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Utility Of 3-Methyl-2-Benzothiazolinone Hydrazone Hydrochloride (MBTH) For Colorimetric Determination Of Some Drugs Containing Methoxyl Groups

Corresponding Author

Gamal H.Ragab
Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, (EGYPT)
E-mail : ghragab@hotmail.com

Co-Authors

Manal S.Elmasry, Afaf A.Aboul Kheir
Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, (EGYPT)

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ABSTRACT

Simple, rapid and accurate method was described for the determination of mebevrine HCl (I), trimebutine maleate (II) and verapamil HCl (III) either in pure form or in pharmaceutical preparations. The method based on oxidation of the methoxyl groups of the cited drugs into the corresponding o-quinone, then coupling the resulted o-quinone for (I), (II) and (III) with 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) to produce the corresponding coloured species. The wavelengths for maximum absorption were 670 nm for (I) and 640 nm for both (II) and (III), respectively. Beer's law was obeyed in the concentration range 2-14, 1.25-5 and 0.5-2.5 mg/ml for (I), (II) and (III) respectively. The corresponding molar absorptivities were 0.295×10^3, 0.435×10^3 and 10^4 L.mol.$^{-1}$cm^{-1} for (I), (II) and (III), respectively. Sandell's sensitivities were also calculated. Results of analysis of pure drugs by the proposed method were in good agreement with the official and reference methods. The proposed method was successfully applied for the determination of these drugs in their pharmaceutical dosage forms without interference from other ingredients or common additives.

KEYWORDS

Mebevrine HCl;
Trimebutine maleate and verapamil HCl;
Methoxyl groups;
Potassium periodate;
MBTH;
Colorimetry.

INTRODUCTION

Mebevrine HCl (RS)-4-[ethyl(4-methoxy-α-methylphenethyl) amino]butyl veratrate hydrochloride[1] is an antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract[2]. The reported methods for its determination were derivative spectrophotometry[3], ion pair formation[4,5], high performance liquid chromatography [HPLC][6,7] and capillary chromatography[8].

Trimebutine maleate 3,4,5-trimethoxybenzoic acid 2-(dimethylamino)-2-phenylbutyl ester[9] is used in treatment of irritable bowel syndrome due to its action on opioid receptors in the gastrointestinal tract[2]. It was determined by ion-pair formation with bismuth(III)-iodide[10], first derivative spectrophotometry[11] and HPLC methods[12,13].

Verapamil HCl (RS)-5-[2(3,4dimethoxyphenyl) ethyl]methylamino-2-(3,4-dimethoxy-phenyl)-2-isopropylvaleronitrile hydrochloride[1] a calcium-channel blocker and class IV antiarrhythmic. It is also used in treatment of hypertension as it decreases the peripheral vascular resistance[2]. Ion pair formation[14], charge transfer complexation[15], metal complexation[16], gas chromatography[17,18], HPLC[19,20]. potentiometric[21,22] and voltametric[23] methods were reported in the literature for the assay of verapamil HCl.

Simple and accurate spectrophotometric methods are still required for routine analysis and quality control of the studied drugs. MBTH was widely used as a sensitive reagent for the determination of phenolic drugs[24-26]. There were no reports in the literature for its use for determination of the methylated phenolic groups. In the present work, trials were made to use MBTH as colorimetric reagent for determination of o-methylated phenolic groups of the studied drugs. In presence of potassium periodate the methoxyl groups were oxidized into the corresponding o-quinones[27] which was coupled with MBTH to produce highly colored products.

EXPERIMENTAL

Apparatus

SHIMADZU uv-1201 uv-vis spectrophotometer, with 10 mm matched quartez cells, was used for all spectral measurments.

Materials and reagents

MBTH, Sigma (USA), 0.4 % w/v solution in water was freshly prepared before use. Potassium periodate, 0.5 % w/v solution in distilled water was used.

Pharmaceutically pure mebevrine HCl (E.I.P.I. CO., Tenth of Ramadan City, Egypt), trime butine maleate (Amoun Pharmaceutical Co., El-Obour City, Egypt), verapamil HCl (The Arab Drug Co., Cairo, Egypt) were used as working standards.

The following pharmaceutical preparations were analysed

Colospasmin tablets(E.I.P.I.CO., Egypt) each tablet labelled to contain 100 mg of mebevrine HCl. Gast-regular tablets (Amoun Pharmaceutical Co., Egypt) each tablet labelled to contain 100 mg of trimebutine maleate. Isoptin tablets (The Arab Drug Co., Egypt) each tablet labelled to contain 80 mg of verapamil HCl.

Stock solutions

Stock solutions of 0.125, 0.25 and 10 mg/ml in water for trimebutine maleate, verapamil HCl and mebevrine HCl were used.

General procedure

Into a 10-ml calibrated flask, aliquot volumes containing 2-14 mg of mebevrine HCl, 1.25-5 mg of trimebutine maleate, or 0.5-2.5 mg of verapamil HCl were transferred, 2.5 ml of 0.5 % potassium periodate solution for mebevrine HCl and verapamil HCl or 1ml for trimebutine maleate were added respectively. MBTH solution 2, 1 ml, were added for mebevrine HCl or for both trimebutine maleate and verapamil HCl, respectively. Mixed well, left for 10 min at room temperature and diluted to volume with water. The absorbances were measured at 640 nm for trimebutine maleate and verapamil HCl, or 670 nm for mebevrine HCl against a reagent blank.

Procedure for pharmaceutical preparation

A portion of the powdered tablets equivalent to 500, 6.25, or 12.5 mg of mebevrine HCl, trimebutine maleate, or verapamil HCl was accurately weighed, extracted with water, and filtered. The residue was washed twice with water. The filtrate and the washings were collected in a 50-ml calibrated flask,

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and diluted to volume with water. Aliquot volumes of the tablets solution equivalent to 2-14 mg of mebevrine HCl, 1.25-5 mg of trimebutine maleate, or 0.50-2.5 mg of verapamil HCl were transferred into 10-ml calibrated flasks and proceeded as directed under the general procedure.

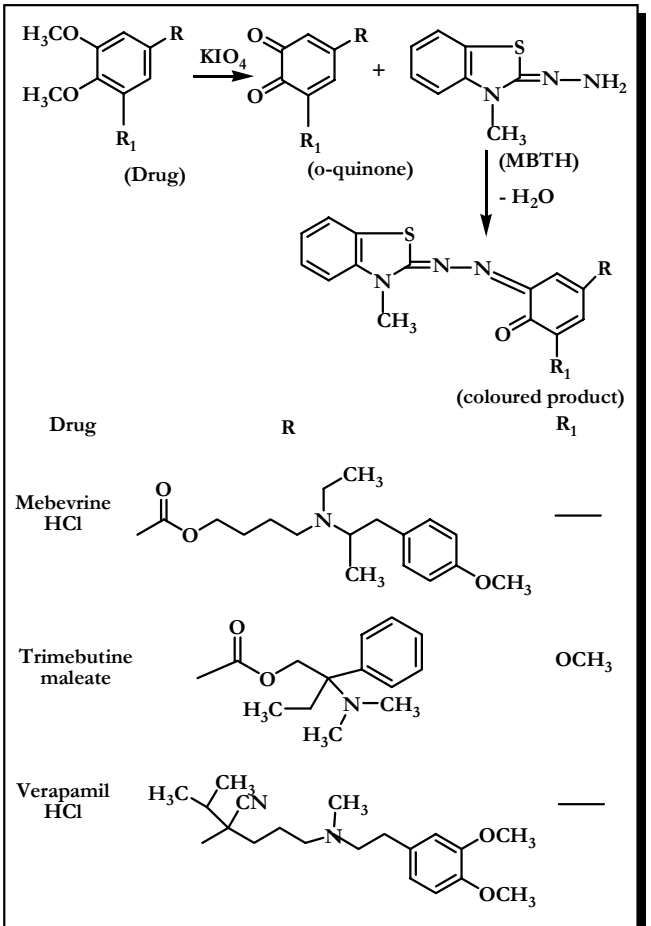
RESULTS AND DISCUSSION

Mechanism of the reaction

It is suggested that the methoxyl groups in the studied drugs were oxidised with potassium periodate to the corresponding o-quinone[27] which was suggested to condense with the amino group of MBTH to produce the colored products (SCHEME 1). The absorption spectra of the colored reaction product at the optimum conditions recorded in the general procedure show a characteristic λ_{max} at 640 nm for trimebutine maleate and verapamil HCl and 670 for mebevrine HCl as shown in figure 1.

Effect of reaction variables

MBTH reacts with the studied drugs to produce a bluish green color. Investigations were carried out to establish the most suitable reaction conditions for the formation of the colored product. The reaction



SCHEME 1: Proposed reaction mechanism

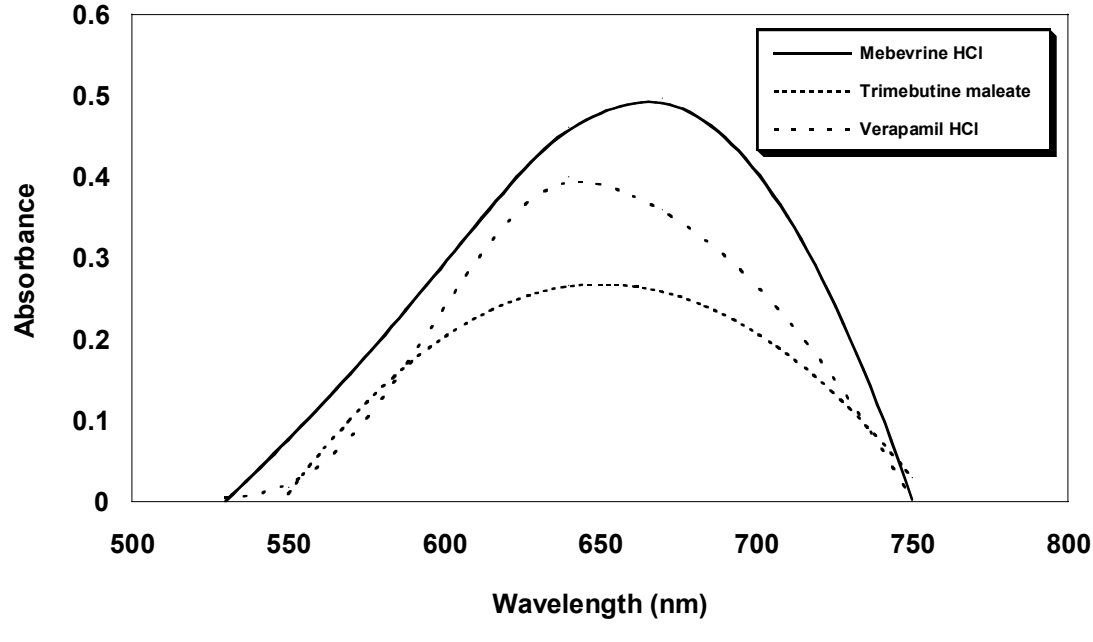


Figure 1: Absorption spectra of the reaction product of MBTH with mebevrine HCl (800 µg ml^{-1}), trimebutine maleate (312.5 µg ml^{-1}) and verapamil HCl (200 µg ml^{1})

variables were studied and optimized, then, applied as in the general procedure.

Different oxidizing agents were tried to affect the oxidative coupling reaction between the cited drugs containing methoxyl groups and MBTH e.g. potassium permenganate, cerric ammonium sulphate, potassium dichromate, ferric chloride and potassium periodate. The oxidative coupling reaction of MBTH with the cited drugs was only produced in the presence of potassium peiodate. Concentration and volume effects of potassium periodate on the oxidative coupling reaction were investigated. It was found that 2.5 ml of 0.5% potassium periodate solution for both mebevrine HCl and verapamil HCl or 1 ml for trimebutine maleate were sufficient to obtain maximum absorbance (Figure 2).

Applying the proposed procedure on a fixed concentration of each drug, several MBTH solutions in the concentration range of 0.1-1% w/v were studied. It was found that 1 ml of 0.4 % MBTH solution was sufficient for maximum color production for trimebutine maleate and verapamil HCl. While 2 ml of MBTH solution was required for mebevrine HCl to produce maximum absorbance. Standing time after mixing reactants and before completing to volume was investegated and 10 min interval was sufficient for complete color development. The effect of time elapsed after volume completion was studied for a period of 60 min and it was found that time had no effect on the reaction over the investigated period and the product was stable.

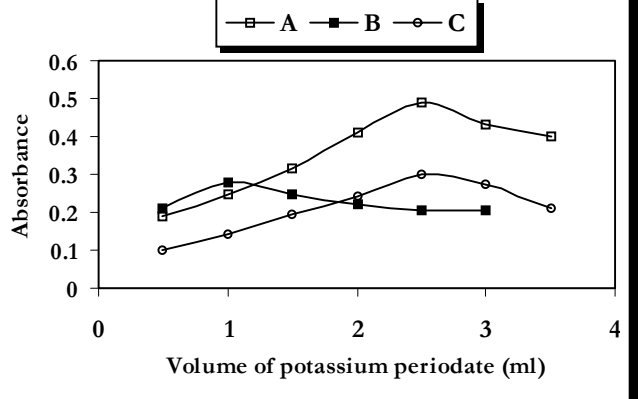


Figure 2: Effect of volume of 0.5% potassium periodate on the reaction of:
(A)Mebevrine HCl (800 μg ml^{-1}) with 2 ml of 0.4 % MBTH. (B) Trimebutine maleate (312.5 μg ml^{-1}) with 1 ml of 0.4 % MBTH. (C) Verapamil HCl (150 μg ml^{-1}) with 1 ml of 0.4 % MBTH.

Stoichiometry of the reaction

Upon applying Job's method of continuous variation under optimized conditions of the reaction using master equimolar solutions of 5×10^{-3} M, the results revealed 1:1 drug to MBTH for trimebutine maleate and 1:2 drug to MBTH ratio for mebevrine HCl and verapamil HCl. (Figure 3).

Quantification

Under the specified reaction conditions, the absorbancies were correlated well with the concentrations of the studied drugs at the specified λ_{max}. Linear correlations were found between absorbance and concentration at the specific λ_{max} for each drug in the range of 200-1400 μg/ml, 125-500 μg/ml and 50-250 μg/ml for mebevrine HCl, trimebutine maleate and verapamil HCl, respectively. Ringbom was found to be 251.18-1258.92, 144.54-436.51 and 60.25-218.77 μg/ml for mebevrine HCl, trimebutine maleate and verapamil HCl, respectively. Standard deviation, relative standard deviation, standard error, molar absorpativities and Sandell's sensitivities for the studied drugs were presented in TABLES 1 and 2.

Accuracy

Applying proposed method on pure form of the studied drugs resulted in excellent recovery as proved

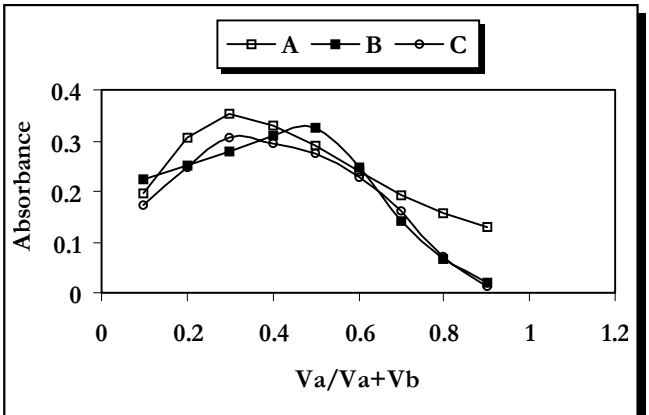


Figure 3: Determination of the stoichiometry of the reaction of:
(A)Mebevrine HCl (5 × 10^{-3} M) and MBTH (5 × 10^{-3} M). (B)Trimebutine maleate (5 × 10^{-3} M) and MBTH (5 × 10^{-3} M). (C)Verapamil HCl (5 × 10^{-3} M) and MBTH (5 × 10^{-3} M) by continuous variation method

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TABLE 1: Quantitative parameters for determination of mebevrine HCl, trimebutine maleate and verapamil HCl using MBTH

Parameter	Mebevrine HCl	Trimebutine maleate	Verapamil HCl
λ_{max}	670	640	640
Beer's law limits (μg ml^{-1})	200-1400	125-500	50-250
Ringbom concentration range (μg ml^{-1})	251.18-1258.92	144.54-436.51	60.25-218.77
Detection limit (μg ml^{-1})	2428.57	1058.82	586.63
Quantitation limit (μg ml^{-1})	8095.23	3529.41	1955.44
Molar absorpitivity (1 mol^{-1} cm^{-1})	0.295×10^3	0.435×10^3	0.992×10^3
Sandell sensitivity (μg ml^{-1})	1.57	1.157	0.491
Regression equation[a]			
Intercept (a)	-0.00014	0.00089	-0.00014
Slope (b)	0.00063	0.00085	0.00202
Correlation coefficient (r)	0.9999	0.9999	0.9999
Standard deviation (%)	0.578	0.3	0.395
Range of error (%)	±.0.258	±.0.1002	±.0.161

[a]**A = a +bC (where C is the concentration in μg ml^{-1})**

TABLE 2: Statistical analysis of results obtained by the proposed method compared with the official[1] methods (non aquous titration) for mebevrine HCl and verapamil HCl and reference method[2] for trimebutine maleate

	Mebevrine HCl		Trimebutine maleate		Verapamil HCl	
	Proposed method	B.P. method	Proposed method	Nce	sed	B.P. method
Mean*	99.83	100.23	100.47	100.52	99.791	100.21
N	6	7	7	7	6	9
V	0.261	0.309	0.0904	0.116	0.156	0.14
S.D.	0.51	0.556	0.3	0.341	0.395	0.375
R.S.D.	0.511	0.554	0.299	0.339	0.395	0.374
S.E.	0.208	0.21	0.1002	0.129	0.161	0.125
t	-	1.34(2.201)	-	0.311(214)	-	2.08(2.16)
F	-	1.18(4.39)	-	1.28(3.59)	-	1.114(3.69)

***Average of 6 determinations**

by statistical comparison of the results obtained by the proposed method and those of the B.P. or reference methods using student (t-test) and the variance ratio (F-test) that showed no significant difference between them as presented in TABLE 2.

Precision

Six replicates of different concentrations of working standards were analysed applying the proposed method. The results of their analysis were summarized in TABLE 1. The results indicated reasonable repeatability of proposed method making it adequate for quality control analysis.

Analysis of pharmaceutical preparation

Applying the proposed method for the determination of the cited drugs in their pharmaceutical preparations, the results summarized in TABLE 3 were obtained. The results were checked through application of standard addition technique and proved the suitability of proposed method for assay of drug in pharmaceuticals without interference from additives.

CONCLUSION

The proposed method was simple, accurate, reproducible, and the colored product was stable for about one hour. The proposed method can be ap-

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TABLE 3: Statistical analysis of results obtained by the proposed method for the studied drugs in their pharmaceutical preparations applying the standred addition technique

Preparation	Taken	Recovered	Recovery%	Mean	SD	RSD	SE	V	N
Colospasmin tablets	200	200	100	100.81	0.578	0.574	0.258	0.334	5
	400	403.18	100.79						
	600	606.35	101.05						
	800	812.7	101.58						
	1000	1006.35	100.63						
Gast-regular tablets	125	125.09	100.07	100.392	0.419	0.417	0.187	0.176	5
	187.5	189.37	101						
	250	250.09	100.03						
	312.5	313.18	100.21						
	375	377.47	100.65						
Isoptin tablets	50	50.74	101.49	100.66	0.494	0.491	0.186	0.244	7
	75	75.37	100.505						
	100	100.502	100.502						
	125	125.62	100.5						
	150	151.73	101.15						
	175	175.87	100.49						
	200	200	100						

plied for routine analysis and in quality control laboratories for the quantitative determination of the studied drugs in pure form and in their pharmaceutical formulations depending on the availability of the chemicals and apparatus. The method can be modified for the analysis of the methylated phenolic drug metabolites.

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