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Simultaneous determination of benazepril hydrochloride and hydrochlorothiazide in tablets by second-order derivative spectrophotometry

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Abstract

A second-order derivative spectrophotometric method for the simultaneous determination of benazepril hydrochloride and hydrochlorothiazide in pharmaceutical dosage forms is described. The determination of benazepril hydrochloride in the presence of hydrochlorothiazide was achieved by measuring the second-order derivative signals at 253.6 and 282.6 nm, while the second-order derivative signal at 282.6 nm was measured for the determination of hydrochlorothiazide. The linear dynamic ranges were 14.80–33.80 μg ml^{-1} for benazepril hydrochloride and 18.50–42.20 μg ml^{-1} for hydrochlorothiazide, the correlation coefficient for the calibration graphs were better than 0.9998, $n = 5$, the precision (%RSD) was better than 1.43% and the accuracy was satisfactory ($E_r < 0.99\%$). The detection limits were found to be 2.46 and 1.57 μg ml^{-1} for benazepril hydrochloride and hydrochlorothiazide, respectively. The method was applied in the quality control of commercial tablets and proved to be suitable for rapid and reliable quality control.

Keywords: Benazepril hydrochloride; Hydrochlorothiazide; Derivative spectrophotometry; Tablet formulations

1. Introduction

Benazepril hydrochloride [1], Scheme 1(I), is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor, which is shown to be effective in the treatment of hypertension and congestive heart failure. The compound is a prodrug, which is hydrolysed in vivo to its active form, benazeprilat [2]. Hydrochlorothiazide [3], Scheme 1(II), is an antihypertensive diuretic agent which is indicated in the management of hypertension. Its combination with benazepril increases the antihypertensive effects.

Benazepril hydrochloride is not official in any pharmacopoeia and a literature survey reveals several methods including gas chromatography–mass spectroscopy (GC–MS) [4], high performance liquid chromatography (HPLC) [5,6], and derivative spectrophotometric [7]. A variety of

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methods have also been reported for the determination of hydrochlorothiazide including near-IR spectroscopy [8], derivative spectrophotometry [9,10], thin layer chromatography (TLC) [11], and HPLC [12,13]. Recently, an absorbancy ratio method and a first-order derivative spectrophotometric method have been described for the simultaneous determination of both of these two compounds in pharmaceutical tablet [14]. However, no HPLC procedure has been described for their simultaneous determination in pharmaceutical formulations or in biological fluids. The proposed second-order derivative spectrophotometric method was compared to a HPLC method, which is under development in our laboratory.

As the combination of these two compounds in antihypertensine therapy has become popular in recent years, we thought that it would be of particular interest to develop a rapid, simple, sensitive and reliable method for their simultaneous determination. This paper describes another application of derivative spectrophotometry using also the simultaneous equation method for the determination of benazepril hydrochloride and hydrochlorothiazide in tablet formulations.

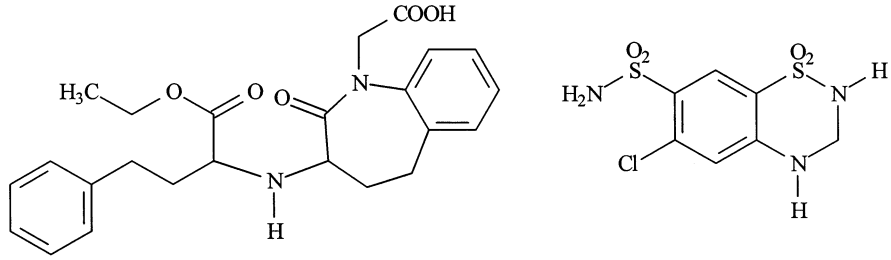
Derivative spectrophotometry consists of calculating and plotting one of the mathematical derivatives of a spectral curve. Thus, it offers a convenient solution to a number of analytical problems, such as resolution of multicomponent systems, reduced sample turbidity and enhancement of spectral details. Several papers on the theoretical aspects of derivative spectrophotometry have been reported [15,16]. Moreover, the recognised resolution enhancement of derivative UV spectrophotometry has been used advantageously in the determination of drugs in biological fluids [17–21], in the analysis of multicomponent mixtures in pharmaceutical preparations [22–25], and in stability studies of drugs [26,27].

In this work, the derivative UV–Vis spectrophotometric technique has been utilised successfully to overcome the problem of interference due to irrelevant spectral overlapping caused by excipient matrices present in the pharmaceutical formulations. Moreover, it offers an enhancement of sensitivity without the requirement of extraction or separation of the tested compounds. The reduction of solvent usage and short analysis time, are also important advantages towards the previously mentioned spectrophotometric method [14], allowing the application of the method to quality control laboratories were a great number of samples are analysed. The method described here, yielded accurate, rapid and reproducible results for the determination of these two compounds in tablet formulations. Results obtained by the proposed method are in good agreement with those obtained by the HPLC procedure that is under development in our laboratory.

2. Experimental

2.1. Materials

Methanol and hydrochloric acid (analytical-reagent grade) were purchased from E. Merck,



I II

Scheme 1. Chemical structure of: (I) benazepril hydrochloride; and (II) hydrochlorothiazide.

Darmstadt, Germany. Water was deionised and further purified by means of a Milli-Q Plus Water Purification System, Millipore Ltd. Benazepril hydrochloride, and hydrochlorothiazide of pharmaceutical purity grade were kindly provided by Novartis Pharma AG, Basel, Switzerland. All substances were used without any further purification. Cibadrex (10 + 12.5) and Cibadrex (20 + 25) tablets are products of Novartis Pharma AG; each tablet was labelled to contain 10.0 and 20.0 mg of benazepril hydrochloride, and 12.5 and 25.0 mg of hydrochlorothiazide, respectively. The excipients present in tablets are: Hydroxypropyl methylcellulose (hypromellose), hydrogenated castor oil, lactose, polyvinylpyrrolidone XL, iron oxide red, E172, macrogol 8000, talk and titanium oxide.

2.2. Apparatus

Spectra were recorded on a Perkin-Elmer, Model Lambda 7, double-beam UV–Vis spectrophotometer with the capability of derivative mode. The optimised operating conditions for spectrophotometric measurements were: derivative mode ^2D ($d^2A/d\lambda^2$), scan speed 240 nm min^{-1}, response 2 s, slit-width 2 nm, delta-wavelength ($\Delta\lambda$), 6 nm. Derivative UV–Vis spectra were recorded over a wavelength range 235–310 nm using 1.0 cm matched quartz cells. A Metrohm, Model 654 Herisau pH meter was used for all pH measurements.

2.3. Standard solutions

Stock standard solutions of benazepril hydrochloride, Bz, 1.0 mg ml^{-1}, and hydrochlorothiazide, Hy, 1.0 mg ml^{-1}, were prepared by dissolving the compounds in methanol. These solutions were stored in the dark under refrigeration and were found to be stable for several weeks.

Standard solutions of Bz and Hy in the range 14.8–33.8 and 18.5–42.2 μg ml^{-1}, respectively, were prepared daily by the addition of the appropriate stock standard solutions of the compounds in 0.1 M HCl. Mixed standard solutions containing 14.8–33.8 and 18.5–42.2 μg ml^{-1} of Bz and Hy in a ratio 0.8: 1.0, respectively were also prepared in 0.1 M HCl. All standard solutions were measured during a period of two days and found to be stable.

2.4. Procedure

A calibration curve was constructed by assaying mixed standard solutions of Bz and Hy in a ratio 0.8:1.0, in 0.1 M HCl. The second-order derivative spectra of these solutions were recorded over the wavelength range 220–310 nm against a blank of 0.1 M HCl. The derivative value at 282.6 nm, $^2D^t_{282.6}$ was measured for the determination of Hy in the presence of Bz.

The Bz determination was achieved by measuring the derivative value at 253.6 nm, $^2D^t_{253.6}$ to which both substances contribute; this can be corrected by a simple mathematical equation for the contribution deriving from Hy (determined as previously described). Therefore, the total derivative value at 253.6 nm, $[^2D^t_{253.6}]$ obtained from the analysis of mixed standard solutions of Bz and Hy in a ratio 0.8: 1.0 was measured. The contribution due to Bz was calculated, by subtracting from $^2D^t_{253.6}$ the derivative value $[^2D'_{253.6}]$ determined for Hy alone. The derivative value $^2D'_{253.6}$ was determined using another calibration curve, which was constructed by assaying standard solutions of Hy alone, in 0.1 M HCl. The derivative values at 253.6 nm, $^2D_{253.6}$ were measured and found linearly related to the Hy concentration. Through this calibration curve, the derivative values at 253.6 nm, $^2D'_{253.6}$ were then evaluated using the experimental concentrations of Hy in a mixture with Bz. The difference of these derivative values $[^2D^t_{253.6} - ^2D'_{253.6}]$ was found to be linearly related to the concentration of Bz.

From the above mentioned equations, the following expression can be derived which gives the concentration of Bz (C_{Bz}) as a function of the derivative values at 253.6 nm $[^2D^t_{253.6}]$ for Bz and Hy and at 282.6 nm $[^2D_{282.6}]$ for Hy:

$$C_{Bz} = \frac{^2D^t_{282.6}}{\alpha_3} - \frac{(\alpha_1 \times {}^2D^t_{282.6}) + (\alpha_1 \times b_2)}{(\alpha_2 \times \alpha_3)} - \frac{b_1 - b_3}{\alpha_3}$$

where: C_{Bz}, concentration of Bz in μg ml^{-1}; $^2D^t_{253.6}$ and $^2D^t_{282.6}$, derivative values at 253.6 and 282.6 nm, respectively, of mixed standard solution

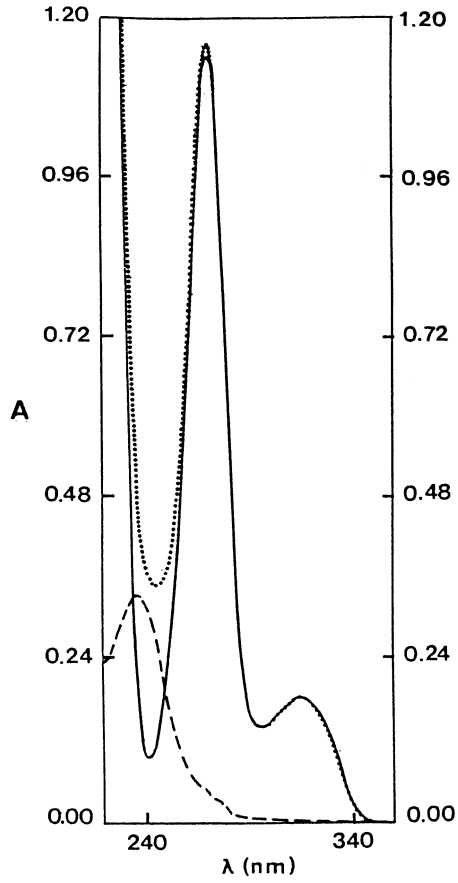


Fig. 1. Absorption (zero-order) UV spectra of benazepril hydrochloride (20.0 μg ml^{-1}, broken line), hydrochlorothiazide (25.0 μg ml^{-1}, continuous line), and their mixture (dotted line).

of Bz and Hy in a ratio 0.8: 1.0; α_1 and b_1, slope and intercept, respectively, of the regression equation ($^2D^t_{253.6}$ versus concentration of Hy (C_{Hy}) in μg ml^{-1} of mixed standard solutions;α_2 and b_2, slope and intercept, respectively, of the regression equation ($^2D_{282.6}$ versus C_{Hy}); α_3 and b_3, slope and intercept, respectively, of the regression equation ($[^2D^t_{253.6} - {}^2D'_{253.6}]$ versus C_{Bz}).

The precision and accuracy of the derivative spectrophotometric method for the determination of Bz and Hy, were evaluated by analysing three series of mixed standard solutions of the compounds, at concentrations of 14.8, 24.4 and 33.8 μg ml^{-1} for Bz and 18.5, 30.5 and 42.2 μg ml^{-1} for Hy.

In order to determine the effect of the excipients used in the formulation of tablets on the determination of Bz and Hy, the standard addition method [28] was used. Thus, five equal amounts of powdered tablets equivalent to 4.0 mg of Bz and 5.0 mg of Hy, were spiked with different amounts of reference standards of Bz and Hy. The samples were analysed as mentioned in the assay procedure. The second order derivative values at 253.6 nm, $^2D^t_{253.6}$, and 282.6 nm, $^2D^t_{282.6}$, were then measured and the simultaneous equation method was used for the determination of both compounds.

2.5. Assay of pharmaceutical preparations

A total of 20 tablets were weighed and finely pulverised. An appropriate portion of this powder, equivalent to 10.0 mg of Bz and 12.5 mg of Hy was transferred to a 25-ml volumetric flask with 20 ml of methanol. The solution was sonicated for 10 min, followed by shaking by mechanical means for 20 min and finally diluted to volume with methanol. A portion of this solution was centrifuged at 4000 rev min^{-1} ($2890 \times g$) for 15 min. A 1.5-ml aliquot was transferred to a 25-ml volumetric flask and diluted to volume with 0.1 M HCl. The same procedure was followed for the content uniformity test, using one tablet per sample.

3. Results and discussion

3.1. Spectrophotometric measurements

A thorough investigation was conducted in order to choose the optimum solvent medium for the spectrophotometric determination of Bz and Hy. The best results for their simultaneous determination in tablet formulations were obtained in acidic solutions (0.1 M HCl).

The zero-order absorption spectra of solutions of 20.0 μg ml^{-1} Bz, 25.0 μg ml^{-1} Hy and their mixture in a ratio 0.8: 1.0, in 0.1 M HCl, over the wavelength range 220–360 nm are shown in Fig. 1. Hy exhibits two peaks at 316.4 and 271.6 nm; Bz also exhibit a peak at 237.2 nm. Due to the

extensive overlap of spectral bands conventional UV spectrophotometry cannot be used for the quantification of both substances in the presence of each other.

Fig. 2 shows the second-order derivative spectra of: (a) Bz at concentrations 14.8, 19.6, 24.4, 29.2 and 33.8 μg ml^{-1}; (b) Hy at concentrations 18.5, 24.5, 30.5, 36.5 and 42.2 μg ml^{-1}; and (c) their mixture in a ratio 0.8: 1.0, in 0.1 M HCl. The derivatization of the zero-order spectra leads to an improvement of the spectral details as several sharp peaks appear. Moreover, any irrelevant absorption caused by formulation components of the tablets makes little contribution to the derivative spectrum. Therefore, this technique in combination with the simultaneous equation method permits a more selective identification and determination of the two compounds in mixture.

The determination of Hy was performed by measuring the derivative signals at 282.6 nm, $^2D^t_{282.6}$. Preliminary experiments showed the derivative signals at 253.6 nm, $^2D_{253.6}$ were proportional to the concentrations of Bz alone. Thus, the determination of Bz in the presence of Hy can

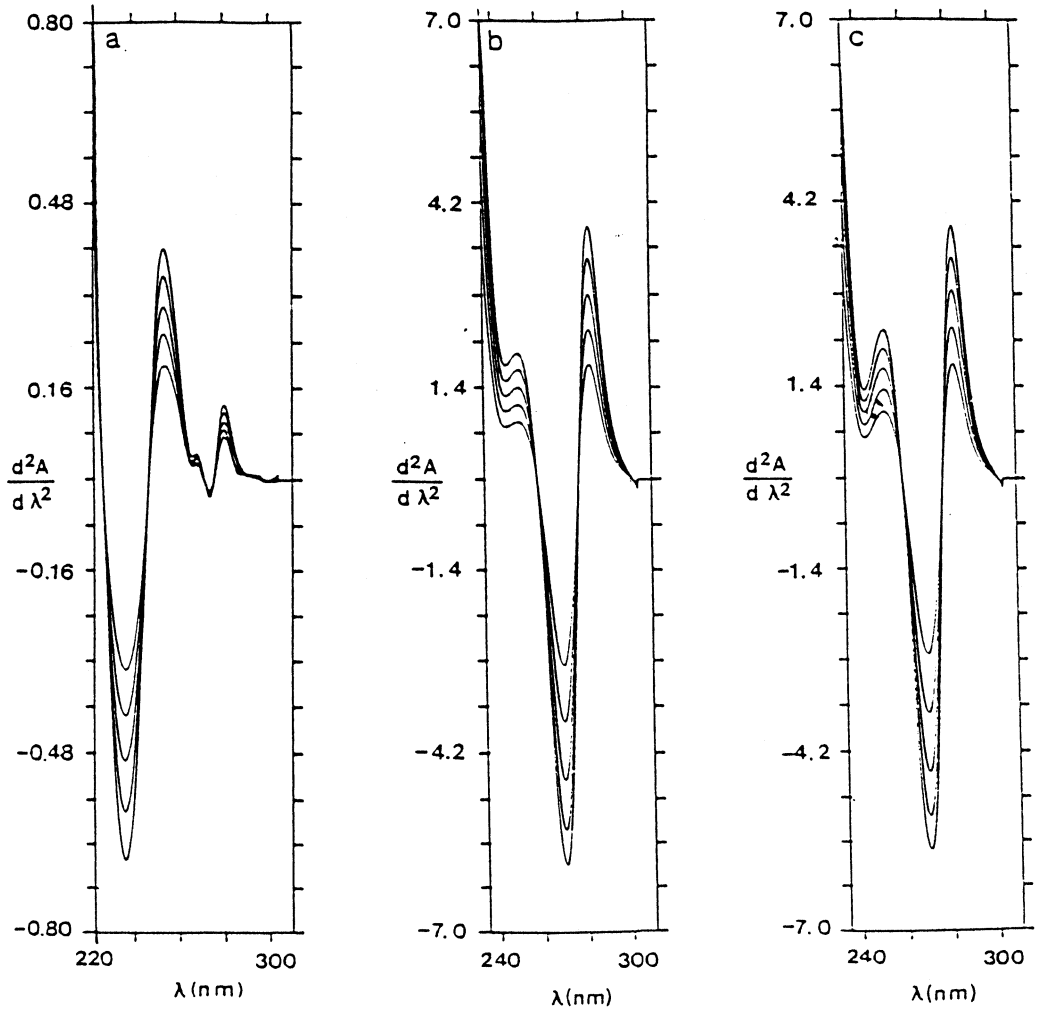


Fig. 2. Second-order derivative UV–Vis spectra of different concentrations of: (a) benazepril hydrochloride (14.8–33.8 μg ml^{-1}); (b) hydrochlorothiazide (18.5–42.2 μg ml^{-1}); and (c) their mixture in a ratio 0.8:1.0.

Table 1
Calibration data for the determination of benazepril hydrochloride and hydrochlorothiazide by second-order derivative spectrophotometry

Concentration range of benazepril (μg ml^{-1})	Concentration range of hydrochlorothiazide (μg ml^{-1})	Regression equations*		r[§]	SE[‡]
–	18.50–42.20	${}^2D_{282.6} = 0.081\ (\pm 0.009)C_{Hy} - 0.014\ (\pm 0.031)$	(1a)	0.9998	0.022
–	18.50–42.20	${}^2D_{253.6} = 0.041\ (\pm 0.003)C_{Hy} - 0.022\ (\pm 0.011)$	(2a)	0.99991	0.018
14.80–33.80	–	${}^2D_{253.6} = 0.013\ (\pm 0.002)C_{Bz} - 0.013\ (\pm 0.004)$	(3a)	0.9998	0.010
14.80–33.80	18.50–42.20	${}^2D^t_{282.6} = 0.086\ (\pm 0.005)C_{Hy} - 0.059\ (\pm 0.017)$	(4a)	0.99993	0.012
Equations for the determination of benazepril hydrochloride $\Delta D = {}^2D^t_{253.6} - {}^2D'_{253.6}$ versus C_{Bz}		$\Delta D = 0.014\ (\pm 0.004)C_{Bz} + 0.011\ (\pm 0.011)$	(5a)	0.9991	0.025
Combination of the calibration Eqs. (1a), (2a), (4a) and (5a)		$C_{Bz} = 71.43 \times {}^2D_{253.6} - 33.06 \times {}^2D_{282.6} + 2.79$		0.9998	–

* Derivative value at the corresponding wavelength versus amount of the concentration of the compound measured (μg ml^{-1}); five standards.
§ Correlation coefficient.
‡ Standard error of the estimate.

be achieved by measuring the derivative signals of the second order derivative spectrum at 253.6 nm, ${}^2D^t_{253.6}$, and at 282.6 nm, ${}^2D^t_{253.6}$, and using the previously described simultaneous equation method.

3.2. Selection of optimum instrumental conditions

The wavelength scanning has virtually no effect on the derivative signal obtained digitally. Hence, a fast scan speed of 240 nm min^{-1} was selected. The main instrumental parameter that affects the shape of the derivative spectra and the signal to noise ratio is the wavelength increment over which derivatives are obtained, delta-wavelength ($\Delta\lambda$). Increasing $\Delta\lambda$ improves the signal to noise ratio, thus decreasing the fluctuation in a derivative spectrum. Several $\Delta\lambda$ values were tested and $\Delta\lambda = 6$ nm was chosen in order to give an adequate signal to noise ratio. A response time of 2 s was also chosen as the optimum in order to achieve a satisfactory signal to noise ratio.

3.3. Statistical analysis of spectrophotometric data

Under the experimental conditions described above, linear relationships between the selected derivative values and the corresponding concentrations of the compounds tested were observed, as shown by the equations presented in Table 1.

Data for the variation of precision and accuracy given in Table 2, indicate for Bz%RSD = 0.16–1.43% and $E_r\% = -0.6$–0.2 and for Hy%RSD = 0.05–0.22% and $E_r\% = -0.4$–0.2.

The detection limits, determined experimentally, were found to be 2.46 and 1.57 μg ml^{-1} for Bz and Hy, respectively.

3.4. Assay of tablets-content uniformity

The proposed methods were evaluated in the assay of commercially available tablets containing mixture of Bz and Hy in a ratio 0.8: 1.0. A total of ten replicate determinations were carried out on an accurately weighted amount of the pulverised tablets equivalent to 10.0 mg of Bz and 12.5 mg of Hy. The results obtained by the derivative spectrophotometric method gave a mean of 9.95 ± 0.32 with a percentage relative standard deviation (%RSD) of 3.21 for Bz, and of 12.43 ± 0.37 with a %RSD of 2.98 for Hy.

The proposed method is suitable for the content uniformity test, where a great number of assays on individual tablets are required. Commercially available tablets containing mixture of Bz and Hy in a ratio 0.8: 1.0 were analysed and the results are given in Table 3. The indicated values are the mean of ten different analyses of the same commercial batch. Recoveries achieved were in accordance with the actual content of these two compounds in tablets.

In order to assess the specificity of the proposed method, recoveries studies were performed by spiking sample powders with appropriate amounts of the reference standard of both compounds. Two calibration curves were then constructed by plotting the amount of the drug found (mg), versus the amount of the drugs added (mg) for each of the two compounds. The following linear regression equations were obtained through regression analysis of data:

Table 2
Accuracy and precision for the determination of benazepril hydrochloride and hydrochlorothiazide by second-order derivative spectrophotometry

Nominal concentration (μg ml^{-1})		Assayed concentration (μg ml^{-1})					
Benazepril	Hydrochlorothiazide	Benazepril			Hydrochlorothiazide		
		Mean ± SD ($n = 5$)	RSD%*	E_r%§	Mean ± SD ($n = 5$)	RSD%*	E_r%§
14.80	–	14.77 ± 0.11	0.74	−0.2	–	–	–
–	18.50	–	–	–	18.46 ± 0.04	0.22	0.2
14.80	18.50	14.72 ± 0.21	1.43	−0.5	18.51 ± 0.01	0.05	0.1
24.40	–	24.42 ± 0.04	0.16	0.1	–	–	–
–	30.50	–	–	–	30.38 ± 0.06	0.20	−0.4
24.40	30.50	24.36 ± 0.05	0.20	−0.2	30.44 ± 0.05	0.16	−0.2
33.80	–	33.89 ± 0.08	0.24	0.3	–	–	–
–	42.20	–	–	–	42.13 ± 0.02	0.05	−0.2
33.80	42.20	33.59 ± 0.23	0.68	−0.6	42.23 ± 0.04	0.09	0.1

* Percentage relative standard deviation.
§ Relative percentage error.

Table 3
Assay of commercial formulations containing benazepril hydrochloride and hydrochlorothiazide by second-order derivative spectrophotometry

Commercial formulation	Benazepril hydrochloride found (mg/tablet)*		Hydrochlorothiazide found (mg/tablet)*	
	Mean ± SD ($n = 10$)	Recovery (%)	Mean ± SD ($n = 10$)	Recovery (%)
Cibadrex (10/12.5)	9.94 ± 0.13	99.4	12.49 ± 0.12	99.9
Cibadrex (20/25)	19.91 ± 0.21	99.6	24.83 ± 0.09	99.3

* The indicated values are the means of ten different analyses of the same commercial batch.

Table 4
Recoveries of benazepril hydrochloride and hydrochlorothiazide in spiked commercial samples

Drug	Amount added (mg/tablet)	Amount found (mg/tablet)	m*	Recovery (%)§
Benazepril	5.0	8.99	*0.998*	*99.8*
	8.0	11.98		
	10.0	13.95		
	12.5	16.49		
Hydrochlorothiazide	6.25	11.19	*1.004*	*100.4*
	10.0	14.99		
	12.5	17.43		
	15.6	20.60		

* m is the slope of the linear regression analysis of the amount found versus the amount added.
§ Recovery (%) $= m \times 100$.

Table 5
Relative differences between second-order derivative spectrophotometry and high performance liquid chromatography in the assays of commercial formulations

Commercial formulation	Benazepril hydrochloride found (mg/tablet)			Hydrochlorothiazide found (mg/tablet)		
	$^2D_{253.6}$ and $^2D_{282.6}$	HPLC method	Relative difference (%)	$^2D_{282.6}$	HPLC method	Relative difference (%)
Cibadrex (10/12.5)	9.95	9.97	−0.2	12.45	12.47	−0.1
Cibadrex (20/25)	19.93	19.87	0.3	25.01	24.82	0.7

$$C^{f}_{Bz} = 0.999(\pm 0.004) \times C^{a}_{Bz} + 3.99(\pm 0.04), \quad r = 0.99998 \quad (1)$$

$$C^{f}_{Hy} = 1.004(\pm 0.005) \times C^{a}_{Hy} + 4.91(\pm 0.06), \quad r = 0.99997 \quad (2)$$

where: C^{f}_{Bz} and C^{f}_{Hy} are the amounts found (mg) for Bz and Hy, respectively; and C^{a}_{Bz} and C^{a}_{Hy} are the amounts added (mg) for Bz and Hy, respectively; r is the correlation coefficient of the calibration equation.

The y-axis intercept of the above mentioned linear regression equations indicate the amount (mg) of the drug found in the powdered tablets, while the percentage of each slope was used to calculate the %recovery. The results presented in Table 4, indicate that there is no interference from the excipients used in the formulation of the tablets.

The second-order derivative spectrophotometric method was further evaluated by comparison with an HPLC method, which is under development in our laboratory was carried out. Commercially available tablets containing mixture of Bz and Hy in a ratio 0.8: 1.0 were analysed by both methods and the results are presented in Table 5. The indicated values are the mean of ten different analyses of the same commercial batch. The relative difference between the proposed derivative spectrophotometric method and HPLC varied from −0.2 to 0.3% for the determination of Bz and from −0.1 to 0.7% for the determination of Hy. No significant difference was observed between these two methods.

The proposed procedure was successfully applied to the determination of benazepril hydrochloride and hydrochlorothiazide in tablets. It is a simple, reliable and rapid method that could be used for routine analysis in quality control laboratories.

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