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Dissolution tests of benazepril–HCl and hydrochlorothiazide in commercial tablets: comparison of spectroscopic and high performance liquid chromatography methods

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Abstract

Simple, rapid and reliable spectroscopic methods (absorbance ratio and Vierordt) were compared with HPLC for quantitative determination in dissolution tests of benazepril–HCl (BNZ) and hydrochlorothiazide (HCT) in commercial tablets. A 249 nm wavelength was chosen as the isosbestic point in the absorbance ratio method, and the absorbance ratios A_{236}/A_{249} nm for BNZ and A_{269}/A_{249} nm for HCT were used for calculation of regression equations. For the Vierordt method, A_1^1 values (% 1.1 cm) obtained at 236 and 269 nm for both substances were used for quantitative analyses of BNZ and HCT. In the HPLC method, simultaneous determination of BNZ and HCT from dissolution medium was achieved using the mobile phase containing phosphate buffer (0.01 M, pH 6.2) and acetonitrile (65:35) on a Supelcocil LC-18 (4.6 × 250, 5.6 mm) reversed phase column. Dissolution tests of commercial tablets were carried out according to USP XXII paddle method in 0.1 N HCl at 50 rpm at 37 ± 0.5°C. Comparison of the dissolution data from the HPLC and two spectroscopic methods indicated that spectroscopic and HPLC methods were in good correlation with each other. Therefore, it was concluded that both spectroscopic methods as well as HPLC can be used in routine analyses of BNZ and HCT in dissolution tests of commercial tablets.

Keywords: Benazepril–HCl; Hydrochlorothiazide; Dissolution rate; Spectroscopy; High performance liquid chromatography

1. Introduction

Benazepril–HCl (BNZ) (3-[(1-ethoxycarbonyl-3-phenyl-(1S)-propyl)amino]-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1-acetic acid hydrochloride), an angiotensin-converting enzyme (ACE) inhibitor, is currently used as a new substance in the treatment of hypertension [1]. The antihypertensive effect of BNZ is known to occur after the biotransformation to benazeprilat, which is the actual substance which inhibits the transformation of angiotensin I to angiotensin II by inhibiting ACE [1]. Hydrochlorothiazide (HCT) (6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide) is a diuretic which inhibits the active reabsorption of sodium from distal tubulus, also included in antihypertensive drugs [2].

As is known, dissolution testing is a regular quality control procedure in good manufacturing practice, and the dissolution data are also a substantial parameter for evaluation of bioavailability of drugs. So far, BNZ and HCT binary mixture has not been monographed in pharmacopoeia, and therefore no analytical procedure has been found in the literature survey for determination of BNZ and HCT binary mixtures for quality control and dissolution tests of tablets containing these substances. According to the literature survey, quantitative determination of HCT alone and its binary mixtures with different substances other than BNZ were conducted using visible spectrophotometry [3–5], UV

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Table 1
The slope (a), intercept (b), and correlation coefficients (r^2) for BNZ and HCT were determined according to the absorbance ratio method

$y = ax + b$	BNZ	HCT
Slope (a)	0.976	4.629
Intercept (b)	0.884	0.343
r^2	0.9968	0.9997

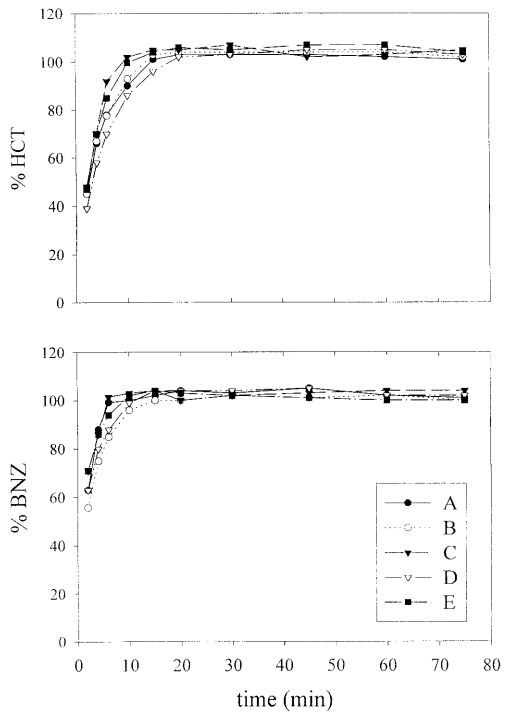

Fig. 1. Dissolution profiles of HCT and BNZ in commercial tablets (A–E) determined according to the absorbance ratio method as described in Section 2. Data points are observed values with the lines representing each tested tablet.

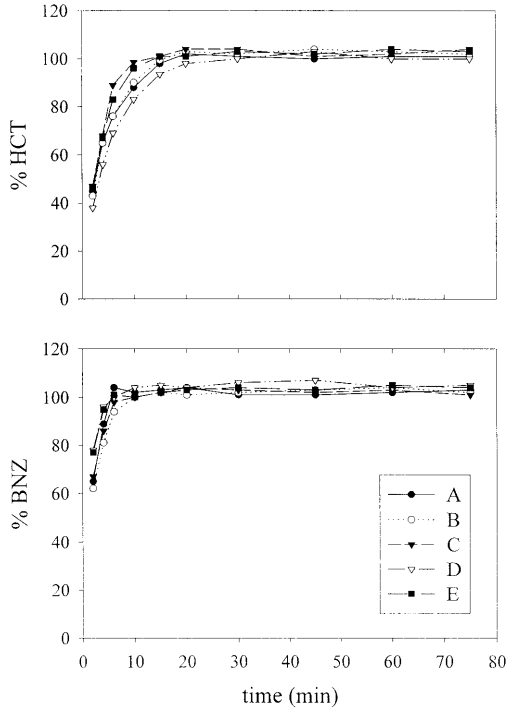

Fig. 2. Dissolution profiles of HCT and BNZ in commercial tablets (A–E) determined according to the Vierordt method as described in Section 2. Data points are observed values with the lines representing each tested tablet.

Table 3
The slope (a), intercept (b), and correlation coefficients (r^2) for BNZ and HCT were determined according to the HPLC method

$y = ax + b$	BNZ	HCT
Slope (a)	0.0886	0.0755
Intercept (b)	0.075	0.0001
r^2	0.9966	0.9998

Table 2
The $A\begin{matrix}1\\1\end{matrix}$ values for BNZ and HCT were determined according to the Vierordt method

a_1	a_2	b_1	b_2	a	b	m
599	112.6	23.6	199.1	0.188	8.44	A_2/A_1

a_1: $A\begin{matrix}1\\1\end{matrix}$ value for HCT in 0.1 N HCl at 269 nm
a_2: $A\begin{matrix}1\\1\end{matrix}$ value for HCT in 0.1 N HCl at 236 nm
b_1: $A\begin{matrix}1\\1\end{matrix}$ value for BNZ in 0.1 N HCl at 269 nm
b_2: $A\begin{matrix}1\\1\end{matrix}$ value for BNZ in 0.1 N HCl at 236 nm
A_1: The absorbance value measured at 269 nm
A_2: The absorbance value measured at 236 nm
$a = a_2/a_1$
$b = b_2/b_1$

spectroscopy [6–8], fluorimetry [9], derivative spectrophotometry [10,11], gas–liquid chromatography [12], and high performance liquid chromatography (HPLC) [11,13–15]. For BNZ alone, so far, a few analytical procedures have been reported for determination of BNZ and its active metabolites in plasma. These methods were based on gas chromatography–mass spectrometry (GC–MS) [16], and enzyme immunoassay [17]. In this study, we aimed to prove that spectroscopic methods (absorbance ratio and Vierordt) would be less time consuming and more reliable for convenient dissolution tests of HCT and BNZ binary mixtures in pharmaceutical preparations as well as the HPLC method.

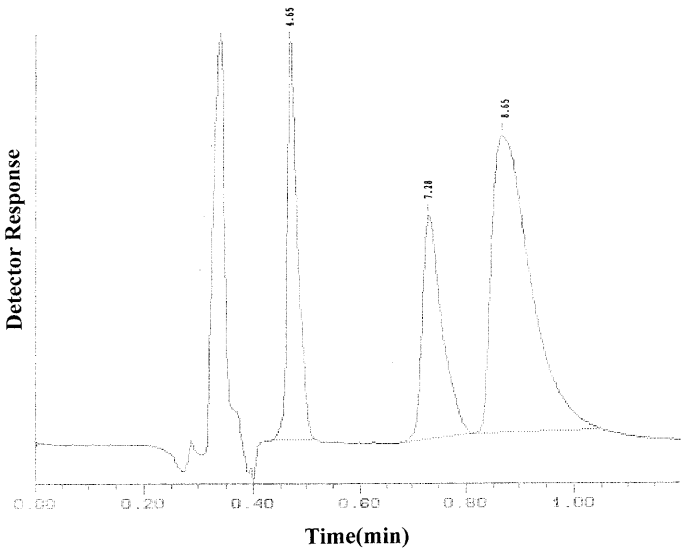

Fig. 3. HPLC separation profile of HCT, BNZ and internal standard TMP. HCT, 4.65 min; TMP, 7.28 min; BNZ, 8.65 min.

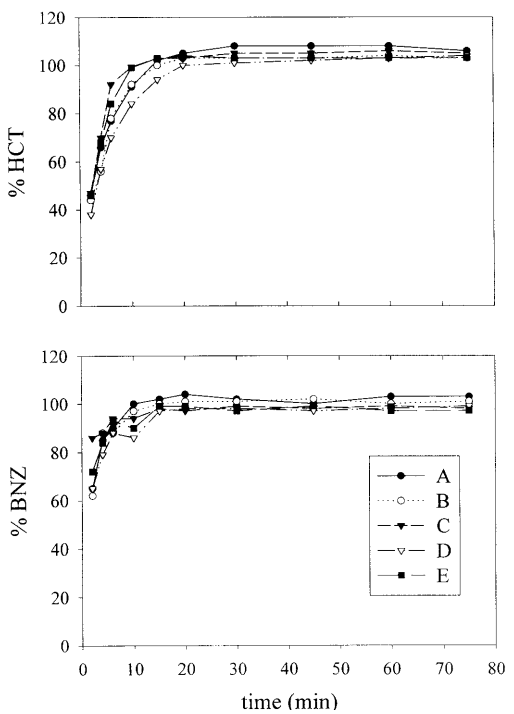

Fig. 4. Dissolution profiles of HCT and BNZ in commercial tablets (A–E) determined according to the HPLC method as described in Section 2. Data points are observed values with the lines representing each tested tablet.

2. Experimental

2.1. Chemicals

Standard BNZ and HCT were obtained from Novartis Inc. (Istanbul, Turkey), and internal standard trimethoprim (TMP) was received from Roche Inc. (Istanbul, Turkey). Tablets of Cibadrex® (5 mg BNZ + 6.25 mg HCT) with two different serial numbers were procured from Novartis Inc. (Istanbul, Turkey). Tablets coded as A, B, C for serial no. 1, and D, E for serial no. 2 were applied in dissolution tests. HPLC grade acetonitrile was purchased from Merck (Germany). All other assay reagents and buffer components were analytical grade. The water used was double distilled.

2.2. Apparatus

2.2.1. Spectrophotometer

A Beckmann DU 650 series, double beam spectrophotometer with a fixed slit width (2 nm), a 1 cm quartz cell over the range 200–400 nm was employed.

2.2.2. High performance liquid chromatography

HPLC analyses were carried out with a Waters Systems chromatograph equipped with a Waters model 481 variable wavelength UV detector, a model 510 pump, a model 717plus refrigerated autosampler, and a Waters Baseline 810 data workstation. All HPLC analyses were carried out on a Supelcoil LC-18 (Supelco, USA) reversed phase column (5 μm, 4.6 × 250 mm).

2.2.3. Dissolution apparatus

The dissolution rates of BNZ and HCT from commercial tablets were measured using Caleva 7 ST dissolution apparatus (G.B. Caleva Inc., UK).

2.3. Methods

2.3.1. Spectroscopic methods

2.3.1.1. Vierordt method. The following stock solutions of BNZ and HCT were prepared for determination of A_1^1 values. Sol-H_1: 0.1% w/v solution of HCT was prepared in methanol. Sol-H_2: 10 ml of Sol-H_1 was diluted to 100 ml in 0.1 N HCl. Sol-B_1: 0.1% w/v solution of BNZ was

Table 4
The kinetic assessment of release data of the HPLC method [a]

F	First order			Hixson–Crowell			Peppas equation			RRSBW			
	k_r	r^2	SWSD	K	r^2	SWSD	k_p	n	r^2	T	β	r^2	SWSD
HA	13.48	0.854	2.59	1.33	0.886	1.98	0.658	0.110	0.813	2.98	0.819	0.821	2.362
HB	17.93	0.521	0.11	1.47	0.505	1.49	0.473	0.210	0.746	3.1	1.1	0.835	0.459
HC	6.61	0.424	1.25	1.23	0.607	1.99	0.493	0.197	0.679	3.83	0.712	0.818	1.074
HD	16.86	0.654	0.39	1.43	0.638	1.22	0.413	0.244	0.799	4.22	1.16	0.891	0.835
HE	17.98	0.522	0.016	1.48	0.488	1.77	0.535	0.177	0.682	2.59	1.03	0.844	0.236

[a] F, code of formulation; k_r, first order release rate constant; K, rate constant obtained from Hixson–Crowell kinetic; k_p, release constant; n, diffusional exponent; $T_{63.2\%}$, time for release of 63.2% of the drug; β, shape factor; r^2, determination coefficient; SWSD, sum of weighed squared deviations.

Table 5
The kinetic assessment of release data of the Vierordt method [a]

F	First order			Hixson–Crowell			Peppas equation			RRSBW			
	k_r	r^2	SWSD	K	r^2	SWSD	k_p	n	r^2	T	β	r^2	SWSD
HA	16.96	0.657	0.085	1.44	0.614	1.51	0.492	0.197	0.770	3.49	1.09	0.898	0.194
HB	15.95	0.801	0.249	1.44	0.691	2.24	0.699	0.0987	0.712	2.26	0.862	0.933	0.197
HC	17.07	0.659	0.059	1.45	0.579	1.54	0.489	0.200	0.749	3.38	1.09	0.904	0.153
HD	18.04	0.522	0.061	1.48	0.456	1.89	0.555	0.168	0.645	1	0.742	0.845	2.071
HE	17.98	0.521	0.016	1.48	0.489	1.75	0.405	0.248	0.814	2.61	1.04	0.844	0.248

[a] F, code of formulation; k_r, first order release rate constant; K, rate constant obtained from Hixson–Crowell kinetic; k_p, release constant; n, diffusional exponent; $T_{63.2\%}$, time for release of 63.2% of the drug; β, shape factor; r^2, determination coefficient; SWSD, sum of weighed squared deviations.

Table 6
The kinetic assessment of release data of the absorbance ratio method [a]

F	First order			Hixson–Crowell			Peppas equation			RRSBW			
	k_r	r^2	SWSD	K	r^2	SWSD	k_p	n	r^2	T	β	r^2	SWSD
HA	5.65	0.238	0.95	1.19	0.563	3.17	0.448	0.221	0.778	3.91	0.736	0.781	0.84
HB	5.48	0.187	1.75	1.19	0.500	6.07	0.674	0.107	0.719	1.01	0.445	0.653	0.34
HC	6.48	0.409	2.17	1.21	0.577	1.62	0.429	0.234	0.778	4.22	0.774	0.827	5.21
HD	5.22	0.182	1.63	1.19	0.409	4.36	0.484	0.202	0.674	1.04	0.441	0.705	1.23
HE	5.17	0.224	0.84	1.14	0.592	1.82	0.373	0.268	0.809	5.13	0.782	0.786	1.07

[a] F, code of formulation; k_r, first order release rate constant; K, rate constant obtained from Hixson–Crowell kinetic; k_p, release constant; n, diffusional exponent; $T_{63.2\%}$, time for release of 63.2% of the drug; β, shape factor; r^2, determination coefficient; SWSD, sum of weighed squared deviations.

prepared in methanol. Sol-B_2: 10 ml of Sol-B_1 was diluted to 100 ml in 0.1 N HCl.

20, 30, 40, 50, and 60 μg/ml solutions of HCT in 0.1 N HCl were prepared from Sol-H_1 by appropriate dilutions. The absorbances of solutions were measured at 236 nm. A series of 4, 6, 8, 10, and 12 μg/ml solutions of HCT in 0.1 N HCl were prepared from Sol-H_2, and absorbances of these solutions were measured at 269 nm.

100, 150, 200, 250, and 300 μg/ml solutions of BNZ in 0.1 N HCl were prepared by appropriate dilutions from Sol-B_1. The absorbances of prepared solutions were measured at 269 nm. The solutions of BNZ at concentrations of 8, 16, 24, 32, and 40 μg/ml in 0.1 N HCl were also prepared from Sol-B_2 by appropriate dilutions, and absorbance values of each solution were measured at 236 nm.

2.3.1.2. Absorbance ratio method. For obtaining standard calibration mixtures of Sol-H_2 and Sol-B_2 at different concentrations, different volumes of Sol-H_2 and Sol-B_2 were transferred into 50 ml flasks, and diluted to the volume with 0.1 N HCl. The absorbances of these solutions were measured at 236, 269, and 249 nm (isosbestic point).

2.3.2. HPLC method

BNZ and HCT binary mixture was analysed on a Supelcoil LC-18 column at the flow rate of 1 ml/min. Sample volumes of 50 μl were injected, and the column eluent was monitored at 251 nm for 10 min. TMP was utilized as the internal standard in quantitative analyses. The mobile phase utilized for HPLC analyses consisted of acetonitrile and 0.01 M phosphate buffer at pH 6.2 (35:65, v/v).

2.3.2.1. Calibration for HPLC method. Stock solutions of 0.01% w/v BNZ, HCT, and internal standard TMP were prepared in the mobile phase system (acetonitrile/0.01 M KH_2PO_4, 35:65, v/v). 0.1, 0.3, 0.5, and 0.7 ml of BNZ and HCT solutions were micropipetted into 10 ml volumetric flasks. Then, 1 ml of the internal standard solution was added to each sample solution, and each flask was added to the volume with the mobile phase. HPLC injections of 50 μl were made in triplicate, and the average peak areas were used for calculation of regression equations.

Linear standard calibration curves relating HPLC peak areas to concentrations of drugs were constructed for BNZ and HCT by plotting the ratio of peak area of drug (BNZ or HCT) to the peak area of internal standard TMP against the concentration of drug (μg/ml).

2.3.3. Dissolution tests of commercial tablets

Dissolution testing was performed according to the paddle method defined in USP XXII. 0.1 N HCl (pH 1.2) was used as the dissolution medium at 37 ± 0.5°C. The rate of paddles was set as 50 rpm.

Automatically millipore filtered aliquots (3 ml) were removed from dissolution medium at periodic times (2, 4, 6, 10, 15, 20, 30, 45, 60, and 75 min) used for quantification of the dissolved drug according to the two distinct spectrophotometric methods (absorbance ratio and Vierordt) described above.

For the quantification of dissolved drugs according to the HPLC method, automatically millipore filtered 4 ml aliquots from the dissolution medium were transferred into 10 ml volumetric flasks. After addition of 1 ml of internal standard solution, flasks were added to the volume with mobile phase. 50 μl of injection from each sample was made in triplicate, and the average peak areas were used for quantification of the concentrations of BNZ and HCT using regression equations.

3. Results and discussion

In this study, dissolution testing of an antihypertensive drug containing BNZ and HCT as effective substances was performed using HPLC and two distinct spectrophotometric methods.

In the absorbance ratio method, 249 nm was chosen as the isosbestic point. Absorbance ratios A_{236}/A_{249} for BNZ and A_{269}/A_{249} for HCT were obtained by measuring the absorbances of different mixtures of BNZ and HCT at wavelengths of 236, 249 and 269 nm. Then, using these absorbance ratios, the linear calibration curves were calculated, and utilized for quantitative determination of drugs.

To calculate the regression equations, concentration ratios $c_{BNZ}/c_{BNZ} + c_{HCT}$ for BNZ and the ratios $c_{HCT}/c_{BNZ} + c_{HCT}$ for HCT were used as the X-axis values. For the Y-axis values, the ratios A_{236}/A_{249} and A_{269}/A_{249} were used for BNZ and HCT, respectively. Values for regression equations were shown in Table 1.

For quantification of BNZ and HCT concentrations in aliquots according to the absorbance ratio method (mg/ml), the following equation was used:

$$c = \frac{Q-b}{a} \quad \frac{A_{iso}}{a_{iso}} \times 10^3$$

where Q is the ratio A_{236}/A_{249} and A_{269}/A_{249} for BNZ and HCT, respectively, a is the previously determined slope value for both of the drugs (Table 1), b is the previously determined intercept value for both of the drugs (Table 1), A_{iso} is the absorbance determined at 249 nm (isosbestic point), and a_{iso} is the absorptivity value determined at the isosbestic point (a_{iso} was determined as 11.4 for this study).

As a result, determined concentrations (mg/ml) from the equation above for each aliquot were plotted against time, and dissolution profiles of effective substances from commercial tablets were obtained as shown in Fig. 1.

The Vierordt method is another spectrophotometric method used to determine the dissolution profiles of effective substances. The A_1^1 (% 1.1 cm) values of BNZ and HCT in 0.1 N HCl were determined at 236 and 269 nm, respectively. Determined a_1, a_2, b_1 and b_2 values for both BNZ and HCT are listed in Table 2.

Absorbances at 269 nm (A_1) and 236 nm (A_2) of aliquots from dissolution medium taken at periodic times were applied to Vierordt equation for quantification of BNZ and HCT concentrations (mg/100 ml) in commercial tablets:

Vierordt equation for HCT

$$c = \frac{A_1}{\alpha_1 \times 10^{-3}} \times \frac{b-m}{b-a}$$

Vierordt equation for BNZ

$$c = \frac{A_2}{\beta_2 \times 10^{-3}} \times \frac{b(m-a)}{m(b-a)}$$

Determined concentrations (mg/100 ml) of each substance from the equations above for each periodic time

were plotted against time to obtain the dissolution profiles according to the Vierordt method (Fig. 2).

In the HPLC method, TMP was chosen as the internal standard, and calculated regression equations for each substances are given in Table 3.

A mixture of phosphate buffer (0.01 M) and acetonitrile (65:35, v/v) was found to be an appropriate mobile phase for adequate separation of active substances (BNZ and HCT) and internal standard TMP. The separation profile in HPLC is shown in Fig. 3.

Determined concentrations of BNZ and HCT in aliquots relating to HPLC peak areas were plotted against time to obtain dissolution profiles (Fig. 4).

3.1. Drug release mechanism

Different kinetics such as first order, Hixson–Crowell, RRSBW and Peppas equation were applied to the results obtained from the dissolution studies analysed by the Vierordt, absorbance ratio and HPLC methods for hydrochlorothiazide. The results were evaluated kinetically [18–24]. According to the kinetic assessment of release data, the best release kinetic was found to be RRSBW for all formulations, because of the highest determination coefficient, the lowest sum of weighed squared deviation values than the other kinetics. For this kinetic, $T_{63.2\%}$ results changed between 1–5.5 min. The shape factor (β) obtained from RRSBW kinetics was found to be generally smaller than 1 or equal to 1, showing that the initial release rate is high (Tables 4–6). In order to understand the magnitude of the diffusional exponent n of drug from tablets, dissolution data were fitted to the Peppas equation [20–24]. Exponent values of about 0.2 were found using the three methods (Tables 4–6). According to the Peppas equation, results were not in agreement with the $Q\sqrt{t}$ and zero order kinetics.

All this indicates that there are no significant differences between the three methods. The release percentages at all time periods are very similar for the three methods.

4. Conclusions

As a result of our work using HPLC and two distinct spectrophotometric methods, it is found that all active substances were dissolved in 15 min in the whole tablets tested. In addition, it was shown that all three profiles (Figs. 1, 2 and 4) were significantly correlated with each other, indicating that easily accessible spectroscopic methods were quite applicable for dissolution tests. Because the mentioned spectrophotometric methods are rather simple and fairly reliable, it should facilitate analysis of both drugs, when access to other analytical instrumentation such as HPLC is not available.

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