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SPECTROPHOTOMETRIC DETERMINATION OF HYDRALAZINE HYDROCHLORIDE, OXPRENOLOL HYDROCHLORIDE & CHLORTHALIDONE IN COMBINATION AND FOR OXPRENOLOL HYDROCHLORIDE AS SINGLE COMPONENT DOSAGE FORM.

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ABSTRACT

Three component tablet assay and single component tablet assay are presented. The first is performed for hydralazine hydrochloride, oxprenolol hydrochloride & chlorthalidone existing in a ratio 2.5:8:1 respectively. Hydralazine is estimated through absorbance measurements at 314 nm, D_1 at 315 nm or D_2-at 316 nm. Modified Vierordts method-after absorbance correction from hydralazine hydrochloride interference and also D_2 methods are applied for oxprenolol hydrochloride assay. Chlorthalidone, the minor component, is assayed after its extraction using D_1 or D_2 measured at 282 nm & 268-284 nm

respectively. For single tablet assay, oxprenolol hydrochloride is assayed using A_{max} at 272 nm, D_1-measurement at 252-274 nm & D_2-measurement at 260-278 nm. The first method is suffering from systematic error corrected by the latter two methods.

INTRODUCTION

Hydralazine, oxprenolol & chlorthalidone are extensively used in the treatment of cardiovascular disorders. Hydralazine has been assayed as single component in different pharmaceutical dosage forms using different methods such as chromatography (1), fluorimetry (2), amperometry (3) and colorimetry (4). The different methods for estimation of oxprenolol in its dosage forms include chromatographic (5) and colorimetric (6) techniques. Chlorthalidone assay was performed through the use of chromatographic (7) or colorimetric (8)methods. Hydralazine was estimated in presence of propranolol or hydrochlorthiazide using chromatographic (10) methods. Oxprenolol & chlorthalidone were analysed in presence of each other using derivative spectrophotometry (11).

The present work deals with the assay of three components mixture of hydralazine, oxprenolol and chlorthalidone in a ratio 2.5:8:1. Oxprenolol is here also estimated in single dosage tablet form.

MATERIALS AND METHODS

All reagents used were analytical grade.

Apparatus

A Perkin-Elmer Model 550S UV-VIS spectrophotometer with 1-cm quartz cuvettes. For recording different curves, use the following settings; initial wavelength 360 nm; scan speed 120 nm/min; chart speed 60 mm/min. Ordinate maximum and minimum: 1 and 0 for A, ± 0.18 for D_1 and ± 0.018 for D_2. Response: 1 for A and 6 for D_1 & D_2. Unless otherwise indicated D_1,D_2-values were measured using absolute peak technique.

Preparation of Standard Calibration Curves

a) For hydralazine hydrochloride (I) and oxprenolol hydrochloride (II): accurate volumes of 2.5-4.5 (in 0.5-ml steps) of both (I)(25 mg%) and (II)(80 mg%) standard solutions in 0.1 N HCl were transferred into two separate sets of 50-ml calibrated flasks & diluted to volumes with 0.1 N hydrochloric acid solution. The first and second derivative spectra were recorded using 0.1 N hydrochloric acid blank. A-values at 314 & 302 nm, D_1-values at 315 nm & D_2-values at 316 nm were measured for I. For II the D_1-values at 275 nm & D_2-values at 278 nm were measured.

b) For chlorthalidone: 50.0 mg chlorthalidone were dissolved in 50.0 ml methanol. 10.0 ml of the methanol solution were diluted to 100.0 ml with 0.1 N hydrochloric

acid solution (solution A). An aliquot of 40.0 ml of solution A was transferred into 250-ml separatory funnel and extracted with four 50-ml portions of ether. The combined ether extracts were filtered through anhydrous sodium sulfate into a 100-ml beaker, evaporated to dryness on water bath at 70°C. The residue was dissolved in about 50 ml 0.1 N hydrochloric acid solution, transferred quantitatively into a 100-ml calibrated flask and completed to volume with 0.1 N hydrochloric acid solution(solution B). Accurate volumes of 4.0-12.0 ml (in 2.0-ml steps) of solution B were transferred into a series of 50-ml calibrated flasks & diluted to volume with 0.1 N hydrochloric acid solution. The first and second derivative spectra were recorded using 0.1 N hydrochloric acid solution blank. D_1-values at 282 nm and D_2-values (peak-through) at 268-284 nm were measured.

Three-Component Tablet Assay

a) For hydralazine hydrochloride and oxprenolol hydrochloride: an accurate weight(equivalent to one tablet)-from previously powdered and mixed twenty tablets-was transferred into a 100-ml calibrated flask, shaked for thirty minutes with 50 ml methanol, made up to volume. This was filtered, the first portion was rejected,then 3.0 ml of the filtrate were transferred into a 50-ml calibrated flasks and diluted to volume with 0.1 N hydrochloric acid solution. The D_1-and D_2-curves were recorded

using 0.1 N hydrochloric acid solution blank. A-values at 314,283 & 274 nm, D_1-values at 315,275 nm and D_2-values at 316,278 nm were measured.

b) For chlorthalidone: an accurate weight of previously powdered and mixed twenty tablets (equivalent to one tablet) was transferred into a 250-ml calibtated flask. This was shaked for 2 hours and completed to volume with 0.1 N hydrochloric acid solution. The tablet solution was filtered, the first portion was rejected and a 100.0 ml aliquot was transferred into 250-ml separatory funnel. For extraction the same procedure given under preparation of standard solution was followed starting from "extracted with four 50-ml portions of ether ....". Then 10.0 ml of the final solution were diluted to 50.0 ml with 0.1 N hydrochloric acid solution. The first and second derivative were recorded using 0.1 N hydrochloric acid balnk. D_1-value at 282 nm D_2-value (peak-trough) at 268-284 nm were measured.

Oxprenolol Tablet Assay

An accurately weighed amount of the powdered tablets (equivalent to one tablet) was transferred into 100-ml calibrated flask. The procedure was then continued as under the three-component tablet assay for oxprenolol hydrochlride starting from "shaked for thirty minutes .....". The D_1-value (peak-trough) at

252-274 nm, D_2-value (peak-trough) at 260-278 nm and A-value at 272 nm were measured.

RESULTS AND DISCUSSION

The Zero-Order Absorption Spectrophotometric Method

The zero-order absorption spectra of hydralazine hydrochloride in 0.1 N hydrochloric acid exhibits three distinct maxima at 262,302 & 314 nm (with $E^{1\%}_{1\ cm}$ 499,278 & 234 respectively) with decreasing absorbance from shorter to longer λ_{max}. The coexisting components oxprenolol hydrochloride & chlorthalidone in a ratio similar to that of commercial tablets show almost negligible absorbance at long wavelengths 302&314 nm. Accordingly, A_{max}-method could be directly applied for hydralazine assay without the appearance of any systematic positive error from the contribution of oxprenolol hydrochloride & chlorthalidone absorbances. On the other hand, a serious problem arose on absorbance measurement in the vicinity of short wavelengths. Again in the concentrations similar to their existance in commercial tablets, chlorthalidone exhibited minor contribution while oxprenolol had a maximum absorbance at 272 nm. Such maximum was obscured by the sloping absorbance of hydralazine hydrochloride (FIG. 1). Such phenomenon created a problem during oxprenolol hydrochloride determination.

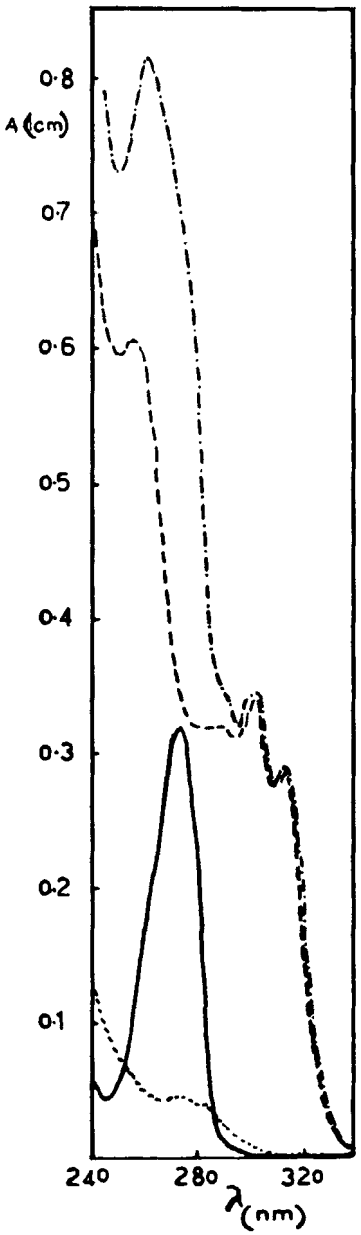

FIGURE 1

Zero order spectra of 4.0 mg% oxprenolol hydrochloride (——), 1.25 mg% hydralazine hydrochloride (---), 0.5 mg% chlorthalidone (...) and their mixture(-.-.) in 0.1 N hydrochloric acid solution.

This could be solved by the application of modified Vierodt's method to the absorbance readings at 283 & 272 nm after subtracting the major absorbance contribution of hydralazine hydrochloride. The total absorbance of the mixture at 283 & 272 nm can be represented by the following linear equations:

$$A_1 = Cx\,\alpha_1 + Cy\,\beta_1 + Cz\,\gamma_1$$

$$A_2 = Cx\,\alpha_2 + Cy\,\beta_2 + Cz\,\gamma_2$$

Where A_1 & A_2 are the absorbances of the mixture; Cx, Cy & Cz are the concentrations of oxprenolol hydrochloride, chlorthalidone & hydralazine hydrochloride respectively; α, β & γ are their respective absorbtivities. 1 & 2 denote wavelengths 272 & 283 nm respectively. By rearrangement, the following aquations are obtained.

$$(A_1 - Cz\,\gamma_1) = Cx\,\alpha_1 + Cy\,\beta_1$$

$$\text{or } (Ac)_1 = Cx\,\alpha_1 + Cy\,\beta_1$$

$$(A_2 - Cz\,\gamma_2) = Cx\,\alpha_2 + Cy\,\beta_2$$

$$(Ac)_2 = Cx\,\alpha_2 + Cy\,\beta_2$$

Where $(Ac)_1$ & $(Ac)_2$ are the corrected absorbances at 272 & 283 nm respectively. These above equations could be solved for oxprenolol hydrochloride, while chlorthalidone showed very low contribution to the absorbance values of the mixtures at the concentration

level of the commercial tablets. It can not be therefore estimated under the same conditions, since the absorbance ratio of chlorthalidone/oxprenolol hydrochloride was lying within the range specified by Glenn (12) for application of modified Vierodt's method.

The Derivative Spectrophotometric Method: The first & second derivative spectra of hydralazine hydrochloride in 0.1 N hydrochloric acid solution (FIG. 2&3) show maximum D_1-value at 315 nm & D_2-value at 316 nm. Meanwhile the other two coexisting components exhibit zero contribution at such wavelengths. Therefore, the absolute D_1-value at 315 nm D_2-value at 316 nm could be used to quantitate hydralazine hydrochlride without the interference from the other two components. D_1-/D_2-values as a function of hydralazine concentration in a range of 1.25-2.25 mg% was linear with negligible intercept. The corresponding regression equations were derived to be:

$$D_1 = -0.001692 + 0.006381C \quad (r=0.9999)$$

$$D_2 = -0.0002076 + 0.0004608C \quad (r=0.9999)$$

Oxprenolol hydrochloride in 0.1 N hydrochloric acid solution exhibits maximum D_1-value at 275 nm & D_2-value at 278 nm. The former suffers from contribution of the coexisting two components, while the latter coincide more or less with the zero crossing point of the other two components. Thus the D_2-

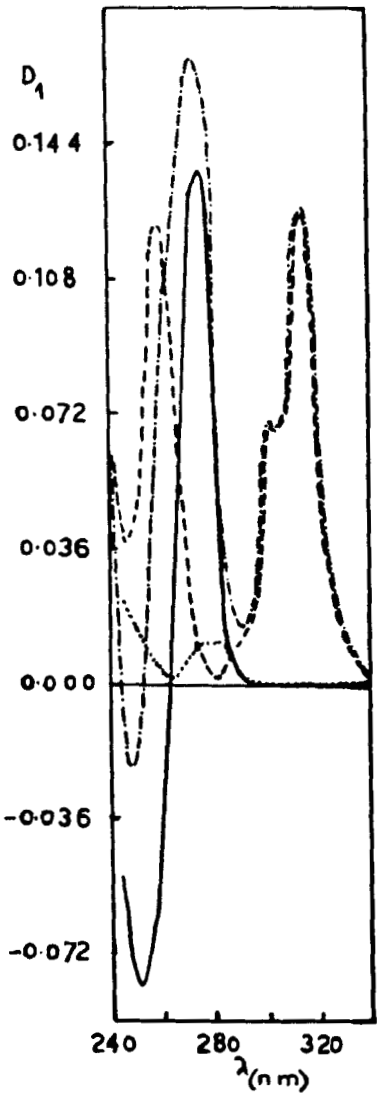

FIGURE 2

First order spectra of 6.4 mg% oxprenolol hydrochloride (——), 2.0 mg% hydralazine hydrochloride (---), 0.8 mg% chlorthalidone (...) and their mixture (-.-.) in 0.1 N hydrochloric acid solution.

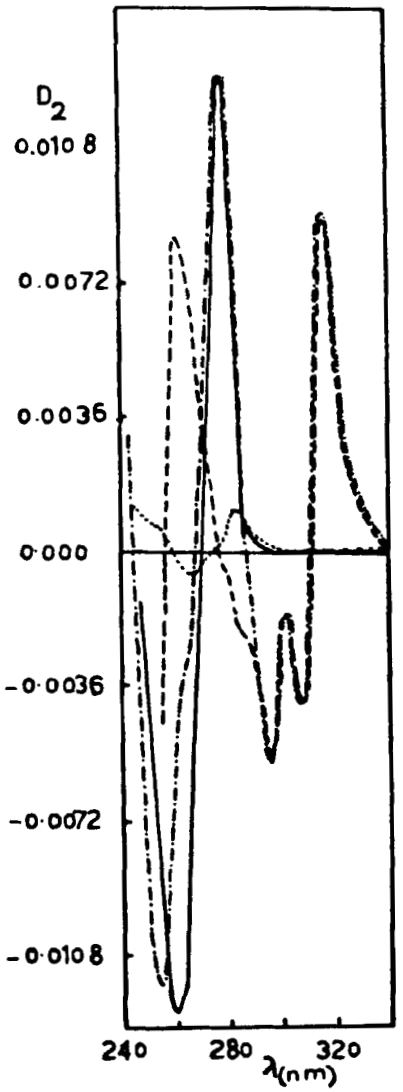

FIGURE 3

Second order spectra of 6.4 mg% oxprenolol hydrochloride (——), 2.0 mg% hydralazine hydrochloride (---), 0.8 mg% chlorthalidone (...) and their mixture (-.-.) in 0.1 N hydrochloric acid solution.

value at 278 nm could be selected to oxprenolol quantitation without interference from the other two components. Plots of D_2-values versus oxprenolol hydrochloride concentration was linear over the range 4.0 to 7.2 mg%. The regression equation derived from the results of five separate concentrations was found to be:-

$$D_2 = 0.000167 + 0.0001944 \quad (r=0.9998).$$

Chlorthalidone Assay in the Three Component Mixture

The zero order absorbance spectrum of chlorthalidone exhibits one maximum & shoulder (at 276 & 283 nm respectively). Its D_1 & D_2 spectra show maximum D_1-value at 282 nm & maximum D_2-value (at 268-284 nm). Meanwhile these different maxima cannot be directly used for chlorthalidone quantitation. This is partly because of its low absorbivity value & partly due to small contribution in the three components mixture (2 parts in 23 parts). Such phenomenon necissitate the prior ether extraction of chlorthalidone from the mixture & subsequent evaporation and dissolution in 0.1 N hydrochloric acid solution. Such solution exhibits D_1-value at 282 nm & D_2-value at 268-284 nm (peak-trough). These values were linear versus chlorthalidone concentration range from 0.32 to 0.96 mg%. The regression

equations derived from these data are:-

$$D_1 = 0.000131 + 0.001316C \quad (r=0.9999)$$

$$D_2 = -0.0000416 + 0.000201C \quad (r=0.9996)$$

To conclude, the mixture components oxprenolol hydrochloride, hydralazine hydrochloride & chlorthalidone in a ratio of 16:5:2 could be quantitated using the following:

1) The measurement of absorbance value at 314 nm, D_1-value at 315 nm or D_2-value at 316 nm for hydralazine hydrochloride estimation.

2) Modified Vierodt's method using corrected absorbance value (from hydralazine hydrochloride component) or D_2 measurement at 278 nm for exprenolol hydrochloride assay.

3) D_1-measurement at 282 nm or D_2-measurement (peak-trough) at 268-284 nm after extraction procedure for chlorthalidone.

To asses the validity & applicability of the above proposed methods, laboratory made mixtures were prepared in the ratio of commercial tablets and assayed for the three components. The mean % recovery & coefficient of variation of the obtained results were encouraging (Table 1). The proposed methods were also appraised through the assay of commercial tablets for the three components, results

TABLE 1

Spectrophotometric Determination of Hydralazine Hydrochloride, Oxprenolol Hydrochloride and Chlorthalidone in Combination.

	Mean recovery[a], (CV%)						
	Hydralazine hydrochloride			Oxprenolol hydrochloride		Chlorthalidone	
Method	A_{max}	D_1	D_2	Vierordt's	D_2	D_1	D_2
Mixtures	99.81	99.99	100.00	99.48	100.01	99.93	100.01
	(0.0016)	(0.0019)	(0.0017)	(0.0015)	(0.0012)	(0.0018)	(0.0019)
Trepress[b] tablets	92.62	92.56	92.65	94.41	95.21	92.66	92.45
	(0.0025)	(0.0025)	(0.0016)	(0.0018)	(0.0025)	(0.0014)	(0.0024)

a) Average of 5 determinations

b) From Swiss Pharma, Egypt; labelled to contain 25 mg hydralazine HCl, 80 mg oxprenolol HCl and 10 mg chlorthalidone.

of which are presented in Table 1. The % recovery of the labelled concentrations were found to be within the pharmacopeial limits of the corresponding single component preparation. Accordingly the proposed method for the assay of the three components mixture could be successfuly used in routine analysis & quality control lab. for the solution of similar three component mixtures.

Single Component Tablet Assay for Oxprenolol Hydrochloride.

Oxprenolol was assayed also in single component dosage tablet form (Trasicor 80 tablet) using A-, D_1- & D_2-measurements at 272, 252-274 nm & 260-278 nm respectively. The corresponding regression equations were derived using the data of at least five different concentrations of the standard oxprenolol hydrochloride solutions. These equations are:

$A = 0.0237 + 0.00726C \quad (r=0.9995)$

$D_1 = 0.0008 + 0.00341C \quad (r=0.9997)$

$D_2 = 0.000318 + 0.00039222C \quad (r=0.9996)$

The mean % recovery (and coefficient of variation) of oxprenolol hydrochloride in tablet* was found to be

* Trasicor tablets (from Swiss Pharma, Egypt) labelled to contain 80 mg oxprenolol HCl.

115.8% (1.37), 101.0% (0.72) and 100.3 (0.65) using A_{max}, D_1-and D_2-methods respectively. Compared with A_{max} method, the D_1 & D_2-methods gave more accurate results as indicated by t-test.

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