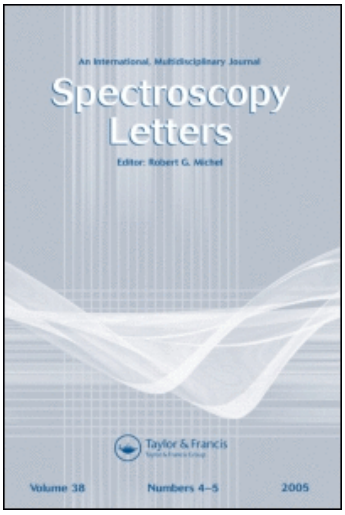

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DETERMINATION OF CERTAIN ANTISPASMODIC DRUGS AS SINGLE INGREDIENT, MEBEVERINE HYDROCHLORIDE, AND IN TWO COMPONENT MIXTURES, MEBEVERINE HYDROCHLORIDE-SULPIRIDE AND ISOPROPAMIDE IODIDE-TRIFLUOPERAZINE HYDROCHLORIDE

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DETERMINATION OF CERTAIN ANTISPASMODIC DRUGS AS SINGLE INGREDIENT, MEBEVERINE HYDROCHLORIDE, AND IN TWO COMPONENT MIXTURES, MEBEVERINE HYDROCHLORIDE–SULPIRIDE AND ISOPROPAMIDE IODIDE–TRIFLUOPERAZINE HYDROCHLORIDE

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ABSTRACT

Two simple and sensitive methods are described for the quantitative determination of mebeverine hydrochloride as single ingredient. The first method depends on the application of quantitative ^{1}H-NMR spectroscopy using deuterated chloroform and hexamine as an internal reference standard. The second method is based on measuring the native fluorescence of mebeverine hydrochloride in 0.1 N sulphuric acid at 360 nm with excitation at 290 nm. Furthermore simultaneous determinations of two component mixtures, mebeverine hydrochloride with sulpiride and isopropamide iodide

with trifluoperazine hydrochloride are presented using first-derivative and second-derivative UV-spectrophotometry, respectively. The proposed methods have been successfully applied to the determination of the cited drugs in commercial tablets.

Compared with the reference methods, the proposed methods are more sensitive, with good accuracy and reproducibility.

Key Words: Mebeverine hydrochloride; Sulpiride; Isopropamide iodide; Trifluoperazine hydrochloride; ^{1}H-NMR spectroscopy; Spectrofluorimetry; First-derivative and Second-derivative UV-spectrophotometry

INTRODUCTION

Mebeverine hydrochloride and isopropamide iodide are used as antispasmodic drugs for the treatment of spastic colon[1]. Mebeverine hydrochloride is marketed either individually or in combination with a tranquilizer, sulpiride. Isopropamide iodide is marketed in combination with a tranquilizer, trifluoperazine hydrochloride[2,3].

Mebeverine hydrochloride was determined by several methods including colorimetry[4], first-derivative UV–spectrophotometry[5–7] and HPLC[8,9]. Few accepted methods are available for the simultaneous determination of the investigated drugs in mixtures. Mebeverine hydrochloride and sulpiride were simultaneously determined with first-derivative UV-spectrophotometry, TLC-densitometry and liquid chromatography[10]. Isopropamide iodide–trifluoperazine hydrochloride combination was estimated using second derivative method, after pre-extraction procedure for the separation of isopropamide iodide from the co-existing trifluoperazine hydrochloride[11]. In this connection, it seemed to be necessary to develop simple, accurate and reproducible methods for the determination of these drugs as single ingredient and in mixtures.

This work deals with the quantitation of mebeverine hydrochloride with ^{1}H-NMR spectroscopy and spectrofluorimetry. In addition two-component mixtures mebeverine hydrochloride–sulpiride and isopropamide iodide–trifluoperazine hydrochloride were simultaneously determined without previous separation by zero—crossing first-derivative and second-derivative spectrophotometry respectively. The proposed methods were proved using laboratory prepared mixtures of the drugs and successfully applied to their analysis in tablets form.

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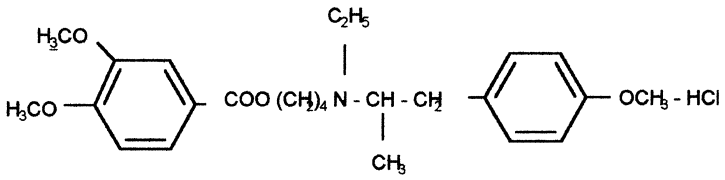
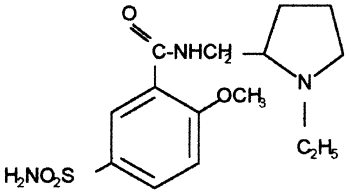


Mebeverine hydrochloride



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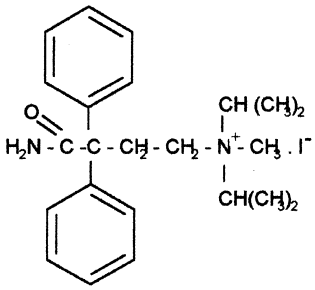
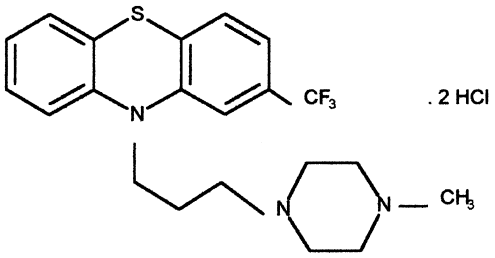


Isopropamide iodide



Trifluoperazine hydrochloride

EXPERIMENTAL

Apparatus

–Joel Fx90 Q–FTNM spectrometer.
–Shimadzu spectrofluorimeter RF-540 (Japan), the conditions were: sensitivity, high (× 100); ordinate scale, 3; excitation wavelength, 291 nm.

–Shimadzu UV-visible recording spectrophotometer UV-265 (Japan). Conditions are shown in Table 1.

Materials

1. Mebeverine hydrochloride and colospasmin tablets (batch no. 962825) claimed to contain 100 mg mebeverine hydrochloride were supplied by the Egyptian International Pharmaceutical Industries Company (EIPICO) Tenth of Ramadan City, Egypt.
2. Sulpiride and colona tablets (batch no. 70660) claimed to contain 100 mg mebeverine hydrochloride and 25 mg sulpiride were supplied by Rameda Company for Pharmaceutical Industries and Diagnostic Reagents, Tenth of Ramadan City, Egypt.
3. Isopropamide iodide, trifluoperazine hydrochloride and stelabid tablets (batch no. 510831) claimed to contain 5 mg isopropamide base and 1 mg trifluoperazine base were supplied by Kahira Pharmaceutical and chemical Industries Company, Cairo, Egypt.

Reagents

The reagents and solvents used were of analytical and spectroscopic grades respectively.

Chloroform, deuterated chloroform (d_6), hexamine, TMS, hydrochloric acid and methanol were purchased from E. Merck Company, Germany. Sulphuric acid (Prolabo), 0.1 N solution.

Table 1. Derivative Spectrophotometry Settings Used

Parameter	First-Derivative	Second-Derivative
Mode	^1D	^2D
Wavelength range (nm)	250–330	200–300
$\Delta\lambda$	2	2
Scale (nm cm^{-1})	10	10
Speed	Fast	Fast
Slitwidth (nm)	1	1
Cyc. T. (min)	0	0
Ordinate range	0.1–+1	−0.5–+0.5

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General Considerations

1. For the determination of tablets, twenty tablets were accurately weighed after removing their sugar coat and dried (if necessary), powdered and thoroughly mixed.
2. To assess the validity of the proposed methods the standard addition technique was applied.

^{1}H-NMR Method for the Determination of Mebeverine Hydrochloride

Standard Solutions for Linearity

Prepare mebeverine hydrochloride solution (5 mg mL^{-1}) and hexamine solution (25 mg mL^{-1}) each in chloroform. Into a series of NMR tubes, transfer aliquot volumes of mebeverine hydrochloride solution containing 2.5–12.5 mg, add aliquot volume of hexamine solution equivalent to 0.5 mg (internal standard), evaporate the solutions to dryness and dissolve the residues into 1 mL deuterated chloroform.

Procedure

Construction of Calibration Curve

Record the NMR spectra of the prepared standard solutions after the addition of drops of TMS, whores singlet is positioned at 0.00 ppm. Measure the integrals of the sharp singlets at 4.05 and 4.95 ppm for mebeverine hydrochloride and hexamine respectively. To calculate the weight of the drug substitute in the following Eq.:

$$W_m = (H_h/H_m)(M_m/M_h)(I_m/I_h)(W_h)$$
$$= \frac{12}{6}\, x\, (466.04/140.19) I_m/I_h\, x\, 0.5 = 3.3243455\, I_m/I_h \ldots\ldots \qquad (1)$$

Where I is the average integral of the signal (mm), H is the number of protons corresponding to the signal, M is the molecular weight, W is the weight (mg). The subscript m and h stand for the mebeverine hydrochloride and hexamine respectively. Construct the calibration curve relating the amount of mebeverine hydrochloride in mg to I_m/I_h and compute the corresponding regression equation (Table 2).

Table 2. Linearity Study and Regression Equations of the Proposed Methods

Drug	Method	Wavelength (nm)	Concentration Range	Regression Equation	Correlation Coefficient (r)
Mebeverine HCl*	^{1}HNMR	–	2.5–12.5 mg	$C = 3.353\ I_m/I_h - 0.0322$ (2)	0.9998
Mebeverine HCl*	Spectrofluorimetric	Excitation 360 Emission 291	1–14 μg mL^{-1}	$C = 0.0015\ F - 0.0027$ (3)	0.9976
Mebeverine HCl§	^{1}D	266	0.01–0.1 mg mL^{-1}	$C = 0.0199\ H_{m\ 266} - 0.0231$ (4)	0.9996
Mebeverine HCl§	^{1}D	299.5	0.01–0.1 mg mL^{-1}	$C = 0.0264\ H_{m\ 299.5} - 0.0151$ (5)	0.9996
Sulpiride§	^{1}D	299.5	0.015–0.12 mg mL^{-1}	$C = 0.0458\ H_s - 0.0119$ (6)	0.9999
Isopropamide I@	^{2}D	244.5	0.075–0.225 mg mL^{-1}	$C = 0.0658\ H_i - 0.0135$ (8)	0.9996
Trifluoperazine HCl@	^{2}D	254	0.015–0.045 mg mL^{-1}	$C = 0.009\ H_t - 0.007$ (9)	0.9983

*Individually §, @ in combination, C is the concentration (mg/10 mL), I is the average integral of the signal (mm), F is the fluorescence intensity, H is the ordinate values of ^{1}D or ^{2}D at the respective wavelength, the subscripts m, h, s, i and t denote mebeverine HCl, hexamine, sulpiride, isopropamide I and trifluoperazine HCl respectively.

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Assay of Colospasmin Tablets

Weigh accurately a quantity of the mixed powder tablets equivalent to 500 mg mebeverine hydrochloride, extract with chloroform (3×10 mL), filter into 50 mL volumetric flask and complete to volume with chloroform. Treat aliquot volumes containing 4–6 mg mebeverine hydrochloride according to the procedure for the construction of calibration curve.

Spectrofluorimetric Method for the Determination of Mebeverine Hydrochloride

Standard Solution for Linearity

20 μg mL^{-1} mebeverine hydrochloride solution in 0.1 N sulphuric acid.

Procedure

Construction of Calibration Curve

Transfer aliquot volumes of the standard solution containing 10–140 μg mebeverine hydrochloride into a series of 10 mL volumetric flasks and complete to with 0.1 N sulphuric acid.

Record the fluorescence intensities (F) at 360 nm emission with excitation at 291 nm against reagent blank. Construct the calibration curve by plotting the fluorescence intensities (F) vs. the concentration of mebeverine hydrochloride and compute the corresponding regression equation Table 2.

Assay of Colospasmin Tablets

Weigh accurately a quantity of the mixed powder tablets equivalent to 40 mg mebeverine hydrochloride, extract with 0.1N sulphuric acid (3×20 mL), filter and complete to 100 mL into a volumetric flask with 0.1 N sulphuric acid. Apply the procedure of calibration curve to aliquot volumes containing 16–72 μg mebeverine hydrochloride after carrying out the proper dilution.

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First-Derivative Spectrophotometry for the Simultaneous Determination of Mebeverine Hydrochloride–Sulpiride Combination

Drug Solutions for Linearity

For each drug, prepare a 200 μg mL^{-1} solution in methanol.

Dilute accurately measured volumes of each solution with methanol to obtain 10–100 μg mL^{-1} mebeverine hydrochloride solutions and 0.15–10.2 mg mL^{-1} sulpiride solutions.

Laboratory Prepared Mixture

Into a series of 10 mL volumetric flasks, prepare mixtures containing 250–960 μg mebeverine hydrochloride and 25–1080 μg sulpiride in methanol.

Construction of Calibration Curves

Record the ^{1}D spectra of the standard solutions of mebeverine hydrochloride and sulpiride against methanol. Construct two calibration curves relating the ordinate values of the first mode at 266 nm and 299.5 nm (for mebeverine hydrochloride) and a third one at 299.5 nm (for sulpiride), to the corresponding concentrations, and compute the corresponding regression equations Table 2.

Assay of Laboratory Prepared Mixture

Record the ^{1}D spectra of the prepared mixtures and measure the ordinate values at 266 nm and 299.5 nm. Substitute the value at 266 nm in the regression Eq. (4) to calculate the concentration of mebeverine hydrochloride. Calculate the concentration of sulpiride by the use of Eq. (6) after subtracting the interference of mebeverine hydrochloride on sulpiride at 299.5 nm (Eq. (7)) from the ordinate value of the mixture at 299.5 nm.

$$H_{m299.5} = 0.7538H_{m266} - 0.303\ldots. \quad (7)$$

Where $H_{m299.5}$ is the interference of mebeveriney hydrochloride on sulpiride at 299.5 nm and H_{m266} is the ordinate value of mebeverine hydrochloride at 266 nm. Results are shown in Table 4.

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Assay of Colona Tablets

Weigh accurately a quantity of the mixed powder tablets equivalent to 80 mg mebeverine hydrochloride and 20 mg sulpiride, extract with methanol (3×20 mL), filter into a 100 mL volumetric flask and make up to volume with the same solvent. Dilute 20 mL of this solution with methanol into a 50 mL volumetric flask (solution A). Into two separate series of 10 mL volumetric flasks, transfer aliquot volumes of solution A containing 0.16–0.48 mg mebeverine hydrochloride (series 1) and 0.1–0.24 mg sulpiride (series 2). Add 1 mL sulpiride solution (0.4 mg mL^{-1}) to each flask of series 2 and make up to volume with methanol. Record the ^1D spectra for series 1,2 and a (solution B) containing 1 mL of sulpiride solution (0.4 mg mL^{-1}) into 10 mL methanol. Measure the ordinate values at 266 nm for (series 1 and 2) and at 299.5 nm for (series 2) and (solution B). Calculate the amount of sulpiride in solution B from Eq. (6) and subtract it from the total amount of sulpiride found in tablet solution. Calculate the concentration of mebeverine hydrochloride and sulpiride from Eqs. (4–7) as explained under laboratory prepared mixture.

Second-Derivative Spectrophotometry for the Simultaneous Determination of Isopropamide Iodide–Trifluoperazine Hydrochloride

Drug Standard Solutions for Linearity

(1) 50 mg mL^{-1} isopropamide iodide solution in 0.1 N hydrochloric acid.
(2) 10 mg mL^{-1} trifluoperazine hydrochloride in 0.1 N hydrochloric acid.

Dilute accurately measured volumes of each of the standard solutions with methanol to obtain 75–22.0 μg mL^{-1} isopropamide iodide solutions and 15–45 μg mL^{-1} trifluoperazine hydrochloride solutions.

Laboratory Prepared Mixture

Prepare a mixture solution containing a concentration ratio of isopropamide iodide: trifluoperazine hydrochloride as (0.48 mg:0.08 mg) in 0.1 N hydrochloric acid. Dilute aliquot volumes of this mixture containing isopropamide iodide (0.96–2.16 mg) and trifluoperazine hydrochloride

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(0.16–0.36 mg) into a series of 10 mL volumetric flasks with 0.1 N hydrochloric acid.

Procedure

Construction of Calibration Curves

Record the ^{2}D spectra of the diluted standard solutions of isopropamide iodide and trifluoperazine hydrochloride against 0.1 N hydrochloric acid. Construct two calibration curves relating the ordinate values of the second mode at 244.5 nm and 254 nm to the corresponding concentrations of isopropamide iodide and trifluoperazine hydrochloride respectively. Compute the corresponding regression equations Table 2.

Assay of Laboratory Prepared Mixture

Record the ^{2}D spectra of the prepared mixture and measure the ordinate values at 244.5 nm and 254 nm. Calculate the concentrations of isopropamide iodide and trifluoperazine hydrochloride in the mixture from Eqs. (8) and (9) respectively.

Results are shown in Table 4.

Assay of Stelabid Tablets

Weigh accurately a quantity of the mixed powder tablets equivalent to 272.2 mg isopropamide iodide and 46.88 mg trifluoperazine hydrochloride, extract with 0.1 N hydrochloric acid (3×20 mL), filter and complete to 100 mL into a volumetric flask with 0.1 N hydrochloric acid. Apply the procedure of calibration curve to aliquot volumes containing isopropamide iodide (1.008–1.663 mg) and trifluoperazine hydrochloride (0.188–0.281 mg). Calculate the concentrations of both drugs using Eqs. (8) and (9).

RESULTS AND DISCUSSION

^{1}H-NMR Method

Figure 1 shows the NMR spectrum of mebeverine hydrochloride in chloroform (d_6) containing hexamine as internal standard. The sharp singlet

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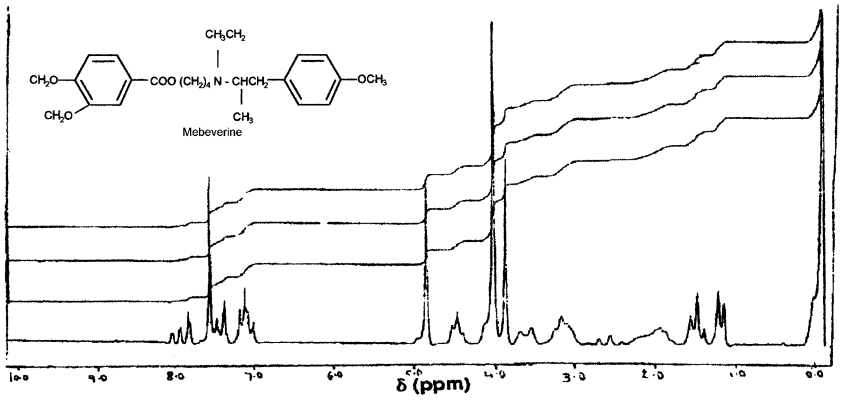

Figure 1. ^{1}H-NMR spectrum of mebeverine hydrochloride (12.5 mg), mixed with hexamine (0.5 mg) in chloroform (d).

at 4.05 ppm which corresponds to the six aromatic protons of the two adjacent methoxy groups in mebeverine hydrochloride was used for its quantitative determination by comparing its integral to that of the sharp singlet at 4.95 ppm of the twelve protons of hexamine. Linear relationship was obtained over the concentration range 2.5–12.5 mg. It was possible by the use of Eq. (1) and (2) to determine mebeverine hydrochloride with mean accuracies 99.9 ± 1.9 and 100.15 ± 2.11 respectively Table 3.

Spectrofluorimetric Method

As can be seen from Fig. 2, the native fluorescence excitation and emission of mebeverine hydrochloride in 0.1 N sulphuric acid occur at 291 nm and 360 nm respectively. Linear relationship was obtained over the concentration range 1–14 $\mu g\,mL^{-1}$. Table 3 shows the results obtained for the determination of mebeverine hydrochloride using Eq. (3).

Commercial tablets (colospasmin tablets) containing mebeverine hydrochloride were successfully analysed by the proposed methods and recovery experiments of standard added were performed as shown in Table 4.

Derivative Spectrophotometry of Drug Combinations

Figs. 3(a, b) show the zero-order spectra of mebeverine hydrochloride–sulpiride and isopropamide iodide–trifluoperazine hydrochloride

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Table 3. Determination of Mebeverine Hydrochloride by ^{1}HNMR and Spectrofluorimetric Methods

	^{1}HNMR Method						
	Equation 1		Equation 2		Spectrofluorimetric Method		
Taken mg	Recovered mg	Recovery %	Recovered mg	Recovery %	Taken mg/10 mL	Recovered mg/10 mL	Recovery%
3	2.933	97.77	2.927	97.55	0.02	0.0200	100.00
3.75	3.674	97.97	3.674	97.97	0.03	0.0297	99.00
6.25	6.419	102.70	6.443	103.09	0.05	0.0504	100.80
8.25	8.865	101.31	8.910	101.83	0.07	0.0701	100.14
11.25	11.220	99.73	11.285	100.31	0.09	0.0903	100.33
					0.11	0.1097	99.73
					0.13	0.1278	98.31
Mean ± SD		99.9 ± 1.90		100.15 ± 2.11			99.76 ± 0.78

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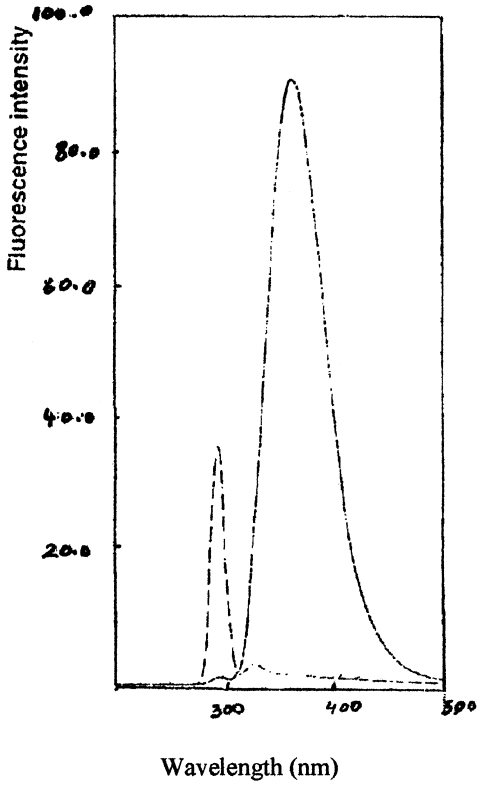

Figure 2. (—) Excitation and (—) emission spectra of mebeverine hydrochloride (20 μg mL^{-1}) in 0.1 N sulphuric acid.

combinations respectively. Because of the extensive overlap of the spectral bands of the two combinations, conventional UV spectrophotometry cannot be used for their determination. However when ^{1}D and ^{2}D UV-spectra were recorded (Figs. 4 a, b), sharp bands were produced which permit determination of the two combinations. Linear relationships were obtained over the concentration ranges found in Table 2. The ^{1}D spectra (Fig. 4a) permit the determination of mebeverine hydrochloride concentration in presence of sulpiride without interference in laboratory prepared mixture, by measuring the ordinate value at 266 nm ($H_{m\ 266}$) (zero-crossing of sulpiride with mean accuracy 99.76 ± 0.45 using Eq. (4), Table 4. Conversely mebeverine hydrochloride interferes with sulpiride determination at 299.5 nm, this problem can be circumvented by equating Eq. (4) and (5) to

Table 4. Determination of Two Component Mixtures Mebeverine Hydrochloride–Sulpiride and Isopropamide Iodide–Trifluoperazine Hydrochloride in Laboratory Prepared Mixtures by the Proposed Methods

Proposed ^{1}D Method				Proposed ^{2}D Method			
Mebeverine HCl		Sulpiride		Isopropamide I		Trifluoperazine HCl	
Added mg/10mL	Recovery %	Added mg/10mL	Recovery %	Added mg/10mL	Recovery %	Added mg/10mL	Recovery %
0.56	100.11	0.56	98.96	0.960	99.08	0.160	99.69
0.64	100.03	0.64	99.62	1.440	99.18	0.240	100.21
0.72	99.97	0.72	99.56	1.336	99.41	0.256	100.08
0.75	100.40	0.88	99.72	1.680	98.72	0.280	99.54
0.82	99.15	0.96	99.52	1.920	100.09	0.320	99.06
0.88	99.52	1.4	99.48	2.016	100.22	0.336	99.70
0.96	99.17	1.08	100.00	2.160	99.63	0.360	99.31
Mean ± SD	99.76 ± 0.45		99.55 ± 0.29		99.48 ± 0.50		99.66 ± 0.37

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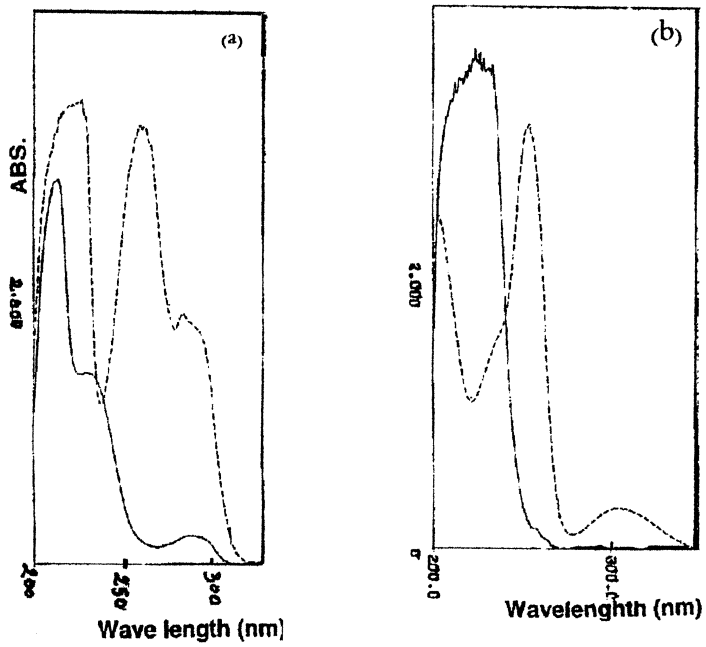

Figure 3. Zero order spectra (a) of mebeverine HCl (—) and sulpiride (...) in (4:1) ratio (b) of 2 mg/10 ml isopropamide I (—) and 0.4 mg/10 ml trifluoperazine HCl (...).

get Eq. (7), from which the interference of mebeverine hydrochloride on sulpiride at 299.5 nm can be obtained. The concentration of sulpiride in the mixture was calculated by the use of Eq. (6) after subtracting the interference of mebeverine hydrochloride at 299.5 nm from the ordinate value of the mixture at 299.9 nm corresponding to the total concentration of the two drugs, with mean accuracy 99.55 ± 0.29 (Table 4). On the other hand the ^{2}D spectra (Fig. 4b) allow the determination of isopropamide iodide at 244.5 nm (zero-crossing of trifluoperazine hydrochloride) and trifluoperazine hydrochloride at 254 nm (zero crossing of isopropamide iodide) in laboratory prepared mixture by the use of Eqs. (8) and (9) with mean accuracies 99.48 ± 0.5 and 99.66 ± 0.37 respectively (Table 4). Commercial tablets, colona and stelabid tablets were successfully analysed by the

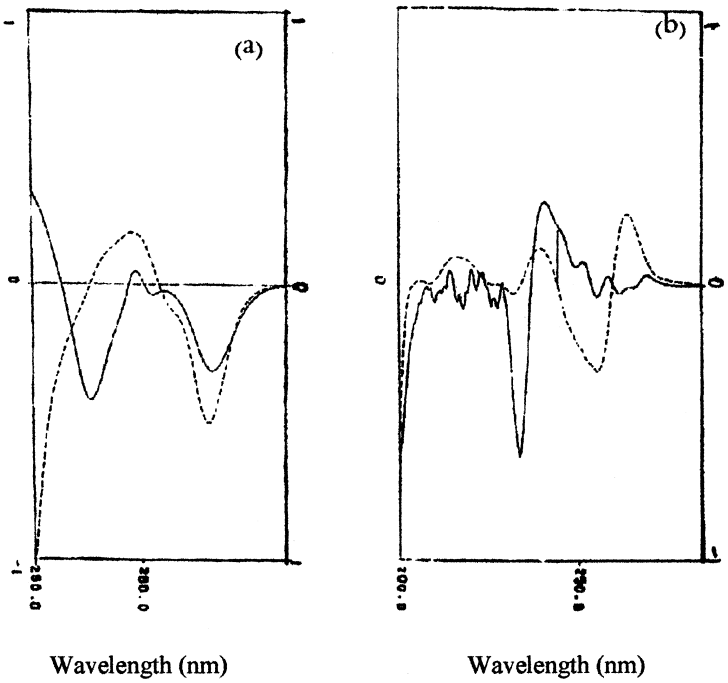

Figure 4. (a) First-derivative spectra of 1 mg/10 mL mebeverine HCl (—) and 1.2 mg/10 ml sulpiride (...). (b) Second-derivative spectra of 2.25 mg/10 mL isopropmide I (—) and 0.45 mg /10 mL trifluoperazine HCl (...).

proposed methods and recovery experiments of added standards were performed as shown in Table 5. It is noteworthy that mebeverine hydrochloride:sulpiride ratio in colona tablets is 4:1 indicating smaller range (0.015–0.12 mg mL^{-1}). This problem was overcome by adding a fixed amount of sulpiride to each experiment and subtract it before calculating the claimed concentration of the drug. Statistical analysis (t-test and F-test) of the results obtained by the suggested methods and official methods[12–15] showed no significant difference in performance (Table 6). The methods proposed have the advantages of being simple, sensitive and there is no need for previous separation compared with the published ^{2}D method which required pre-extraction of isopropamide iodide from the co-existing trifluoperazine hydrochloride.

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Table 5. Application of the Standard Addition Technique to the Analysis of Colospasmin, Colona, and Stelabid Tablets by the Proposed Methods

Colospasmin Tablets				Colona Tablets				Stelabid Tablets			
^{1}HNMR Method		Spectrofluorimetric Method		^{1}D Method				^{2}D Method			
Mebeverine HCl		Mebeverine HCl		Mebeverine HCl		Sulpiride		Isopropamide I		Trifluoperazine HCl	
Added mg	Recovery %	Added mg/10 mL	Recovery %	Added mg/10 mL	Recovery %	Added mg/10ml	Recovery %	Added mg/10 mL	Recovery %	Added mg/10 mL	Recovery %
2.5	98.52	0.016	100.00	0.15	99.53	0.16	100.19	0.24	100.63	0.144	100.00
4.5	98.49	0.016	98.75	0.30	99.50	0.16	100.19	0.48	99.40	0.160	99.88
5.5	99.73	0.024	98.33	0.36	99.56	0.32	100.19	0.48	99.38	0.160	99.88
6.5	99.25	0.032	100.31	0.40	99.50	0.32	100.19	0.84	99.88	0.180	100.00
7.0	100.51	0.032	100.00	0.60	98.93	0.48	98.56	0.84	99.87	0.20	97.90
		0.048	100.63	0.70	99.50	0.48	98.56	0.96	99.39	0.22	100.23
		0.048	1200.31	0.80	99.90	0.48	99.44	1.08	99.01	0.24	99.38
Mean ± SD	99.3		99.81 ± 0.84				99.62 ± 0.72		99.65 ± 0.49		99.61 ± 0.74

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Table 6. Statistical Analysis of the Results of the Proposed Methods and the Official Methods

	Mebeverine HCl					Sulpiride		Isopropamide I		Trifluoperazine HCl	
	^{1}HNMR method										
	Equation 1	Equation 2	Fluorimetric Method	^{1}D Method	Official Method[a]	^{1}D Method	Official Method[b]	^{2}D Method	Official Method[c]	^{2}D Method	Official Method[d]
Mean ± SD	99.9 ± 1.90	100.15 ± 2.11	99.76 ± 0.78	99.76 ± 0.45	100.34 ± 0.64	99.55 ± 0.29	99.77 ± 0.44	99.48 ± 0.50	99.80 ± 0.52	99.66 ± 0.37	99.59 ± 0.69
SE	0.72	0.8	0.29	0.17	0.24	0.11	0.17	0.19	0.20	0.14	0.26
n	5	5	7	7	5	7	5	7	5	7	5
Students t*	0.44	0.37	0.85	1.16		0.41		0.49		0.07	
F**	2.97	3.30	1.22	1.42		1.52		1.05		1.86	

The official methods are mostly dependent on non-aqueous titration methods.

[a] B. P 1998 method [12].

[b] European pharmacopoeia 1996 method [13].

[c] USP 24, NF 19 method [14].

[d] B. P 1998 method [15].

* Tabulated t (n_1, $n_2 = 5$) for 8df and ($P = 0.05$) is 2.2306. ($n_1 = 7$, $n_2 = 5$) for 10df and ($P = 0.05$) is 2.2281.

** Tabulated F (n_1, $n_2 = 5$) for (4,4) df and ($P = 0.05$) is 6.39. ($n_1 = 7$, $n_2 = 5$) for (6,4) df and ($P = 0.05$) is 6.16.

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In conclusion, the proposed methods offer accuracy and precession for the determination of the investigated drugs as found individually or in combination without interference.

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