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Simultaneous determination of cinnarizine and dimenhydrinate in binary mixture using, first derivative of ratio spectra and bivariate spectrophotometric techniques

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ABSTRACT

Two accurate and sensitive spectrophotometric methods have been developed and validated for simultaneous determination of cinnarizine (CINN) and dimenhydrinate (DIM) in binary mixture without previous separation. The first method is based on the first derivative of ratio spectra (^{1}DD) obtained by measurement of the amplitudes at 232.8 and 275.5 nm for cinnarizine and dimenhydrinate, respectively. The second method applies bivariate calibration method using 250 and 276 nm as an optimum pair of wavelength for cinnarizine and dimenhydrinate. The linear ranges are 4–20 and 10–45 μg/mL for cinnarizine and dimenhydrinate, respectively, for both methods. The proposed methods were found to be simple and sensitive for the routine quality control application of cinnarizine and dimenhydrinate in pharmaceutical dosage form and the results have been statistically compared with a reported method.

KEYWORDS

Cinnarizine;
Dimenhydrinate;
Derivative-ratio;
Bivariate;
Spectrophotometry.

INTRODUCTION

Cinnarizine is 1-(diphenylmethyl)-4-(3-phenyl-2-propenyl) piperazine[1], Figure 1a.

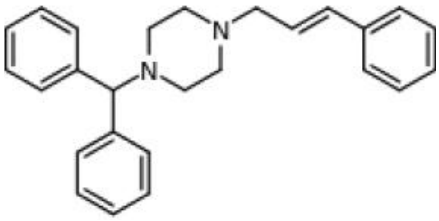

Figure 1a : Structural formula of cinnarizine

It is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders and for the prevention and treatment of motion sickness[2]. Cinnarzine is official in British Pharmacopeia and determined by potentiometric titration and liquid chromatographic method[3].

Literature survey reveals few methods that have been reported for the determination of CINN in pharmaceutical formulation, biological samples and with other drugs in combination; including colorimetry, potentiometric titration[4], spectrophotometry[5] RP-HPLC[6] HPTLC[7].

Dimenhydrinate is 2-benzhydryloxy-N,Ndimethyl-ethanamine; 8-chloro-1,3-dimethyl-7H-purine-2,6-dione) is 8- chlorotheophilline salt of diphenhydramine[1]

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Figure 1b.

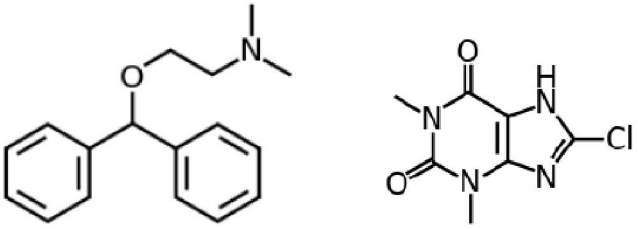

Figure 1b : Structural formula of dimenhydrinate

It is used to prevent motion sickness. It is official in British Pharmacopeia and determined by potentiometric titration and liquid chromatographic method[3]. Few methods have been reported for the determination of DIM in pharmaceutical formulation, biological samples and with other drugs in combination including HPLC[8,9], spectrophotometry[10] and liquid chromatography[11].

The combined dosage forms of CINN and DIM is used as anti-emetic drug. The combination of these two drugs is not official in any pharmacopoeia; hence no official method is available for the simultaneous estimation of CINN and DIM in their combined dosage forms. Literature survey reveals only few methods for simultaneous estimation of CINN and DIM in their combined dosage form, including spectrophotometry[12,13] and HPLC[14]. The objective of the present study is to develop simple, sensitive, rapid, accurate, precise and cost effective spectrophotometric method based on first derivative of ratio spectra (^{1}DD) and bivariate analysis for simultaneous estimation of both drugs in their combined dosage form.

EXPERIMENTAL

Instruments

Spectrophotometer: Shimadzu UV-1650 PC, dual-beam UV–visible spectrophotometer (Japan), with matched 1-cm quartz cells, connected to an IBM-compatible PC and an HP-600 inkjet printer. Bundled, UV-PC personal spectroscopy software Version 3.7 was used to process the absorption and the derivative spectra. The spectral bandwidth was 2nm with wavelength-scanning speed of 2800 nmmin™1.

Materials and reagents

All chemicals and reagents were of analytical grade and the solvents were of spectroscopic grade.

Materials

Pure samples were kindly supplied by the by Amoun Pharmaceutical company, Cairo, Egypt Their purity was found to be 99.75 ± 0.845 and 100.48 ± 0.96, for CINN and DIM, respectively, according to the reported spectrophotometric method[12].

Pharmaceutical formulations

Amocerebral plus tablets Batch No. 124820, were kindly supplied by Amoun Pharmaceutical company, Cairo, Egypt and were claimed to contain 20 mg of CIN and 40 mg of DIM per each tablet.

Standard solutions

- CINN standard solution (0.1 mgmL™1) in methanol.
- DIM standard solution (0.1mgmL™1) in methanol.

Reagents

Methanol (AR Grade, S. D. Fine Chemicals Ltd., India)

Procedures

Spectral characteristics of CINN and DIM.

Two aliquots equivalent to 140 µg of CINN and 100 µg of DIM were transferred separately from their standard solutions (0.1mgmL^{-1}, each) into two 10-mL volumetric flasks. Then the volumes were completed with methanol. The absorption spectra of the prepared solutions were recorded over the range 200–400 nm using methanol as a blank.

First derivative of ratio spectra (^{1}DD) method

Linearity

Aliquots equivalent to (40–200µg) and (100–450µg) of CINN and DIM, respectively were separately transferred from their standard solutions (0.1mgmL^{-1}, each) into two series of 10-mL volumetric flasks. Each flask was completed to the volume with methanol to reach the concentration range of 4–20µgmL^{-1} and 10–45µgmL^{-1} for CINN and DIM, respectively. The spectra of the prepared standard solutions were scanned over the range 200–400 nm and stored into the computer. The stored spectra of CINN were divided (amplitude at each wavelength) by the spectrum of 10µgmL^{-1} of DIM. Also the stored spec-

tra of DIM were divided by the spectrum of 14μgmL^{-1} of CINN. The first derivative of the ratio spectra (^{1}DD) with "λ= 4 nm and a scaling factor = 1 was obtained. The amplitudes of the first derivative peaks of CINN and DIM were measured at 232.8 and 275.5 nm, respectively. Calibration graphs were constructed relating the peak amplitudes of (^{1}DD) to the corresponding concentrations. The regression equations were then computed at the specified wavelengths and used for determination of unknown samples containing CINN and DIM.

Bivariate method

The absorption spectra of 4–20 μgmL^{-1} and 10–45 μgmL^{-1} for CINN and DIM, respectively. were recorded over the range 200–400 nm using methanol as a blank. The regression equations were computed at λ= 250 and 276 nm. The concentrations of CINN and DIM were calculated using the parameters of the linear regression functions evaluated individually for each component at the same wavelength and substituting in the following equations:

$$C_{DIM} = \frac{m_{A2}(A_{AB1} - e_{AB1}) + m_{A1}(e_{AB2} - A_{AB2})}{m_{A2}m_{B1} - m_{A1}m_{B2}}$$

$$C_{CINN} = \frac{A_{AB1} - e_{AB1} - m_{B1}C_{CINN}}{m_{A1}}$$

where A_{AB1} and A_{AB2} are the absorbance's of A and B at λ_1 and λ_2, respectively, e_{AB1} and e_{AB2} the sum of the intercepts of the linear calibration at two, wavelengths λ_1 and λ_2 ($e_{AB1} = e_{A1} + e_{B1}$), m_A and m_B the slopes of linear regression and C is the concentrations in μgmL^{-1}. The accuracy of the results was checked by applying the proposed bivariate calibration method for determination of different blind samples of pure CINN and DIM. The concentrations were obtained from the corresponding regression equations from which percentage recoveries were calculated.

Analysis of laboratory prepared mixtures

Different laboratory prepared mixtures containing different ratios (1:1,1:2, 1:2.5, 1:3, 2:1, 2:3, 2:3.5) of CINN and DIM, respectively were prepared. The concentrations of CINN and DIM in the prepared mixtures were calculated using the corresponding regression equations.

Assay of pharmaceutical formulations

Twenty tablets were accurately weighed and powdered. A portion of the powder equivalent to 10 mg of CINN and 20 mg of DIM was weighed accurately into 100-mL volumetric flask; 50 mL methanol was added and sonicated for 30 min, filtered, and then completed to volume with methanol. The solution was diluted to obtain 0.1 mg mL^{-1} of standard solution. The procedure of each method was followed and the concentration of CINN and DIM was calculated from the corresponding regression equations. The validity of the methods was assessed by applying the standard addition technique.

RESULTS AND DISCUSSION

Derivative-ratio spectrophotometric method

The derivative-ratio spectroscopy is a useful tool in quantification of drugs. It could be used in solving the problem of the overlapping absorption bands.

The zero-order of the absorption spectra of CINN and DIM shows severe overlap, Figure 2.

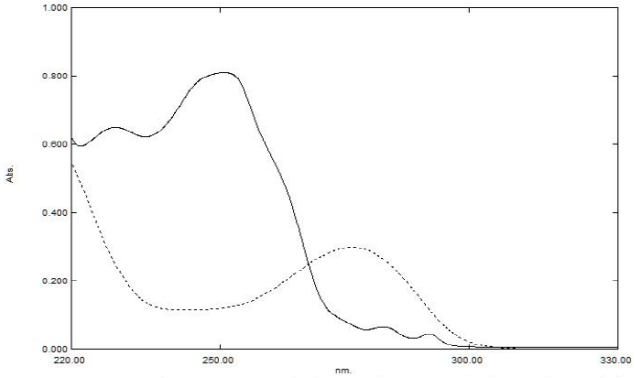

Figure 2 : Absorption spectra of cinnarzine 14μg/ml (___) and dimenhydrinate 10μg/ml (——) using methanol as a blank.

It could be applied for simultaneous determination of CINN and DIM. This could be solved by applying the zero-order of the ratio spectra and the first order of the ratio spectra as presented in Figures 3a, 3b and 4a, 4b.

Linear calibration graphs were obtained in concentration range of 4–20 μgmL^{-1} and 10–45 μgmL^{-1} for CINN and DIM, respectively by recording the peak amplitudes at 232.8 and 275.5 nm for CINN and DIM, respectively.

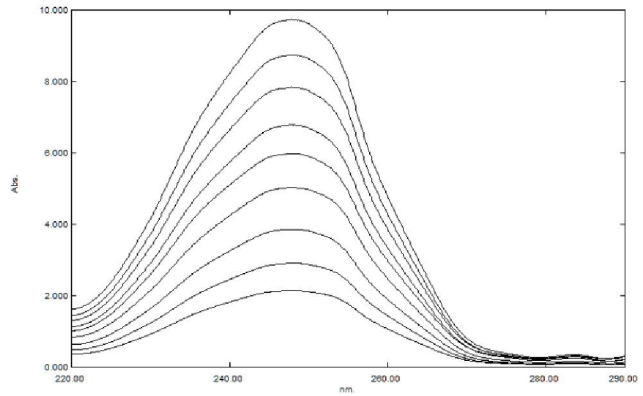

Figure 3a : Ratio spectra of cinnarzine (4-20µg/ml) using the spectrum of 10µg/ml of dimenhydrinate as a divisor.

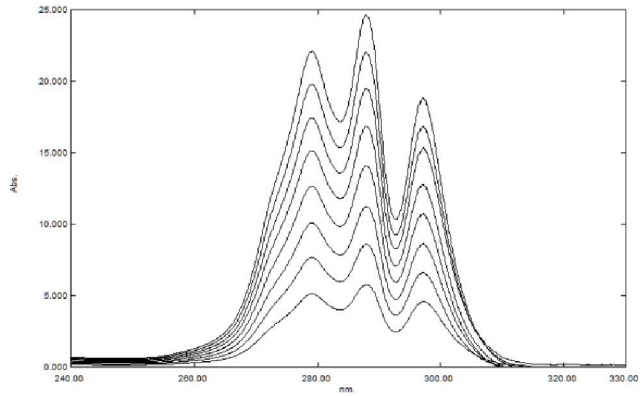

Figure 3b : Ratio spectra of dimenhydrinate (10-45µg/ml) using the spectrum of 14µg/ml of cinnarizine as a divisor.

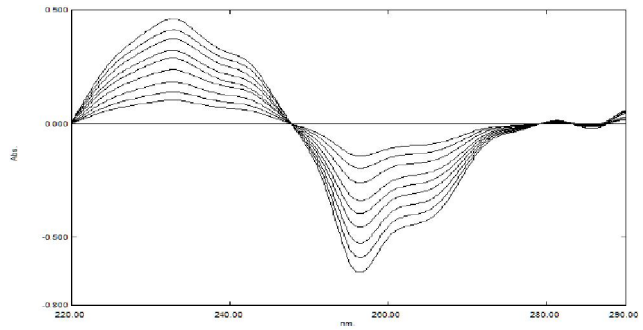

Figure 4a : First derivative of ratio spectra of cinnarizine (4-20 µg/ml) using the spectrum of 10µg/ml of dimenhydrinate as a divisor

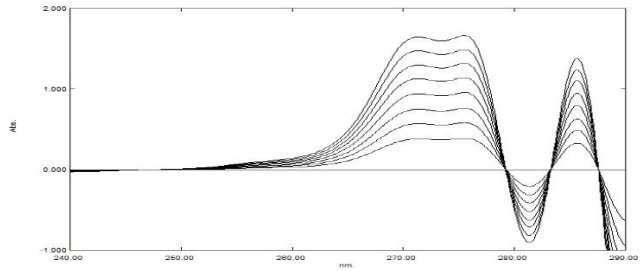

Figure 4b : First derivative of ratio spectra of dimenhydrinate (10-45 µg/ml) using the spectrum of 14µg/ml of cinnarizine as a divisor.

The regression equations were computed and found to be

$^1DD_{CINN}$ = 0.0226 C + 0.0077 (r = 0.9997), at 232.8 nm

$^1DD_{DIM}$ = 0.0364 C + 0.0373 (r = 0.9998), at 275.5 nm

where ^{1}DD is the peak amplitude of the first derivative of ratio spectra, C is the concentration in µgmL^{-1} and r is the correlation coefficient.

The precision of the proposed method was checked by the analysis of different concentrations of samples in triplicates. The mean percentage recoveries were found to be 100.22±1.383 and 99.95±0.986, for CINN and DIM, respectively.

Bivariate method

The bivariate calibration method may be competitive and in some cases even superior to commonly used derivative spectrophotometric methods for the resolution of binary mixtures. The advantage of bivariate calibration method is its simplicity and the fact that derivatization procedures are not necessary. Unlike other chemometric techniques, there is no need for full spectrum information and no data processing is required. Calibration function was calculated (r > 0.9990), m_i- and e_i-values were taken for the bivariate algorithm. In order to apply the bivariate method to the resolution of binary mixture of CINN and DIM, we first select the signals of the two components located at six wavelengths: 230, 240, 250,260, 270 and 276 nm. The calibration curve equations and their respective linear regression coefficients are obtained with the aim of ensuring that there is a linear relationship between the absorbance values and the concentrations. All the calibration curves at the selected wavelengths showed satisfactory linear regression coefficients (r > 0.9990). The slope values of the linear regression were estimated for both components at the selected wavelengths and used for determination of the sensitivity matrices K, proposed by Kaiser's method[13].

The determinants of these matrices were calculated as shown in TABLE 1.

The wavelength set was selected for which the highest matrix determinant value was obtained. For the bivariate determination of CINN and DIM the wave-

lengths 250 and 276 nm were best used. At these selected wavelengths, the one-component calibration curves were obtained in the range of 4–20 μgmL^{-1} and 10-45 μgmL^{-1} for CINN and DIM, respectively. The linear regression calibration formulae used for the bivariate algorithm are presented in TABLE 2.

TABLE 1 : Application of Kaiser's method in the selection of wavelength pair for the mixture of cinnarizine and dimenhydrinate: the absolute values of determinants of sensitivity matrices (K×10^{-4}).

λ/λ	230	240	250	260	270	276
230	0	4.12	5.60	0.06	9.75	0.31
240		0	0.69	3.57	11.15	12.79
250			0	4.87	13.53	15.42
260				0	8.63	10.41
270					0	1.6
276						0

TABLE 2 : Linear regression calibration formulae used for the bivariate algorithm for cinnarizine and dimenhydrinate.

Component	Calibration Equation	
	λ=250nm	λ=276nm
Cinnarizine	A =0.0571C+0.0183 (r =0.9997)	A=0.0052C-0.0001 (r =0.9991)
Dimenhydrinate	A =0.0109C +0.0132 (r =0.9998)	A =0.028C+0.021 (r =0.9999)

The mean percentage recoveries were 100.04±1.240 and101.47±1.121, for CINN and DIM, respectively. The advantage of this method over the other spectrophotometric methods is the ability for simultaneous determination of CINN and DIM in mixtures.

The selectivity of the proposed procedures was assessed by the analysis of laboratory prepared mixtures containing different ratios of the CINN and DIM, with mean percentage recovery of 99.75±0.825, 100.18±0.978for CINN and DIM, respectively, by the first derivative of ratio spectra and 100.45±1.112, 99.63±1.071for CINN and DIM, respectively, by the bivariate method as given in TABLE 3.

The suggested methods were found to be valid and applicable for the analysis of CINN and DIM in their pharmaceutical formulation (Amocerebral plus tablets) with mean percentage recoveries 99.94± 0.934, 100.61±1.142 for CINN and DIM, respectively, by the first derivative of ratio spectra and 99.67±1.421, 98.96±0.892 for CINN and DIM, respectively, by the bivariate method (TABLE 4). The validity of the suggested methods was further assessed by applying the standard addition technique (TABLE 4).

TABLE 3 : Determination of cinnarizine and dimenhydrinate in laboratory prepared mixtures by the proposed spectrophotometric methods

Claimed taken concentration (μg mL^{-1})		Ratio	^{1}DD		Bivariate	
			Recovery %		Recovery %	
Cinnarizine	Dimenhydrinate	Cinnarizine: Dimen- hydrinate ratio	Cinnarizine	Dimenhydrinate	Cinnarizine	Dimenhydrinate
			232.8 nm	275.5 nm	250 nm	276 nm
10.00	10.00	1 : 1	100.51	101.45	100.97	100.04
20.00	40.00	1 : 2	99.78	101.47	100.88	99.60
14.00	35.00	1 : 2.5	99.54	99.77	98.16	101.07
10.00	30.00	1 : 3	98.96	99.17	100.43	99.40
20.00	10.00	2 : 1	98.68	99.07	101.20	100.67
10.00	15.00	2 : 3	99.75	100.31	100.05	98.10
20.00	35.00	2:3.5	101.05	100.01	101.45	98.55
Mean ± S.D.			99.75±0.825	100.18±0.978	100.45±1.112	99.63±1.071

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TABLE 4 : Quantitative determination of cinnarizine and dimenhydrinate in Amocerbral plus tablets by the proposed spectrophotometric methods

Amocerebral plus Tablets	Component	^{1}DD method				Bivariate method			
		Found*	Added	Found	Recovery	Found*	Added	Found	Recovery
Batch No 124820 Mean± S.D.	Cinnarizine mean± S.D. 99.94± 0.934 Dimenhydrinate mean± S.D 100.61± 1.142		6.00	5.98	99.67		6.00	6.01	100.17
			8.00	8.05	100.05		8.00	8.02	100.25
			10.00	9.97	99.86		10.00	9.85	98.50
			15.00	15.28	99.86±0.190	99.67±1.421	15.00	14.91	99.64±0.988
			20.00	20.24	101.87	98.96±0.892	20.00	20.16	99.40
			25.00	24.87	101.20		25.00	25.42	100.80
					99.48				101.68
					100.85±1.233				100.63±1.1498

***Average of three different determinations**

TABLE 5 : Statistical analysis of the results obtained by the proposed spectrophotometric methods and the reported method for the determination of cinnarizine and dimenhydrinate in pure powder form.

Item	^{1}DD method		Bivariate method		Reported method*[12]	
	Cinnarizine	Dimenhydrinate	Cinnarizine	Dimenhydrinate	Cinnarizine	Dimenhydrinate
Mean	100.22	99.95	100.04	101.47	100.24	100.80
S.D.	1.383	0.986	1.240	1.121	0.961	1.245
Variance	1.913	0.972	1.538	1.257	0.924	1.550
n	9	8	9	8	9	8
Student's t test	0.039 (2.120)**	1.610 (2.145)**	0.405 (2.120)**	1.232(2.145)**		
F value	2.070 (3.410)**	1.595 (3.790) **	1.665 (3.410)**	1.233 (3.790)**		

*** First derivative spectrophotometry for determination of cinnarizine at 243.6 nm, and 263 nm for determination of dimenhydrinate using methanol as a solvent.; **the values in parenthesis are the corresponding tabulated t and f values at p=0.05.**

TABLE 6 : Assay validation parameters of the proposed spectrophotometric methods for the determination of pure samples of cinnarizine and dimenhydrinate.

Parameter	DD_1 method		Bivariate method	
	Cinnarizine λ= 232.8 nm	Dimenhydrinate λ= 275.5 nm	Cinnarizine	Dimenhydrinate
Accuracy (mean ± S.D.)	100.22±1.383	99.95±0.986	100.04±1.240	101.47±1.121
Specificity	99.75±0.825	100.18±0.978	100.45±1.112	99.63±1.071
Precision				
Repeatability*	100.42±0.756	99.65±0.781	99.20±0.935	100.11±0.562
Intermediate precision**	101.05±0.630	100.22±1.016	100.35±0.981	98.85±0.945
Linear range (µg/ml)	4-20	10-45	4-20	10-45
Slope	0.0226	0.0364	0.0571	0.028
Standard error of the Slope	0.000203	0.000277	0.000476	0.000224
Intercept	0.0077	0.0373	0.0183	0.021
Standard error of the intercept	0.002655	0.00826	0.006218	0.006673
Correlation (r) coefficient	0.9997	0.9998	0.9997	0.9999

***the intraday and **the inter-day mean values ± standard deviations of samples of concentration of 10, 14, 20 µg/ml, 10, 15, 20 µg/ml of cinnarzine and dimenhydrinate, respectively**

Statistical analysis

Results of the suggested methods for determination of CINN and DIM were statistically compared with those obtained by applying the reported spectrophotometric method[12]. (TABLE 5).

The calculated t- and F-values[10] were found to be less than the corresponding theoretical ones, confirming good accuracy and excellent precision (TABLE 6).

CONCLUSION

The work presents simple, sensitive, and precise

methods for simultaneous determination of CINN and DIM in their combined dosage form. The reagents used in the proposed methods are cheap and readily available So, the proposed methods could be used in routine and quality control analysis of the cited drugs in pharmaceutical formulation without any interference due to the excipients.

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