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Analysis of Syrups Containing Chlorpheniramine Maleate, Codeine Phosphate and Ephedrine Hydrochloride by Derivative UV Spectrophotometry

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Analysis of Syrups Containing Chlorpheniramine Maleate, Codeine Phosphate and Ephedrine Hydrochloride by Derivative UV Spectrophotometry •

Abstract : *A method was presented for the determination of chlorpheniramine maleate (I), codeine phosphate (II) and ephedrine hydrochloride (III) in a mixture of them without any separation step. The compounds I and II can be determined simultaneously by using the second derivative UV spectrophotometry. The compound III can be determined by the same method after the oxidation with sodium metaperiodate. The linear ranges of concentrations for the analysis of I, II and III have been found as 0.001-0.08, 0.001-0.4 and 0.005-1.80 mg/mL, respectively. The method developed was applied to pharmaceutical forms of these compounds. The percent recoveries were found as 101 % for I, 100 % for II and 100 % for III.*

Keywords *: Derivative UV spectrophotometry, chlorpheniramine maleate, codeine phosphate and ephedrine hydrochloride, pharmaceutical preparations.*

Klorfeniramin Maleat, Kodein Fosfat ve Efedrin Hidroklorür İçeren Şurupların Türevsel UV Spektrofotometrisi ile Analizi

Özet: *Klorfeniramin maleat (I), kodein fosfat (II) ve efedrin hidroklorür'ün (III) karışımlardan ayırma işlemi yapılmadan tayini için bir yöntem geliştirilmiştir. Bileşik I ve II ikinci türev UV spektrofotometrisi ile tayin edilmiştir. Bileşik III ise sodyum metaperiodat ile yükseltgendikten sonra aynı yöntemle tayin edilmiştir. I, II ve III'ün analizi için derişimin doğrusal olduğu aralık sırasıyla 0.001-0.08, 0.001-0.4 ve 0.005-1.80 mg/mL olarak bulunmuştur. Geliştirilen yöntem bu bileşikleri içeren şurup farmasötik preparatlara uygulanmıştır. Yüzde geri kazanım I, II ve III için sıra ile % 101, %100 ve % 100 olarak bulunmuştur.*

Anahtar kelimeler *: Türev UV spektrofotometrisi, klorfeniramin maleat, kodein fosfat ve efedrin hidroklorür, şurup.*

Introduction

Chlorpheniramine maleate (I), codeine phosphate (II) and ephedrine hydrochloride (III) are frequently prescribed as a sedative cough mixture. The different methods proposed for I in mixture with II phenylephrine hydrochloride and acetaminophen TLC[1], with phenylpropanolamine hydrochloride by GLC[2], and determinations by Ion-Pair HPLC[3], with III and guaiacolsulfonate potassium using colorimetric method[4] have been reported. Few applications of derivative spectrometric technique to the determination of I, using second derivative pectrophotometry[5], with pseudoephedrine hydrochloride assay first derivative UV spectrophotometry[6], with dextrometorphane hydrobromide, and pseudoephedrine hydrobromide using second derivative diode-array spectrophotometry[7], with pyrilamine maleate, and phenylpropylamine hydrochloride assay difference spectrophotometry[8] and the compound I was determined by polarographic technique[9]. Recently, it has been shown that the application of derivative techniques to spectrophotometry is very useful in resolving spectral overlap and in cancelling irrelevant absorption from the secondary sample ingredients[10].

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The present paper deals with the determination of the compounds I, II and III in three-component mixture using derivative spectrophotometric technique.

Material and Methods

Instrument

Shimadzu 160-A Model UV spectrophotometer was used. It is a microcontrolled double-beam recording spectrophotometer. The spectra of test and reference solutions were recorded in 1.000 cm quartz cells over the range 220 to 400 nm. Suitable settings are; scan speed: 2400 nm/min, mode: D_2 (second derivative) = $(d^2A/d\lambda^2)$, spectral slit width: 2 nm.

Reagents

All reagents and chemicals used were of analytical reagent grade.

1. Phosphate buffer pH 7.00 : Mix 295.4 mL of 0.1 N sodium hydroxide and 250 mL 0.2 M monobasic potassium phosphate in 1 L calibrated flask and complete to volume with water.

2. 0.2 M sodium metaperiodate solution : Dissolve 10.695 g of sodium metaperiodate in 250 mL water. Store in a dark glass bottle.

Materials

1. Chlorpheniramine maleate (SIGMA)
2. Codeine phosphate (SIGMA)
3. Ephedrine hydrochloride (SIGMA)

Dephedrin ® syrup : Labelled to contain 20 mg I, 150 mg II and 150 mg III per 100 mL syrup.

Codis ® syrup : Labelled to contain 20 mg I, 200 mg II and 240 mg III per 100 mL syrup.

Corex ® syrup : Labelled to contain 100 mg I, 250 mg II, and 125 mg III per 100 mL syrup

In order to prepare standard solutions, 20 mg of I, 200 mg of II or 150 mg of III were dissolved in 100 mL 0.1 N HCl. They were prepared separately and combinations of them.

Experimental Data

Preparation of syrup sample

a) For I and II : Transfer accurately 20 mL aliquot of syrup to separatory funnel. Add 50 mL water and 5 mL 1 N HCl and extract for 10 min with 20 mL diethylether saturated with 1 N HCl. Wash the etherial layer with three 10 mL portions of 0.1 N HCl. Made basic the combined washings and aqueous layer with 15 mL 1 N NaOH and extract with four 15 mL portions of chloroform. Collect the organic extracts and re-extracted with six mL portions of 0.1 N HCl. Filter each acidic extract through a filter paper moistured with 0.1 N HCl and collect the filtrate in a 100 mL calibrated flask and make up to volume with 0.1 N HCl.

b) For III : Transfer accurately 10 mL aliquot of syrup to separatory funnel. Made basic with 5 mL 5 N NaOH an add 15 mL saturated NaCl solutions. Extract with three 20 mL portions of chloroform. Collect the chlorformic extracts in another separatory funnel and re-extract with three 25 mL portions of 0.1 N HCl and collect the acidic extracts in a 100 mL calibrated flask and complete to volume with 0.1 N HCl.

General Procedures

a) For I : Transfer from prepared standard solutions containing I or 25 mL syrup sample prepared as explained above into different calibrated flask and complete the volume 50 mL with 0.1 N HCl. D_2 - UV spectra were recorded against 0.1 N HCl and peak amplitude at 288.2 nm was measured.

b) For II : Transfer from prepared standard solutions containing II or 25 mL syrup sample prepared as explained above into different calibrated flask and complete the volume 50 mL with 0.1 N NaOH. D_2-UV spectra were recorded against 0.1 N NaOH and peak amplitude at 292.6 nm was measured.

c) For III : Transfer from prepared standard solutions containing III or 1 mL syrup sample prepared as explained above into separatory funnel. After additions of 0.2 M sodium metaperiodate solution and 2 N NaOH, pH was adjusted to 7.50. The solution was mixed for 10 min. Then, 1 N HCl and n-hexane

were added and mixed thorougly for 5 min. The hexane layer was filtered and complete the volume 25 mL with n-hexane. D_2-UV spectra of the extracts were recorded against n-hexane. Peak amplitude at 255.2 nm was measured.

Results and Discussion

In this study, the nature of the solutions in which active substances were dissolved, degree of derivatives, the range of wavelength, "N" value (N = 3, $\Delta\lambda$= 10.5) and the thickness of the cell were the basic parameters.

Figures 1 a, b and c show the D_2 - UV spectra of I, II and III in 0.1 N HCl, respectively. It was observed that there is no effect of II and III at 288.2 nm. Accordingly, the result was obtained when direct measurement of I using A_{max} D_2 at this analytical wavelength.

Figures 2 a, b and c show the D_2 - UV spectra of II, I and III 0.1 N NaOH, respectively. It was observed that there is no effect of I and III at 292.6 nm. This wavelength was used for the quantitative determination of II in mixture with I and III.

III exhibits very low absorption in the UV region. In addition, the absorption maxima of III are overlaped by the absorption spectra of the other coexisting components. Oxidation of III with sodium metaperiodate as described in experimental part on formation of benzaldehyde which increase the absorptivity of III (11).

Figures 3 a, b and c show the D_2 - UV spectra of III, I and II in n-hexane, respectively. So the application of second derivative technique to the oxidized mixture at 255.2 nm was used to analyse III in the mixture of I and II.

Table 1 has shown that the data of the graphs obtained by plotting the values of D_2 for I, II and III (after oxidation) under the given experimental conditions at the chosen wavelengths against the concentration are within a considerable interval. Calibration curves for I, II and III are shown in Figure 4-6, respectively. The coefficient of determination and regression for I, II and III were determined from the experimental data within working range by linear regression analysis. The deviation from the linearity was found to be insignificant (95 %) after the preparation of synthetic mixtures of I, II and III. These mixtures were analysed using spectrophotometric method following the extraction procedures. Then, percent recoveries of the method was calculated by comparing the amount of compound in synthetic mixtures with the results obtained (Table 2). The proposed method has been applied to the simultaneous determination of the above mentioned mixture in commercial syrups (Table 3). The results obtained have been compared with the methods registered in the Turkish Pharmacopeia (1974), such as spectrophotometry for I, and titrimetry for II and III. No difference has been observed between the I, II and III data. The results taken by two different techniques for Dephedrin ® syrup as an example, were compared as seen on Table 4.

Table 1. The determined parameters for calibration curves of I, II and III

Compound	Solvent	Selected (λ)(nm)	Conc.range (mg/mL)	Intercept (a)	Slope (b)	Deter. coeff.(r^2)
I	0.1 N HCl	288.2	0.001-0.08	-9.37×10^{-4}	2.25	1.00
II	0.1 N NaOH	292.6	0.001-0.40	1.25×10^{-3}	0.723	1.00
III	n-Hexane	255.2	0.005-1.80	0.0111	0.539	1.00

Table 2. The results of percent recovery of standard mixtures of I, II and III

Compound	Added (mg/10mL)	Found (mg/10mL)	Recovery %
I	0.50	0.50	100
	1.00	1.03	103
	1.50	1.50	100
	2.00	2.03	101
II	5.00	5.01	100
	10.00	10.0	100
	15.00	15.0	100
	20.00	20.0	100
III	10.00	10.0	100
	15.00	15.0	100
	20.00	20.0	99.9
	25.00	25.0	100

Table 3. Assay results of I, II and III in commercial syrups.

Pharmaceutical preparations	I	II	III
Dephedrin®	2 mg/10 mL x=2.01±0.01 S=0.02 V=1% CI=1.98-2.04	15 mg/10 mL x=15.0±0.0 S=1.2 V=7.9% CI=13.7-16.3	15 mg/10 mL x=15.0±0.0 S=0.0 V=0.27% CI=15.0-15.1
Codis®	2 mg/10 mL x=2.00±0.01 S=0.02 V=1% CI=1.97-2.03	20mg/10 mL x=20.0±0.0 S=0.1 V=0.35% CI=19.9-20.1	24mg/10 mL x=24.0±0.0 S=0.1 V=0.25% CI=24.0-24.1
Corex®	10mg/10 mL x=10.0±0.0 S=0.1 V=0.7% CI=9.9-10.1	25mg/10 mL x=24.9±0.0 S=0.1 V=0.44% CI=24.8-25.0	12.50mg/10 mL x=12.5±0.0 S=0.0 V=0.32% CI=12.4-12.6

x = mean ± standard error, S = standard deviation, V = variation coefficient, CI = confidence intervals (95%)

Table 4. Statistical evaluation of obtained data from developed D_2-UV technique and comparison with pharmacopeia technique for Dephedrin® syrup.

Compound	Statistical values	D_2-UV technique (mg/mL)	T.F.1974 technique (mg/mL)
			Spectrophotometric
	n	6	6
I	x	2.01	1.97
	S	0.02	0.02
	V(S/x.100)	1	1.01
	CI	1.98-2.04	1.97-2.00
			Titrimetric
	n	6	6
II	x	15.0	14.5
	S	1.2	0.2
	V(S/x.100)	7.9	1.30
	CI	13.7-16.3	14.4-14.8
			Titrimetric
	n	6	6
III	x	15.0	14.6
	S	0.0	0.3
	V(S/x.100)	0.27	1.78
	CI	15.0-15.1	14.3-14.8

n = number of sample, x = mean, S = standard deviation, V(S/x.100) = variation cooficent, CI = confidence intervals (95%)

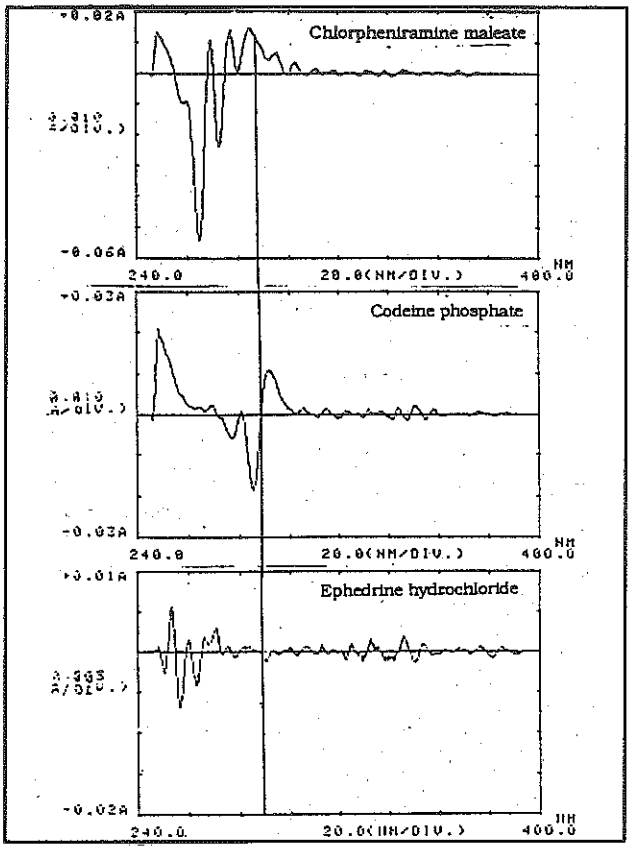

Figure 1. D_2-UV spectra of a) 0.2 mg/mL I, b) 1 mg/mL II and c) 4 mg/mL III in 0.1 N HCl.

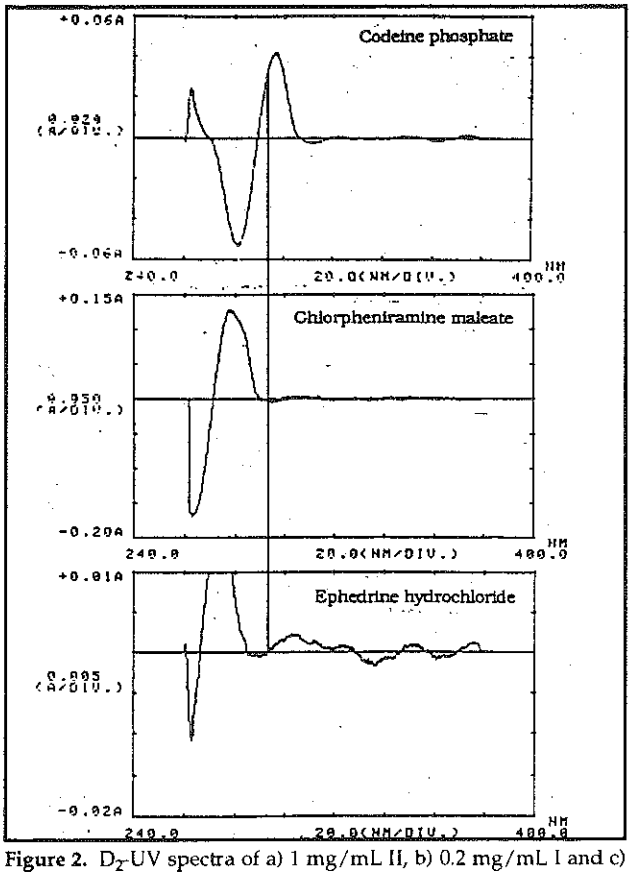

Figure 2. D_2-UV spectra of a) 1 mg/mL II, b) 0.2 mg/mL I and c) 4 mg/mL III in 0.1 N NaOH.

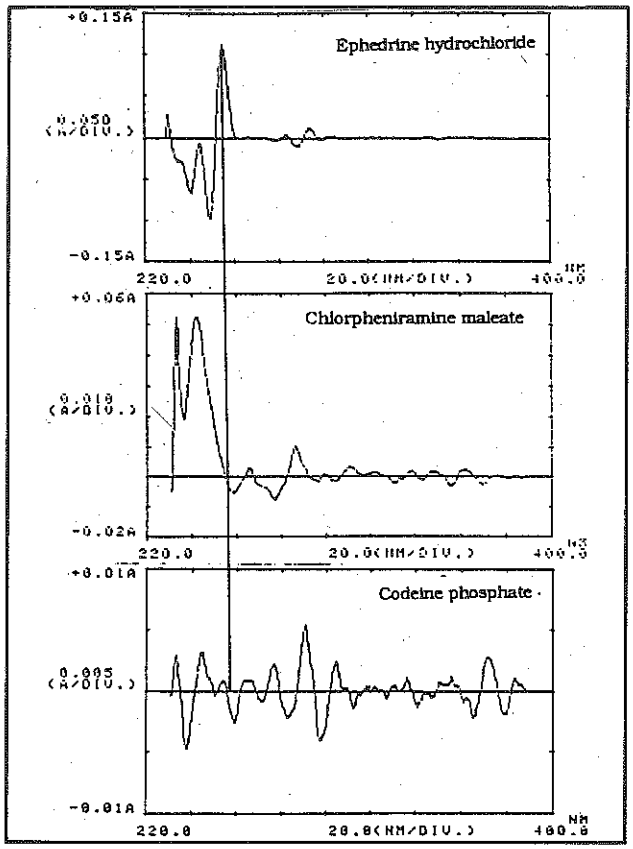

Figure 3. D_2-UV spectra of a) 4 mg/mL III, b) 0.2 mg/mL I and c) 1 mg/mL II in n-hexane.

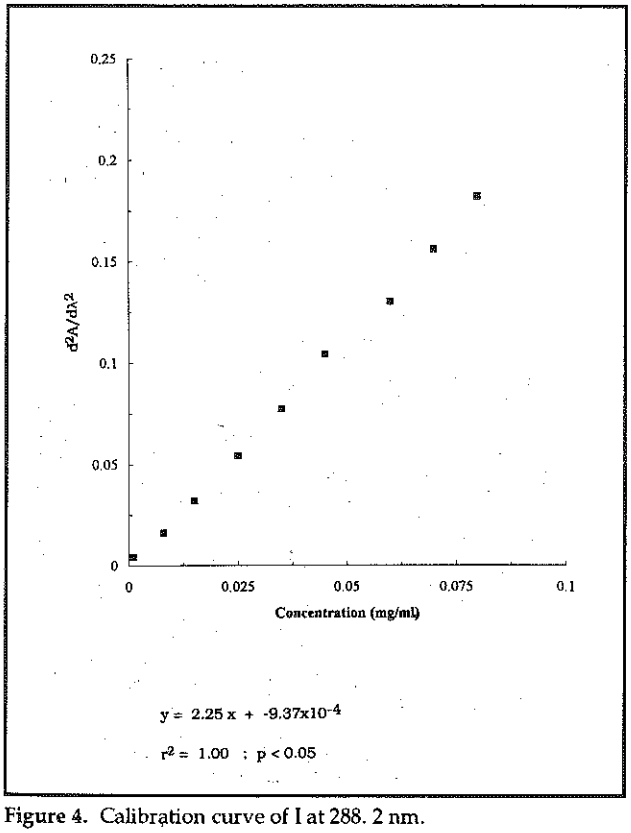

Figure 4. Calibration curve of I at 288. 2 nm.

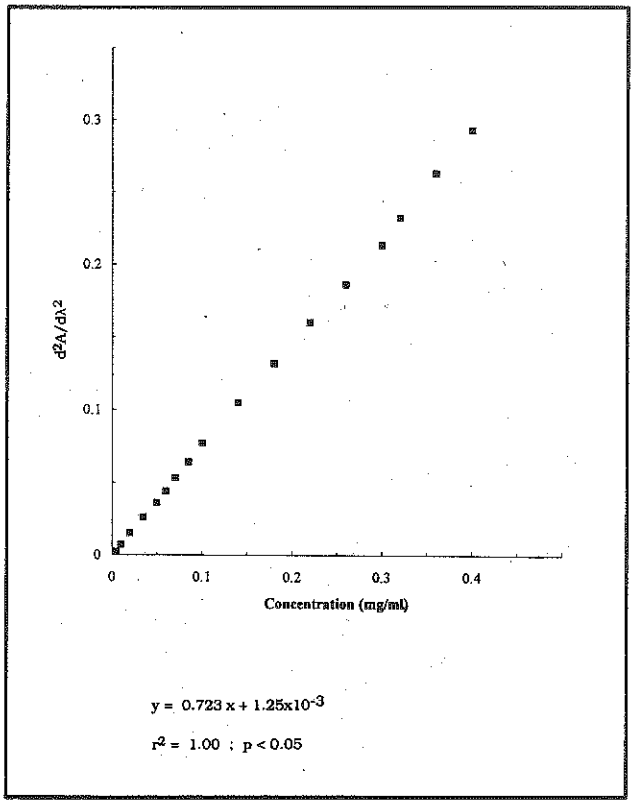

Figure 5. Calibration curve of II at 292.6 nm.

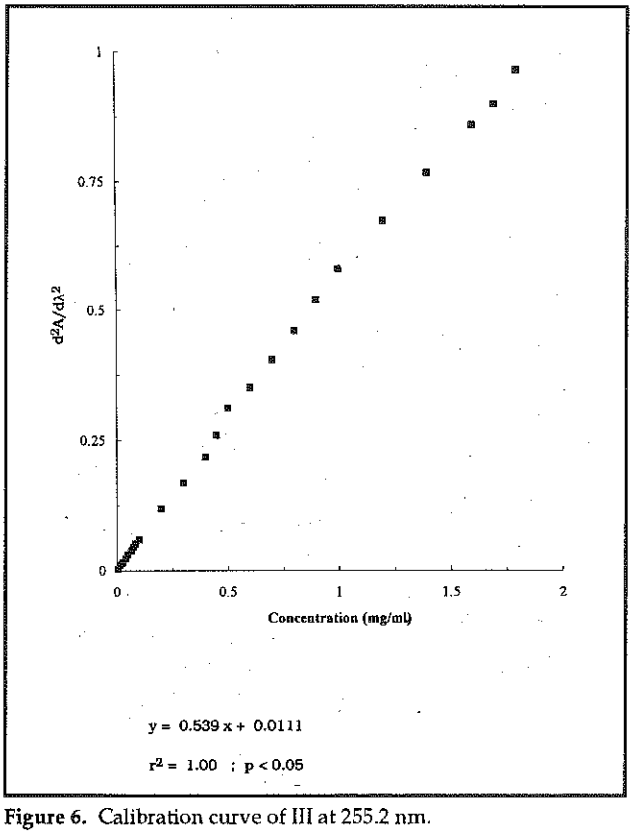

Figure 6. Calibration curve of III at 255.2 nm.

The possibility of the interfering constituents in syrup must not be overlooked. Therefore, the standard addition technique was used to evaluate the accuracy of the proposed method for such samples and to test for interference from the syrup constituents.

It has been concluded, that the method developed, namely derivative UV spectrophotometry is sensitive, accurate, precise and reproducible.

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