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Analysis of binary mixtures of losartan potassium and hydrochlorothiazide by using high performance liquid chromatography, ratio derivative spectrophotometric and compensation technique

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Abstract

A new simple, precise, rapid and selective reversed-phase high performance liquid chromatographic (HPLC) and two spectrophotometric methods have been described for resolving binary mixture of losartan potassium and hydrochlorothiazide in the pharmaceutical formulations. The first method, is based on HPLC on a reversed-phase column using a mobile phase 0.01 N sodium dihydrogen phosphate:methanol:acetonitrile (8:2:1 v/v/v) (pH 5.5) with detection at 265.0 nm. The second method, is depend on ratio derivative spectrophotometry, the amplitudes in the first derivative of the ratio spectra at 238.360 nm and at 230.423 nm were selected to simultaneously determine losartan potassium and hydrochlorothiazide in the mixture. The third method, based on compensation technique is presented for the derivative spectrophotometric determination of binary mixtures with overlapping spectra. By using ratios of the derivative maxima or the derivative minimum, the exact compensation of either component in the mixture can be achieved, followed by its determination. The accuracy and precision of the methods have been determined and they have been validated by analysing synthetic mixtures containing losartan potassium and hydrochlorothiazide. The methods do not require any separation step. The methods were also applied to the determination of losartan potassium and hydrochlorothiazide in pharmaceutical preparations. The analytical results were quite good in all cases.

Keywords: Losartan potassium; Hydrochlorothiazide; Reversed phase high performance liquid chromatography; Simultaneous determination; Ratio derivative spectrophotometry; Compensation technique

1. Introduction

Losartan, 2-butyl-4-chloro-1-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol, is the first member of a new chemical class of a non-peptide angiotensin II receptor

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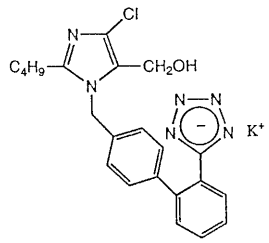
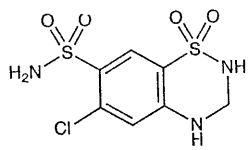
antagonist. The first approved indication for losartan is for hypertension.

Hydrochlorothiazide, or 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide is a diuretic of the class of benzothiadiazines.

Losartan potassium (I) and hydrochlorothiazide (II) have the following structural formulae:



(I)



(II)

A combination dosage form of losartan potassium and hydrochlorothiazide is indicated in the treatment and management of edema and hypertension.

The literature reports many analytical methods for the quantitative determination of these compounds individually or in their combination with other drugs, including, have been in pharmaceutical formulations, there methods use high performance liquid chromatography (HPLC) [1–9], high performance thin layer chromatography (HPTLC) [10], polarography [11], capillary zone electrophoresis [12], and spectrophotometry [13–24].

Molecular absorption spectroscopy has been extensively used for the determination of drugs in pharmaceutical preparations, as well as for the analysis of synthetic mixtures, with a view to the development of analytical methods. The use of this technique for pharmaceutical analyses has the inherent constraint that most active drugs absorb in the UV region and exhibit strongly overlapped spectra that impede their simultaneous determination. This problem has been addressed by using various methods including ratio derivative spectra and compensation technique.

Ratio derivative spectrum method was reported by Salinas et al. [25]. Compensation technique [26–28] is a useful technique for UV and IR spectrophotometric analysis of mixtures of absorbing compounds. This method is a non-mathematical method for the detection and elimination of unwanted absorption during spectrophotometric analysis. In binary mixture analysis, the compensation method involves a comparison of several difference spectra (mixture-reference) using different concentrations of a reference solution in the reference cell. Hence, if A_m and A_r refer to the absorbances of the relevant cells against air at same wavelength λ, then $\Delta A_\lambda = A_{m\lambda} - A_{r\lambda}$, where $A_m = A_a + A_b$ at a given wavelength λ, a and b refer to components a and b, respectively, and A_r refers to A_a or A_b. If c_r for compound a is introduced into the reference cell, the absorption characteristics of the mixture gradually approach that of compound b as c_a increases and finally coincides with the absorption curve of compound b at the end-point, for which $c_r = c_a$, and by analogy c_b can be found by repeating the same steps using c_r for compound b in the reference cell.

The losartan potassium–hydrochlorothiazide mixture is not yet official in any pharmacopoeia.

The aim of this work was the development of simple, sensitive and accurate analytical methods for the simultaneous determination of losartan potassium and hydrochlorothiazide in two component mixtures without the need for prior separation step. The developed methods to determine content of cited drugs in commercial tablets are also demonstrated.

2. Experimental

2.1. Apparatus

The high-performance liquid chromatography system consisted of a JASCO model PU-980 pump with a 7725 Rheodyne value injector 20 μl fixed loop, equipped with a JASCO UV-975 UV/VIS detector. The detector was set at 265.0 nm (0.02 a.u.f.s.) and peak areas were integrated automatically by computer using Borwin software programme.

A double beam, Shimadzu 1601 spectrophotometer model with a fixed slit width (2 nm) connected to an IBM-PC computer loaded with a

Lexmark printer was used for all the absorbance signals and treatment of data.

2.2. Chemicals used

Losartan potassium and hydrochlorothiazide were kindly donated by MSD Pharm. Ind.

Methanol and acetonitrile were of HPLC grade (Merck Chem. Ind.). All other chemicals were of analytical-reagent grade.

2.3. Pharmaceutical preparation

A commercial pharmaceutical preparation (HYZAAR® film tablet MSD Pharm. Ind. TURKEY, batch no: BD3581) was assayed. Its declared content was as follows: losartan potassium: 50.0 mg; hydrochlorothiazide: 12.5 mg/film tablet.

3. Procedures

3.1. Procedure for high performance liquid chromatography

3.1.1. Chromatographic conditions

Solutions and mobile phases were prepared in the moment of use. The mobile phases used were 0.01 M sodium dihydrogen phosphate:methanol:acetonitrile (8:2:1 v/v/v), adjusted to pH 5.5 with phosphoric acid. The analytical column was a RP-YMC pack ODS A A-132 C_{18} (5 μm, 15 cm × 6.0 mm) column. All analysis were done under isocratic conditions at a flow rate of 1.0 ml min^{-1} and at room temperature.

All solvents were filtered through 0.45 μm milipore filter to use and degassed in an ultrasonic bath.

3.1.2. Calibration

An external standard method was used for quantitative determinations. Calibration graphs were prepared from authentic samples of losartan potassium and hydrochlorothiazide in the mobile phase. Triplicate 20 μl injections were made for each solution. The final concentrations of losartan potassium and hydrochlorothiazide in the samples were calculated by comparison of sample and standard peak area obtained with the average of three injections of standard solutions.

3.1.3. Analysis of film tablets for high performance liquid chromatography

Ten commercial film tablets and the contents of 10 tablet ingredients were separately weighed and powdered in a different mortars. A portion of the powder equivalent to about one film tablet and the content of one tablet was weighed accurately, transferred to a 100 ml calibrated flask and suspended in mobile phase for HPLC method. The flasks were completed to volume with the same solvent. The samples were filtered through a 0.45-μm membrane filter, then further diluted to suit the calibration graphs.

3.2. Procedure for spectrophotometric methods

3.2.1. Calibration

Stock solutions of 1 mg ml^{-1} of losartan potassium and hydrochlorothiazide were prepared in acetonitrile:water (1:1 v/v). These solutions were used in the preparation of calibration graphs and for spectra.

3.2.2. Assay procedure for dosage forms

An accurately weighed amount of powdered tablets equivalent to about one tablet was transferred into a 100 ml conical flask in acetonitrile:water (1:1 v/v). 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. Appropriate solutions were prepared by taking suitable aliquots of the clear filtrates and diluting them with acetonitrile:water (1:1 v/v).

3.2.3. Determination of standard ratios for compensation method

The first derivative spectra for each set of reference solutions using the appropriate solution were recorded. The first derivative maxima ($^1D_{\lambda 1}/^1D_{\lambda 2}$), where appropriate at the specified wavelengths (λ_1 and λ_2) as indicated in parentheses in Table 1.

Table 1
Experimental parameters calculated for the simultaneous determination of losartan potassium and hydrochlorothiazide in binary mixture by compensation method

Preparation	Linearity range (μg ml^{-1})	Ratio	Mean[a]	RSD (%)
Losartan potassium	10.0–30.0	^{1}D(218)/^{1}D(236)	0.984	1.691
Hydrochlorothiazide	2.0–30.0	^{1}D(230)/^{1}D(261)	0.681	0.855

[a] Mean of 10 separate determinations.

3.2.4. Spectrophotometric measurements

3.2.4.1. Ratio derivative spectrophotometry. By this method, losartan potassium and hydrochlorothiazide mixtures were analysed by measuring the signals at $^1DD^1_{238.360}$ and $^1DD_{230.423}$ on the derivatives of the ratio spectrum of the mixture using losartan potassium and hydrochlorothiazide, respectively, as divisor.

3.2.4.2. Compensation technique. Prepare a series of solutions containing different concentrations of pure drugs losartan potassium above and below that present in the binary mixture solution and place them in succession in the reference cell. Place the solution of the mixture (containing compounds losartan potassium and hydrochlorothiazide) in the sample cell. The first (^{1}D) absorption spectra of the solutions prepared were recorded and calculated the corresponding ratio (Table 1) in each instance and follow the calculated ratio for pure compound hydrochlorothiazide. Determine the exact balance point (the ratio of the sample is equal to that of pure compound hydrochlorothiazide) at which the concentration of compound losartan potassium in the sample solution is equal to that in the reference solution. The similar procedure, follow the same steps using solutions of pure compound hydrochlorothiazide in the reference cell to determine its concentration in the binary mixture at the balance point.

[1] Derivative Divided$_{\text{wavelength measure}}$.

4. Results and discussion

4.1. High performance liquid chromatography method

Losartan potassium and hydrochlorothiazide are soluble in mobile phase, and their solutions were found to be stable for 3 days at least.

The reversed-phase HPLC method was developed to provide a specific procedure for the rapid quality control analysis of binary mixtures containing losartan potassium–hydrochlorothiazide. As shown in Fig. 1, at a flow rate of 1.0 ml min^{-1}, the retention times were 6.10 min for losartan potassium and 3.45 min for hydrochlorothiazide in combined pharmaceutical dosage. The retention times for the investigated drugs were found to be 6.10 min (losartan potassium) and 3.45 min (hydrochlorothiazide). To find the appropiate HPLC conditions for separation of the examined drugs, various reversed phase columns, isocratic and gradient mobile phase systems were tired. Successfuly attempts were performed using a reversed phase RP-YMC pack ODS A A-132 C_{18} (5 μm, 15 cm × 6.0 mm i.d.) column. The mobile phases used were 0.01 M sodium dihydrogen phosphate:methanol: acetonitrile (8:2:1 v/v/v), adjusted to pH 5.5 with phosphoric acid. The optimum wavelength for detection was 265.0 nm at which much better detector responses for two drug were obtained. Under the described HPLC parameters, the respective compounds were clearly separated and their corresponding peaks were sharply developed at reasonable retention times. For quantitative analysis, the analytical data for the calibration graphs were obtained with correlation coefficients of 0.9998 for losartan potassium and

0.9999 for hydrochlorothiazide in binary mixture (Table 2). The good precision of the HPLC procedure was indicated by the relative standard deviation (0.28–0.51%). Results of HPLC analysis of laboratory-prepared mixtures with different proportions of the drug are given in Table 3. The excipients (corn starch, magnesium stearete, lactose and talc) were added to the drug for recovery 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 detection limits (LOD) [29] were 0.023 μg ml^{-1} for losartan potassium, and 0.048 μg ml^{-1} for hydrochlorothiazide while the quantification limits (LOQ) [30] were 0.42 μg ml^{-1} for losartan potassium, 0.64 μg ml^{-1} for hydrochlorothiazide.

4.2. Ratio spectra derivative spectrophotometry

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

Since both losartan potassium and hydrochlorothiazide dissolve much better in acetonitrile:water (1:1 v/v) than in methanol, acetonitrile:water (1:1 v/v) was used first as the solvent for proposed methods.

Losartan potassium and hydrochlorothiazide absorption spectra are recorded and stored Fig. 2(a). For the determination of losartan potassium, the stored absorption spectra of the mixtures are divided by a standard spectrum of hydrochlorothiazide of 16.0 μg ml^{-1}. The ratio spectra thus obtained are smoothed by the use of 16 experimental points and the first derivatives calculated with $\Delta\lambda = 6$ nm are recorded. From the Fig. 3, losartan potassium can be determined in this binary mixture by measuring the analytical signals at 238.360 nm ($^1DD_{238.360}$) where there is no contribution from hydrochlorothiazide.

For determining hydrochlorothiazide, the stored spectra of the mixtures are divided by a standard spectrum of losartan potassium of 30.0 μg ml^{-1}. In the same way as describe above, the content of hydrochlorothiazide was determined by selecting the first derivative of the ratio spectrum in the range 205.0–290.0 nm and measuring the signals at 230.423 nm ($^1DD_{230.423}$) Fig. 4. The influence of $\Delta\lambda$ for obtaining the first derivative of the ratio spectra was tested to obtain the optimum wavelength interval; $\Delta\lambda = 6$ nm was considered as suitable. Under the experimental conditions described, standard calibration curves

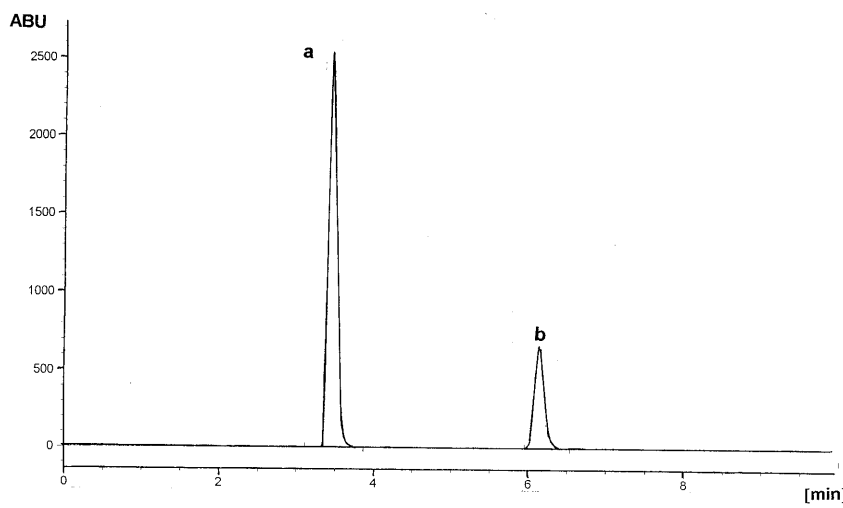


Fig. 1. A typical chromatogram of Hyzaar® film tablet (a) hydrochlorothiazide and (b) losartan potassium.

Table 3
Assay results of losartan potassium and hydrochlorothiazide in laboratory-made mixtures and in commercial film tablets

Sample	Recovery (mean ± S.D.)%[a]					
	Losartan potassium			Hydrochlorothiazide		
	HPLC	Ratio derivative spectrophotometry	Compensation method	HPLC	Ratio derivative spectrophotometry	Compensation method
Synthetic mixtures	99.8 ± 0.5	99.3 ± 0.5	99.0 ± 0.7	99.9 ± 0.87	99.9 ± 0.5	98.6 ± 0.3
	$t = 0.098$[b]	0.658		$t = 0.467$	0.987	
	$F = 1.897$[b]	1.637		$F = 1.402$	1.000	
Commercial tablets[c]	99.8 ± 0.9	99.4 ± 0.6	99.1 ± 0.2	99.2 ± 0.25	99.6 ± 0.9	98.6 ± 0.6
	$t = 0.802$	0.428		$t = 0.331$	0.398	
	$F = 1.048$	1.487		$F = 1.574$	0.289	

[a] Mean and relative standard deviation for ten determinations; percentage recovery from the label claim amount.
[b] Values in parentheses are the theoretical values at $P = 0.95$. Theoretical values at 95% confidence limits $F = 3.18$; $t = 2.26$.
[c] HYZAAR® film tablets were labeled to contain 50.0 mg losartan potassium, 12.5 mg hydrochlorothiazide per tablets respectively.

Table 2
Analytical data for the losartan potassium and hydrochlorothiazide high-performance liquid chromatography and ratio derivative spectrophotometry

Drug	Concentration range (μg ml^{-1})	Linear regression					RSD (%)[a]
		Intercept	±S.E.[b]	Slope	±S.E.[c]	Concentration coefficient (r)	
High-performance liquid chromatography							
Losartan potassium	1.0–30.0	0.001	0.00096	0.025	0.0089	0.9998	0.28
Hydrochlorothiazide	2.0–20.0	0.007	0.00078	0.057	0.0089	0.9999	0.51
Ratio derivative spectrophotometry							
Losartan potassium	10.0–50.0	0.091	0.0008	0.017	0.0008	0.9991	0.63
Hydrochlorothiazide	2.0–30.0	0.019	0.0006	−0.029	0.0010	−0.9984	0.55

[a] RSD, relative standard deviation ($n = 5$).
[b] Standard error of the intercept ($n = 5$).
[c] Standard error of the slope ($n = 5$).

for losartan potassium and hydrochlorothiazide were constructed by plotting absorbance versus concentration.

Various mixture compositions of losartan potassium and hydrochlorothiazide were prepared and tested between 10.0–50.0 μg ml^{-1} for losartan potassium and 2.0–30.0 μg ml^{-1} for hydrochlorothiazide (Table 2). In this method, the synthetic mixtures were prepared by adding known amounts losartan potassium–hydrochlorothiazide. The excipients (corn starch, magnesium stearete, lactose and talc) were added to the drug for recovery studies according to manufacturer's batch formula for per tablets. Recoveries and relative standard deviations of method were found as 99.3% and 0.5% for losartan potassium and 99.9% and 0.5% for hydrochlorothiazide in their binary mixture (Table 3).

Table 2 shows the linearity ranges of the calibration graphs for active ingredients at the suitable wavelengths for determinations of losartan potassium and hydrochlorothiazide. The correlation coefficients were 0.9991 and 0.9984 indicating good linearity. The relative standard deviations were found to be less than 0.63%, indicating reasonable repeatability of the proposed method. The detection limits (LOD) were 0.108 μg ml^{-1} for losartan potassium and 0.326 μg ml^{-1} for hydrochlorothiazide; while the quantification limits (LOQ) were 0.228 μg ml^{-1} for losartan potassium and 0.491 μg ml^{-1} for hydrochlorothiazide.

4.3. Compensation technique

The first derivative spectra of losartan potassium and hydrochlorothiazide in the 210.0–300.0 nm wavelength region are shown in Fig. 2(b). The first derivative spectra were recorded for each reference solution of the analyte components and the ratios of the ^{1}D maxima and ^{1}D minimum were calculated. Table 1 shows the mean values of the ratios calculated for ten different determinations each standard solution. The ratios are constant, characteristic of the pure substance, independent of concentration and whether another absorbing component is present. The determination of losartan potassium concentrations in losartan potassium–hydrochlorothiazide mixtures, the sample cell was filled with the mixture solution and the reference cell was filled, in succession, with a series of reference losartan potas-

sium solutions with different concentrations. The ratios of the mixture calculated from the recorded ^1D spectra was compared with those of hydrochlorothiazide. At the balance point, the ratio of the mixture corresponds to that of hydrochlorothiazide where the concentration of losartan potassium in the mixture in the sample cell is equal to that of the reference solution in the reference cell. For determining the other component, follow the same steps using solutions of pure compound hydrochlorothiazide in the reference cell to determine its concentration in the mixture at the balance point. Conformity with Beer's law was evident in the concentration range from 10.0 to 50.0 μg ml^{-1} of losartan potassium and from 2.0 to 30.0 μg ml^{-1} of hydrochlorothiazide. Five replicate determinations at different concentration levels were carried out to test the precision of the methods. The relative standard deviations were found to be less than 1.69%, indicating reasonable repeatability of the selected method.

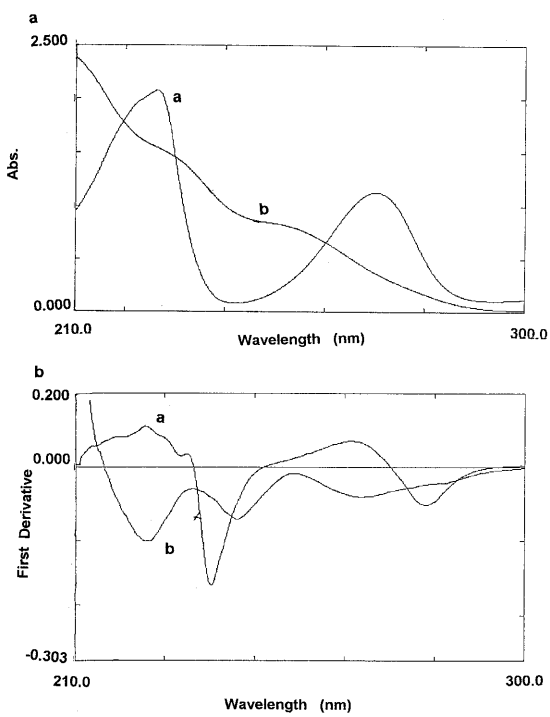


Fig. 2. Zero-order spectra of (a) and first derivative spectra (b) of (a) 25.0 μg ml^{-1} hydrochlorothiazide, and (b) 50.0 μg ml^{-1} losartan potassium in acetonitrile:water (1:1 v/v).

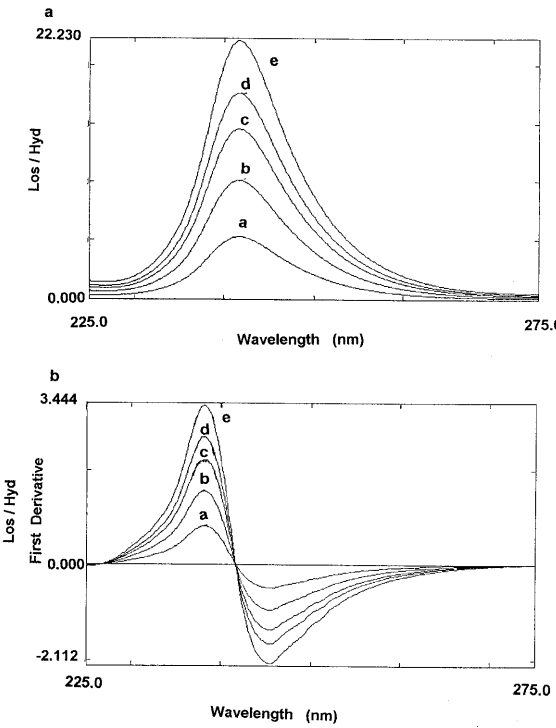


Fig. 3. Ratio spectra (a) and first derivative of the ratio spectra (b) of losartan potassium of (a) 10.0 μg ml^{-1}, (b) 20.0 μg ml^{-1}, (c) 30.0 μg ml^{-1}, (d) 40.0 μg ml^{-1}, (e) 50.0 μg ml^{-1}, when 16.0 μg ml^{-1} hydrochlorothiazide used as divisor in acetonitrile:water (1:1 v/v) ($\Delta\lambda = 6$ nm).

The detection limits (LOD) were 0.64 μg ml^{-1} for losartan potassium, 0.088 μg ml^{-1} for hydrochlorothiazide while the quantification limits (LOQ) were 1.19 μg ml^{-1} for losartan potassium and 0.91 μg ml^{-1} for hydrochlorothiazide.

The HPLC method was chosen as the analytical reference method. Compensation method and ratio derivative spectrophotometry were compared with HPLC method. The results obtained were summarized in Table 3. No significant differences were found between the results obtained by the HPLC method, the compensation method and ratio derivative spectrophotometry, for same batch at the 95% confidence level (student's t-test and F-variance ratio test).

5. Conclusions

The selected methods were found to be sensitive, reproducible and accurate in the analysis of losartan potassium and hydrochlorothiazide in film tablets without the interference any excipients. The most striking feature of the ratio derivative spectrophotometry and compensation technique are its simplicity and rapidity, no requiring time-consuming sample preparation such as filtration, degassing that are needed for HPLC procedure. The HPLC method gives a good resolution between losartan potassium and hydrochlorothiazide within a short analysis time (< 6.1 min). The HPLC method may be considered more specific than other methods, but also more expensive. In general, all the reported methods can be used for the routine quality control analysis of the investigated drugs in two-component pharmaceutical preparations.

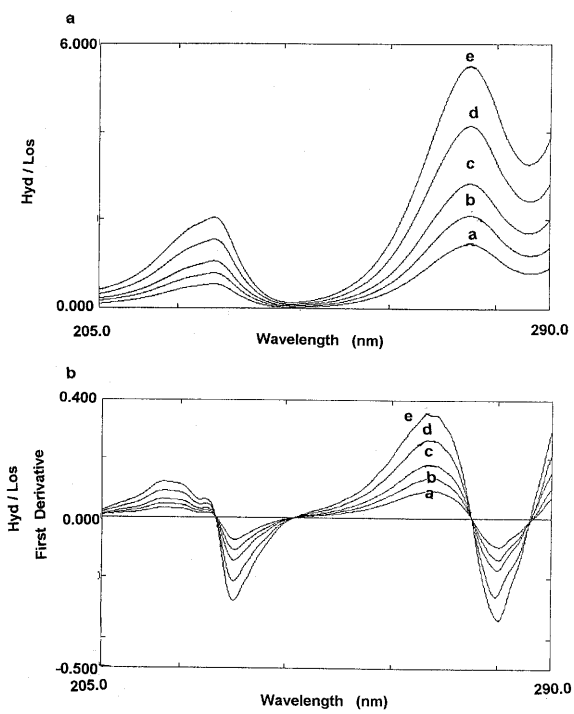


Fig. 4. Ratio spectra (a) and first derivative of the ratio spectra (b) of hydrochlorothiazide of (a) 2.0 μg ml^{-1}, (b) 9.0 μg ml^{-1}, (c) 16.0 μg ml^{-1}, (d) 23.0 μg ml^{-1}, (e) 30.0 μg ml^{-1}, when 30.0 μg ml^{-1} losartan potassium used as divisor in acetonitrile:water (1:1 v/v) ($\Delta\lambda = 6$ nm).

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