorothiazide
Solvent	Methanol	Methanol
λ_{max}	210.0 nm	271.7 nm
λ_{iso}	219.5 nm	219.5 nm
Concentration range for Beer's law compliance	4.0–50.0 μg ml^{-1}	2.0 –14.0 μg ml^{-1}
Correlation coefficient (r)	0.9989	0.9897
$y = ax + b$	$Y = 1.7 \times 10^{-2} C_F + 8.2 \times 10^{-2}$	$Y = 3.7 \times 10^{-2} C_H + 5.2 \times 10^{-2}$

Table 4
The detection and quantification limits of fosinopril and hydrochlorothiazide using the proposed methods

Proposed method	LOD[a]	LOQ[b]
Diffe. Der. Spec.		
Fosinopril	0.068	0.226
Hydrochlorothiazide	0.120	0.893
Ratio Der. Spec.		
Fosinopril	0.061	0.250
Hydrochlorothiazide	0.244	0.806
Absor. Ratio Met.		
Fosinopril	0.052	0.364
Hydrochlorothiazide	0.342	0.895

[a] $LOD = 3S_b/b$; detection limit, S_b standard deviation of blank; b: slope of calibration graph.
[b] $LOQ = 10S_b/b$; quantification limit.

4.2. Ratio first derivative spectrophotometry

The stability of working solutions of fosinopril and hydrochlorothiazide was studied by recording their absorption spectra. At first these spectra were measured. No changes in the spectra were observed for at one day when the solutions are stored at room temperature in the dark.

Fig. 1 shows the absorption spectra corresponding to fosinopril, and hydrochlorothiazide and a mixture of them in methanol. The absorption spectra of the two components are strongly overlapped. On the other hand, this spectral overlapping was sufficiently enough to demonstrate the resolving power of the proposed method. For the determination of fosinopril, the stored absorption spectra of standard solutions of fosinopril and hydrochlorothiazide and a solution of their binary mixture were divided by the absorption spectrum of a standard solution of 6.25 μg ml^{-1} of hydrochlorothiazide, then the first derivative of the obtained ratio spectra were calculated with $\Delta\lambda = 4$ nm (Fig. 3). From this Fig. 3, fosinopril can be determined in this binary mixture by mea-

Table 3
Resolution of fosinopril and hydrochlorothiazide laboratory-made mixtures by using the differential derivative spectrophotometry

Taken (mg/100ml)		Found(mg/100 ml)		Recovery (%)	
Fosinopril	Hydrochlorothiazide	Fosinopril	Hydrochlorothiazide	Fosinopril	Hydrochlorothiazide
20.0	7.5	19.8	7.4	99.0	98.7
20.0	10.0	19.6	9.8	98.0	98.0
20.0	12.5	20.2	12.7	101.0	101.6
20.0	8.5	20.1	8.6	100.5	101.2
20.0	14.0	19.5	14.3	97.5	102.1
10.0	12.5	9.9	12.4	99.0	99.2
15.0	12.5	14.7	12.4	98.0	99.2
20.0	12.5	19.9	12.6	99.5	100.8
25.0	12.5	24.6	12.4	98.4	99.2
30.0	12.5	29.9	12.3	99.7	98.4
				Mean: 99.1	Mean: 99.8
				RSD%: 1.08	RSD%: 1.04

suring the analytical signals at 237.9 ($^1DD_{237.9}$) nm and 243.8 nm ($^1DD_{243.8}$) where there is no contribution from hydrochlorothiazide. For determining the other component, hydrochlorothiazide, an analogous procedure was followed. Fig. 4 shows the ratio-spectra of different concentrations of hydrochlorothiazide and their first derivatives, using the spectrum of a 10.0 μg ml^{-1} solution of fosinopril as the divisor. The concentration of hydrochlorothiazide is proportional to the amplitudes of 262.4 ($^1DD_{262.4}$), 269.3 ($^1DD_{269.3}$) and 278.6 ($^1DD_{278.6}$) nm. The influence

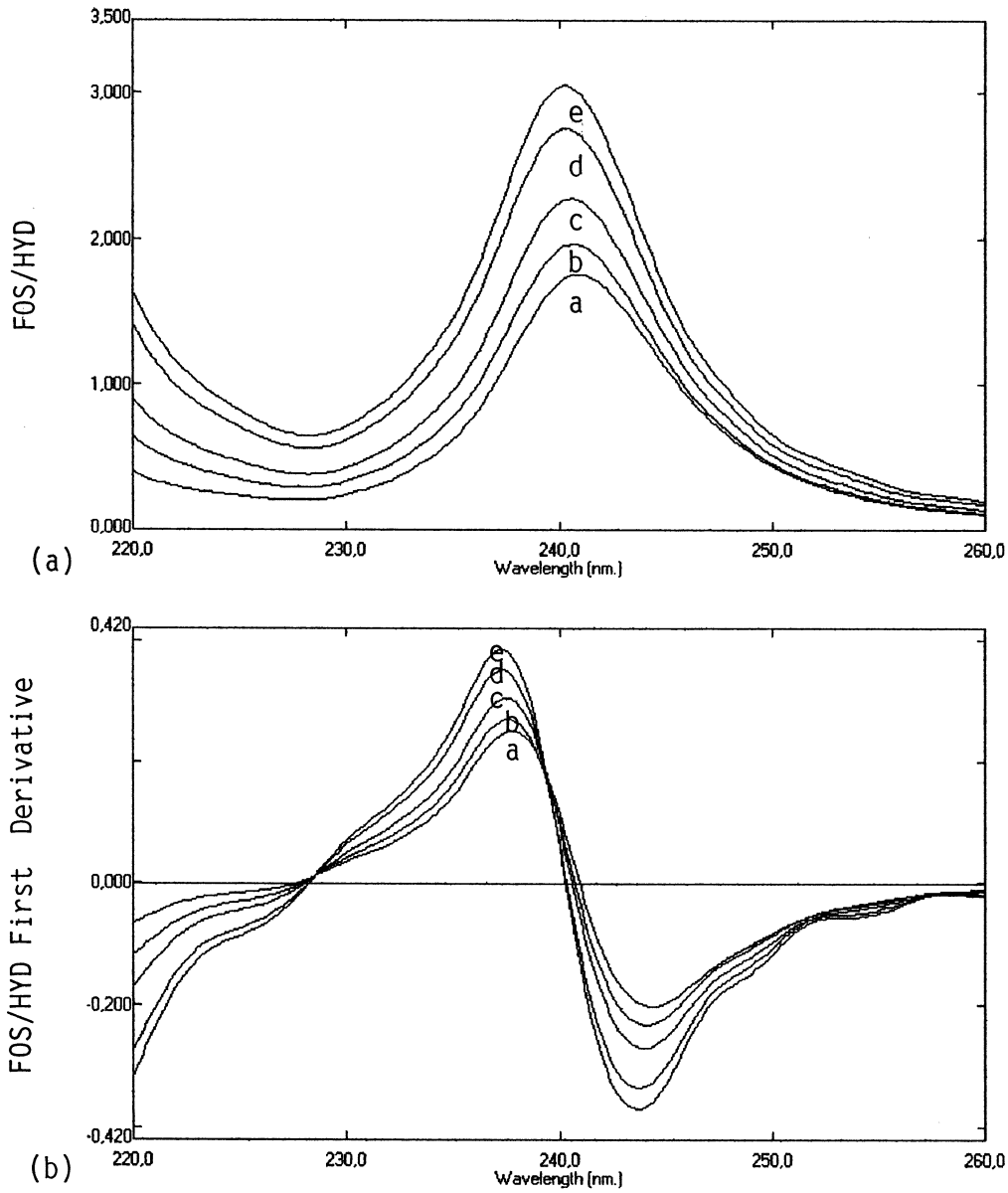

Fig. 3. Ratio spectra (a) and first derivative of the ratio spectra (b) of fosinopril (a) 4.0 μg ml^{-1}; (b) 11.0 μg ml^{-1}; (c) 21.0 μg ml^{-1}; (d) 38.0 μg ml^{-1}; (e) 50.0 μg ml^{-1}, where 6.25 μg ml^{-1} hydrochlorothiazide used as divisor in methanol.

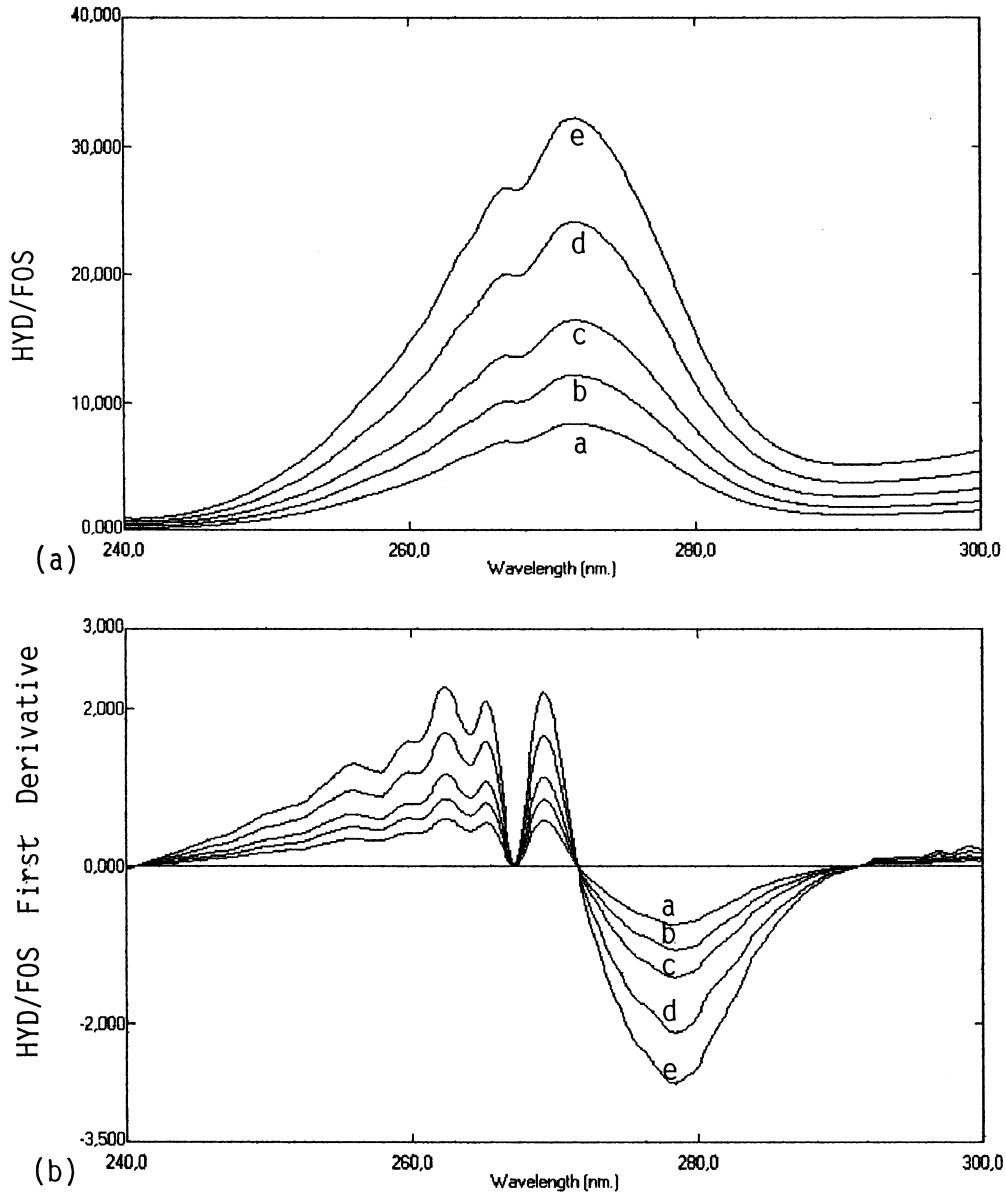

Fig. 4. Ratio spectra (A) and first derivative of the ratio spectra (B) of hydrochlorothiazide of (a) 2.0 μg ml^{-1}, (b) 5.0 μg ml^{-1}, (c) 7.5 μg ml^{-1}, (d) 11.5 μg ml^{-1}, (e) 14.0 μg ml^{-1}, when 10.0 μg ml^{-1} fosinopril used as divisor in methanol.

of $\Delta\lambda$ for obtaining the first derivative of the ratio spectra was tested to obtain the optimum wavelength interval; $\Delta\lambda = 4$ nm was considered as suitable. Under the experimental conditions described, standard calibration curves for fosinopril and hydrochlorothiazide were constructed by plotting first derivative value of the ratio spectrum versus concentration. Conformity with Beer's law was evident in the concentration range of the final dilution cited in Table 1. The ratio-spectra derivative method permits the use of the different concentrations as the divisor to obtain

the different calibration graphs. Various mixture compositions of fosinopril and hydrochlorothiazide were prepared and tested between 4.0–50.0 μg ml^{-1} for fosinopril and 2.0–14.0 μg ml^{-1} for hydrochlorothiazide (Table 1). Table 1 shows the linearity ranges of the calibration graphs for active ingredients at the suitable wavelengths for determinations of fosinopril and hydrochlorothiazide. The correlation coefficients were indicating good linearity. Recovery test also confirmed the accuracy and applicability of the proposed method by analyzing synthetic mixtures of fosinopril and hydrochlorothiazide which reproduced different composition ratios. The percentage recoveries and their relative standard deviations were found to be 99.8, 99.7 and 0.91, 0.84% for fosinopril and 99.6, 99.8, 99.3 and 1.04, 1.24, 0.70% for hydrochlorothiazide, respectively (Table 5). The detection and quantification limits were calculated for the fosinopril and hydrochlorothiazide using the ratio derivative method (Table 4).

4.3. Absorbance ratio method

Differential derivative spectrophotometry, ratio first derivative spectrophotometry tested absorbancy ratio method for resolving the binary mixtures. The zero-order (original) spectra of fosinopril and hydrochlorothiazide are illustrated in Fig. 1. These spectra indicated that binary mixtures containing fosinopril and hydrochlorothiazide could be analyzed by applying the principles absorbance ratio method. By measuring absorbance values at 210.0 nm (λ_{max} for fosinopril), 271.7 nm (λ_{max} for hydrochlorothiazide) and 219.5 nm (isosbestic point) in the original spectra of the binary mixture in methanol, the analysis of the binary mixture containing fosinopril and hydrochlorothiazide was made by using the formulas explained in Section 3.3. A critical evaluation of the proposed method was performed by the statistical analysis of the experimental data. The obtained slopes, intercepts and correlation coefficients obtained are summarized in Table 2.

In order to demonstrate the validity and applicability of the proposed methods, recovery studies were performed by analyzing synthetic mixtures of fosinopril and hydrochlorothiazide which reproduced different composition ratios. The percentage recoveries of fosinopril and hydrochlorothiazide from spiked excipient were summarized in Table 6. The percentage recoveries and their relative standard deviations were found

Table 5
Resolution of fosinopril and hydrochlorothiazide laboratory-made mixtures by using the ratio derivative spectrophotometry

Fosinopril			Hydrochlorothiazide			
Taken (mg ml^{-1})	Recovery (%)		Taken (mg ml^{-1})	Recovery (%)		
	$^1DD_{237.9}$	$^1DD_{243.8}$		$^1DD_{262.4}$	$^1DD_{269.3}$	$^1DD_{278.6}$
20.0	98.7	98.7	7.5	98.1	98.5	99.2
20.0	99.3	100.5	10.0	99.8	99.8	99.5
20.0	101.2	100.6	12.5	99.2	100.5	98.7
20.0	98.8	99.1	8.5	98.2	99.1	98.2
20.0	99.3	99.3	14.0	99.3	102.4	99.4
10.0	99.0	99.5	12.5	100.8	99.4	99.6
15.0	100.6	99.9	12.5	100.2	101.0	100.5
20.0	100.6	98.6	12.5	101.0	99.3	100.3
25.0	101.0	101.0	12.5	98.7	99.5	99.2
30.0	99.4	99.5	12.5	100.5	98.2	98.8
	Mean: 99.8	Mean: 99.7		Mean: 99.6	Mean: 99.8	Mean: 99.3
	RSD (%): 0.91	RSD (%): 0.84		RSD (%): 1.04	RSD (%): 1.24	RSD (%): 0.70

Table 6
Resolution of fosinopril and hydrochlorothiazide laboratory-made mixtures by using the absorbance ratio method

Taken (mg/100 ml)		Found(mg/100 ml)		Recovery (%)	
Fosinopril	Hydrochlorothiazide	Fosinopril	Hydrochlorothiazide	Fosinopril	Hydrochlorothiazide
20.0	7.5	20.1	7.3	100.5	97.3
20.0	10.0	20.1	9.8	100.5	98.0
20.0	12.5	19.5	12.2	97.5	97.6
20.0	8.5	19.8	8.5	99.0	100.0
20.0	14.0	20.1	14.4	100.5	102.8
10.0	12.5	9.7	12.4	97.0	99.2
15.0	12.5	15.1	12.4	100.6	99.2
20.0	12.5	19.9	12.6	99.5	100.8
25.0	12.5	24.8	12.2	99.2	97.6
30.0	12.5	30.2	12.4	100.6	99.2
				Mean: 99.5	Mean: 99.2
				RSD (%): 1.26	RSD (%): 1.71

Table 7
Assay results of fosinopril and hydrochlorothiazide in commercial tablets

Sample	Recovery (mean ± S.D.) %[a]					
	Fosinopril			Hydrochlorothiazide		
	Diff. Der. Spectr.	Rat. Der. Spectr.	Abs. Ratio. Met.	Diff. Der. Spectr.	Rat. Der. Spectr.	Abs. Ratio. Met.
Commercial tablets[b]	98.8 ± 1.81 $t = 1.173$[c] $F = 2.49$[c]	99.2 ± 1.76 0.897 1.440	99.6 ± 1.64	100.3 ± 1.02 $t = 1.134$ $F = 1.943$	98.9 ± 1.04 1.116 1.459	99.6 ± 0.71

[a] Mean and relative standard deviation for ten determinations; percentage recovery from the label claim amount.
[b] Monopril® plus tablets were labeled to contain 20.0 mg fosinopril, 12.5 mg hydrochlorothiazide per tablets, respectively.
[c] Values in parentheses are the theoretical values at $P = 0.95$. Theoretical values at % 95 confidence limits $F = 3.18$; $t = 2.26$.

to be 99.5 and 1.26% for fosinopril and 99.2 and 1.71% for hydrochlorothiazide, respectively. Commercially available tablets containing mixture of fosinopril and hydrochlorothiazide in mixture were analysed by proposed methods and the results are presented in Table 7.

By the fact that there was no official method for the analysis of fosinopril and hydrochlorothiazide in binary mixture. Therefore, the absorbancy ratio method was chosen as the analytical reference method. Differential derivative spectrophotometry and ratio first derivative spectrophotometry were compared with absorbancy ratio method. The intercept values for differential derivative spectrophotometry, ratio first derivative spectrophotometry and absorbancy ratio method were not statistically ($P < 0.05$) different from zero. No significant differences were found between the results obtained by the absorbances ratio method and the differential derivative and first derivative spectrophotometry, for same batch at the 95% confidence level (Student's t-test and F-variance ratio test).

5. Conclusions

The data given above reveal that the proposed methods are simple, accurate and sensitive with good

precision and accuracy. With these methods, one can do the analysis at low cost without losing accuracy. The reported methods is no need for solvent extraction, rapid as it requires measurements of ΔD_1, ratio $dA/d\lambda$ and A values at single wavelength and direct as it estimates each drug independent of the other. Moreover, it has many advantages over other separation techniques such as high-performance liquid chromatography [2] or gas chromatography. HPLC method [2] for simultaneous determination of fosinopril and hydrochlorothiazide needs expensive equipment, requiring time-consuming sample preparation such as filtration, degassing and HPLC grade solvents.

In addition, the proposed methods are widely used for the simultaneous determination of both drugs in pharmacopeias in contrast to the multi-wavelength spectrophotometric method [1]. Also, the proposed methods can be used as alternative methods to reported ones for the routine simultaneous determination of fosinopril and hydrochlorothiazide in the pure form and pharmaceutical formulations depending upon the availability of chemicals and the equipment.

References

[1] A.L. Magri, F. Balestrieri, A.D. Magri, D. Marini, Talanta 42 (1995) 1719.
[2] S. Saglik, O. Sagirli, S. Atmaca, L. Ersoy, Anal. Chim. Acta 427 (2001) 253.
[3] J. Ouyang, W.R.G. Baeyens, J. Delanghe, G. Van Der Weken, W. Van Daele, D. De Keukeleire, A.M. Garcia Campana, Anal. Chim. Acta 386 (1999) 257.
[4] P.B. Shetkar, V.M. Shinde, Anal. Lett. 30 (1997) 1143.
[5] S.T. Hassib, Z.A. El-Sherif, R.I. El-Bagary, N.F. Youssef, Anal. Lett. 15 (2000) 3225.
[6] M.S. Bhatia, S.G. Kaskhedikar, S.C. Chaturvedi, Indian Drugs 34 (1997) 576.
[7] G. Carlucci, V. Di Carlo, P. Mazzeo, Anal. Lett. 33 (2000) 2491.
[8] A.F.M. El-Walily, S.F. Belal, E.A. Heaba, A. El Kersh, J. Pharm. Biomed. Anal. 13 (7) (1995) 851.
[9] A.P. Argekar, J.G. Sawant, Anal. Lett. 33 (2000) 869.
[10] M.E. Martin, O.M. Hernandez, A.I. Jimenez, J.J. Arias, F. Jimenez, Anal. Chim. Acta 381 (1999) 247.
[11] H. Yang, Y. Liu, Z. Wang, T. Ding, Sepu 16 (1998) 158 (CA 128, 312999n, 1998).
[12] E. Martin, O. Hernandez, A.I. Jimenez, J.J. Arias, Anal. Lett. 31 (1998) 1857.
[13] F.A. El-Yazbi, H.H. Abdine, R.A. Shaalan, J. Pharm. Biol. Anal. 20 (1999) 343.
[14] C.V.N. Prasad, V. Bharadwaj, V. Narsimhan, R.T. Chowdhary, J. AOAC Int. 80 (1997) 325.
[15] I.E. Panderi, J. Pharm. Biomed. Anal. 21 (1999) 257.
[16] M. Kartal, N. Erk, J. Pharm. Biomed. Anal. 19 (1999) 477.
[17] C.V.N. Prasad, C. Parihar, K. Sunil, P. Parimoo, J. Pharm. Biomed. Anal. 17 (1998) 877.
[18] E.M. Martin, O. Hernandez, J.J. Arias, A.I. Jimenez, Microchem. J. 56 (1997) 207.
[19] N. Erk, J. Pharm. Biol. Anal. 20 (1999) 155.
[20] V. Ulvi, Pharm. Pharmacol. Commun. 4 (1998) 193.
[21] M.L. Luis, J.M.G. Fraga, A.I. Jimenez, J.J. Arias, Talanta 53 (2001) 761.
[22] B. Morelli, J. Pharm. Sci. 77 (1988) 1042.
[23] B. Morelli, J. Pharm. Sci. 84 (1995) 34.
[24] T.D. Doyle, F.R. Fazzari, J. Pharm. Sci. 63 (1974) 1921.
[25] A.M. Wahbi, M. Barary, H. Mahgab, M.A. El-Sayed, J. Assoc. Off. Anal. Chem. 68 (1985) 1045.
[26] A.G. Davidson, L.M.M. Mkoji, J. Pharm. Biomed. Anal. 6 (1988) 449.
[27] C.V.N. Prasad, A. Gautam, V. Bharadwaj, P. Parimoo, Talanta 44 (1997) 917.
[28] F. Salinas, J.J. Berzas Nevado, M.A. Espinosa, Talanta 37 (1990) 347.
[29] J.J. Berzas Nevado, C.C. Guiberteau, F. Salinas, Talanta 39 (1992) 547.
[30] Nomenclature, symbols, unit and their usege in spectrochemical analysis, II. Spectrochim. Acta B, 33 (1978) 242.
[31] Guidelines for data acquisition and data quality evaluation in environmental chemistry, Anal. Chem. 52 (1980) 2242.