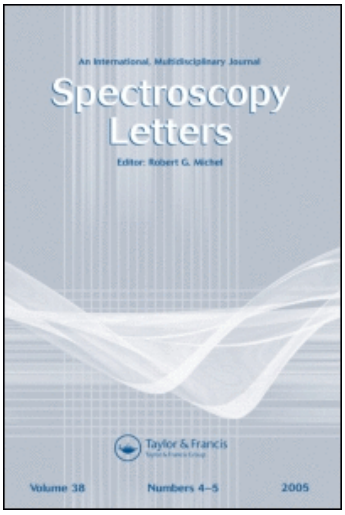

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SPECTROPHOTOMETRIC AND SPECTROFLUORIMETRIC METHODS FOR THE DETERMINATION OF TERAZOSIN IN DOSAGE FORMS

Key Words: Terazosin; Derivative spectrophotometry; Colorimetry; Fluorimetry

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ABSTRACT

Five simple and accurate methods are presented for the determination of terazosin (TZ) in tablets. These methods are based on : the direct measurements of the first and second derivative spectra of samples (A), the reaction of TZ with chloranil (CH) in aqueous solution of pH 9 to give an intense yellow color measured at 340 nm (B), the reaction of the drug with mercurochrome (MER) in aqueous alkaline medium to give an intense red color measured at 543 nm (C), the formation of an ion-pair salt between the drug and bromocresol purple (BCP) with subsequent absorbance measurements at 412 nm (D), and a sensitive fluorimetric method (E). The latter method was extended to determine TZ in presence of its degradation products.

* Correspondence

All variables were studied to optimize the reaction conditions. Beer's law was valid within the specified concentrations and conditions.The proposed methods have been applied for the assay of terazosin in commercial tablets with coefficient of variation less than 1%.

INTRODUCTION

Terazosin, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl) carbonyl] piperazine, is an α_1-adrenergic blocker used in the treatment of hypertension[1]. Few methods have been revealed in the literature for its determination. These include methods for the determination of its purity and its by-products as TLC[2], HPLC[2,3] and titrimetry[2]. In biological fluid, TZ has been determined by HPLC[4,5]. Tablet formulations of TZ have been assayed by HPLC[2] and direct UV method[6].

However, these methods require selective detectors and elaborate multistep reaction procedures. Therefore, it was felt useful to develop spectrophotometric and fluorimetric methods for the determination of TZ in pharmaceutical preparations. As there is no visible-range spectrophotometric method for TZ, sensitive and precise spectrophotometric methods would greatly help in its determination in bulk samples and pharmaceutical formulations.

This paper presents five sensitive, rapid and accurate methods for TZ assay either in powder or in tablets. The first method (A) depends on the use of derivative technique. While the other three methods depend on the measurement of color intensity produced by the reaction of TZ with chloranil at pH 9 (B), with mercurochrome in aqueous medium (C) and with BCP (D). The last method (E) is a sensitive fluorimetric one which determines TZ either pure form or in presence of its degradation products.

EXPERIMENTAL

Instruments

A Perkin-Elmer Model 550 UV-VIS spectrophotometer and a Hitachi Model 561 recorder were used. The spectra of test and reference were recorded in 1 cm quartz cells.

The fluorimetric measurements were carried out on a Perkin-Elmer Model 650-10S spectrofluorimeter equipped with 1 cm quartz cell and a Perkin-Elmer Model 56 recorder, (sensitivity range, 0.3; slit width, 10 nm for both excitation

and emission). Schott-Gerate pH meter Model CG710 was used for pH measurements.

Reagents and chemicals

All the chemicals used were of analytical grade. All solutions were prepared in distilled water.

Pure terazosin was kindly provided by Abbott laboratories and was used without purification. Tablets containing terzosin were purchased from the local market. Itrin tablets (Abbott Laboratories) contain 5 mg terazosin/tablet. Chloranil (BDH Chem. Ltd. Poole, England; 0.246 mg/ml) in ethanol was used. Aqueous solutions of mercurochrome (Sigma Chem. Co., USA; 2 mg/ml) and bromocresol purple (Aldrich Chem. Co., USA; 1.0 mg/ml) were used. Borax and McIlvaine's citric acid buffers (pH 9.0, 8.0 and 3.2) were used[7].

Preparation of Standard solutions

100 mg of terazosin hydrochloride were accurately weighed and dissolved in 100 ml distilled water. Further dilutions were made to suit each method.

Preparation of sample (Assay of tablets)

20 Tablets were weighed and powdered. An accurately weighed amount of the tablet powder equivalent to 50 mg TZ were transferred into a beaker using distilled water and stirred for 45 minutes. The extract was filtered into a 50-ml volumetric flask and completed to volume using the same solvent. The filtrate was diluted to suit each method.

Preparation of the alkaline induced degradation product

About 25 mg terazosin hydrochloride were accurately weighed, transfered into 50-ml volumetric flask and dissolved in the least amount of water. Then 25 ml 0.1 N sodium hydroxide solution were added and heated in a water bath at 75°C for 20 minutes. Then the solution was completed to 50 ml using 0.1 N sodium hydroxide solution.

Calibration Graphs

Method A.

Various portions of the standard solution, within the range stated in Table 1, were transfered into 25-ml volumetric flasks and diluted to volume using distilled water. The D_1 and D_2 spectra were recorded against water over the

TABLE 1

Optical characteristics, precision and accuracy of the proposed methods (A-D)

Parameter	A		B	C	D
	D_1	D_2			
λ_{max}	340	345	340	543	412
Beer's law Limits (ug/ml)	4-18		24-45	4-12	4-20
Molar absorptivity* ($L\ mole^{-1}\ cm^{-1}$)	-		$5.78x10^3$	$3.57x10^4$	$1.78x10^4$
Regression equation					
Intercept (a)	-6.537	-1.273	-0.018	-0.226	$3.1x10^{-3}$
slope (b)	6.806	4.007	0.014	0.084	0.042
Correlation Coefficient (r)	0.9998	0.9995	0.9996	0.9997	0.9996
Variance	0.701	2.438	0.601	1.121	2.281

* Calculated on the basis of the molecular weight of the hydrochloride salt of the compound.

range 220-380 nm. The peak amplitudes at 340 and 345 nm were measured for D_1 and D_2, respectively.

Method B.

Various portions of the standard solution, within the range stated in Table 1, were transferred into 10-ml volumetric flasks. 2 ml buffer pH 9 and 4 ml chloranil solution were added. Then the solutions were heated in water bath (40°C) for 40 min. The volume was completed with water. The absorbance was measured at 340 nm using a blank.

Method C

Various portions of the standard solution, within the range stated in Table 1, were transferred into 25-ml volumetric flasks. 5 ml buffer pH 8 and 2ml MER solution were added. The volume was completed with water and mixed well. The absorbance was measured at 543 nm against a blank.

Method D

Various portions of the standard solution, within the range stated in Table 1, were transferred into 60-ml separating funnels. 5 ml of buffer solution pH 3.2 and 2 ml BCP were added. The contents of each separator were mixed then extracted with 10,5 and 5 ml portions of chloroform. The chloroformic extracts were collected into 25-ml volumetric flasks and completed to volume with chloroform. The absorbance of each solution was measured at 412 nm against a blank.

Method E.

A 1 ml aliquot of standard TZ solution was diluted to 100 ml with water. Several portions of this solution (0.5-2.0 ml) were diluted to 100 ml using the same solvent. The fluorescence emission of each solution was measured at 390 nm and at the wavelength range 360-400 nm using λ_{ex} 342 nm. The coefficient, P_2, was calculated using the following expression:

$$P_2 = [F_o(+5) + F_1(-1) + F_2(-4) + F_3(-4) + F_4(-1) + F_5(+5)]/84$$

where the subscripts 0, 1, 2 ..... represent 360, 368, ..., 400 nm.

RESULTS AND DISCUSSION

Fig. 1 shows the first and second derivative spectra of TZ in distilled water. The D_1 and D_2 spectra of TZ exhibit positive and negative peaks which are used in its quantitation. So, the peak height at 340 and 345 nm were

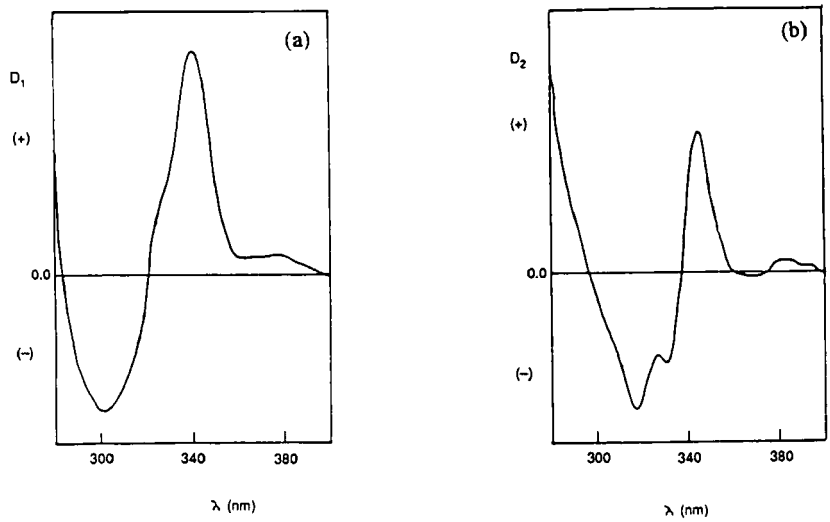

Figure 1: (a) first, and (b) second derivative spectra of 8 μg/ml terazosin hydrochloride in distilled water.

adopted for D_1 and D_2 measurements, respectively. Moreover, the ratios of the D_1 and D_2 maxima were calculated and used for the detection of interference[8]. The D_1 340 nm/D_1 302 nm and D_2 345 nm/318 nm ratios of 6 different concentrations of TZ solutions were calculated (1.64±1.8 and 1.05±1.4, respectively). They are independent of concentration and were reasonably reproducible.

Method B

Chloranil, a π-acceptor, is known to yield charge transfer complexes or radical ions with various electron donors[9]. TZ, being an amine, it forms a complex with CH in aqueous alkaline medium which exhibits a maximum absorption at 340 nm. The reaction time, the volume of CH solution and the volume of the buffer were selected as a compromise between optimum sensitivity, stability and minimum blank reading.

Method C

MER forms products through coordination between its mercury atom and compounds containing basic nitrogen[10]. TZ, being a basic amino compound , it forms a product with MER has an intense red color with maximum absorption at 543 nm. The reaction conditions were studied in order to achieve high sensitivity, low blank readings and high stability. The reaction stoichiometry between TZ and MER has been determined by applying the continuous variation method[11]. The method showed a ratio of 1:1 under the described conditions.

Method D

TZ, containing basic nitrogen, reacts with BCP (an acid dye) to yield a highly colored ion-pair complex[12] which is easily extracted with chloroform. The formed complex has maximum absorption at 412 nm. Maintaining the pH of the solution at 3.2 was found to be the best for maximum sensitivity. The chromogen was stable for 35 minutes. The continuous variation method has been applied to study the reaction stoichiometry between TZ and BCP. The method showed a ratio of 1:1 under the described procedure.

Under the described experimental conditions, the graphs obtained by plotting D_1, D_2 and absorbance values of the colored products versus concentration, within the specified range (Table 1), showed linear relationships. The molar absorptivities, slopes, intercepts, correlation coefficients and the variances obtained by the linear least squares treatment of the results were given in Table 1.

The relative standard deviation (RSD) for five separate determinations of TZ at different concentration levels for the different methods were less than 2%.

Method E

Solutions of TZ in water exhibit a strong fluorescence[2] at 390 nm with λ_{ex} at 342 nm (Fig. 2). A fluorimetric method has been adopted for the determination of TZ in dosage forms. A linear correlation was obtained between the fluorescence (F) and the concentration (C) within the range 0.05-0.2 μg/ml. The linear regression equation was.

$$F\ 390\ nm = 1.6439 + 4039.655\ C \qquad (r = 0.9998)$$

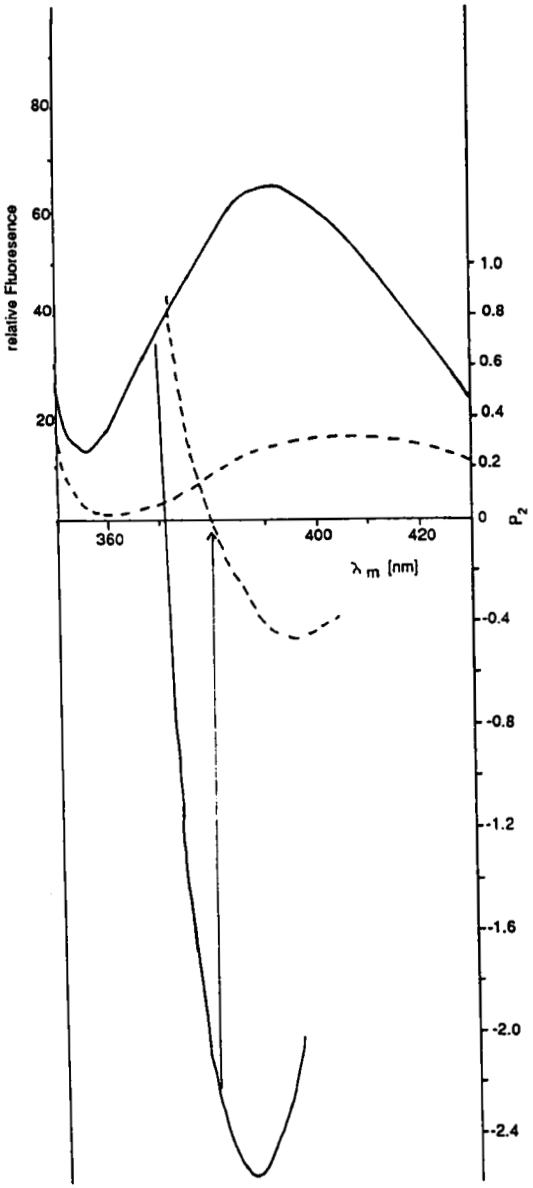

Figure 2: Fluorescence curves of 0.150 µg/ml terazosin hydrochloride (——) and its degradation products (-----) in water, and the corresponding P_2, convoluted curves derived therefrom by use of 6-points orthogonal polynomials at 8- nm intervals.

TZ in alkaline medium, is susceptible to hydrolysis with subsequent cleavage of the amide linkage[2]. The absorption spectra of TZ and its degradation products were so strongly overlapped that cannot be resolved by derivative technique.

Moreover, the products of hydrolysis was found to possess fluorescence emission at the same excitation wavelength of the intact drug (Fig. 2). This interference will lead to unacceptable high results in the determination of TZ using F_{max} method.

Therefore, Glenn's method[13] of orthogonal function was applied for the determination of intact TZ in presence of its degradation products. Accordingly, the fluorescence emission curve, $F_{(\lambda)}$, of compound (X) can be expanded in terms of orthogonal function as follows:

$$F_{(\lambda)} = p_o P_o + p_1 P_1 + p_2 P_2 + ... + p_n P_n$$

Where $F_{(\lambda)}$ denotes the fluorescence emission of the sample measured at wavelength (λ) that belongs to a set of (n+1) equally-spaced wavelengths. P_j are the orthogonal polynomials[14] and p_j are their respective coefficients which are proportional to the concentration of the compound (X).

Thus $P_j = \alpha_j Cx$ where α_j is the coefficient of the constant.

In the presence of fluorescence interferences, each observed coefficient is the sum of two terms:

$P_j = \alpha_j Cx + p_j(Z)$ where (Z) denotes the contribution from the interferences.

By proper choice of polynomial, wavelength range and interval P_j; (Z) can be arranged to be negligibly small relative to $\alpha_j Cx$, in this case the concentration Cx is directly proportional to p_j.

The quadratic polynomial, P_2, was chosen as it makes a large contribution to the fluorescence emission curve of TZ over the wavelength range of 360-400 nm, and makes small contribution to that of the degradation products over the same wavelength range. Thus, the determination of TZ in presence of its degradation products can be carried out by using P_2 for 6-points at 8 nm intervals.

Under these conditions, $[P_2]$ is maximal in the convoluted curve[13] of TZ and negligibly small for the degradation products (Fig. 2). The estimated error as the ratio P_2 (Z)/P_2 (X) was 0.726%.

TABLE 2
Assay of Terazosin in commercial tablets using the proposed methods

Sample	Method, Mean* ±S.D					
	A		B	C	D	E
	$D_{1\ 340\ nm}$	$D_{2\ 345\ nm}$				
Powder	100.08±0.837	-99.76±1.563	99.98±0.775	99.99±1.061	99.86±1.510	99.87±1.133
Tablets	99.89±0.843	98.62±0.493	99.098±0.353	98.59±0.379	98.54±0.536	98.09±0.372
t			1.762	0.108	0.246	
F			1.950	1.692	1.182	

* Mean of five determinations
* Theoretical values for t-and F test at p = 0.05 are 2.31 and 6.39, respectively.

Under the described experimental conditions, a linear correlation was obtained between P_2 and TZ concentration over the range 0.05-0.2 μg/ml. The linear equation was found to be:

$$[P_2] = 7.62 \times 10^{-3} + 146.73\ C \qquad (r = 0.9999)$$

In order to prove the validity and applicability of the method, five synthetic mixtures of TZ and its degradation products in different proportions were prepared and assayed using the proposed method. The results obtained (101.3±0.79) were both precise and accurate. For comparison, recoveries were calculated from F_{max} and were unacceptably high (129.1±26.39).

Analysis of Terazosin tablets

The proposed methods were applied to assay TZ in tablets. The results (Table 2) indicate that the colorimetric and derivative methods are of comparable accuracy and reproducibility (t- and F-tests).

The advantage of the fluorimetric method is its high sensitivity, and it can determine TZ in presence of its degradation products. The proposed methods are simple, sensitive and accurate. They can be applied for either content uniformity or routine quality control. While the fluorimetric method could be applied as a stability-indicating method.

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