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Research Article

New Spectrophotometric Microdetermination of Meclizine Hcl in Pharmaceutical Formulations and Human Plasma

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ABSTRACT

Two simple, rapid, accurate, and sensitive spectrophotometric methods have been developed for the determination of meclizine hydrochloride in pure form, pharmaceutical formulations and in spiked human plasma. The first method (A) is based on the reaction of the drug with potassium permanganate in the presence of sodium hydroxide to produce a water-soluble bluish-green colored species measurable at 610 nm. The absorbance concentration plot is linear over the range (0.1-**7.1 µg/ml). The second method (B) is based on** oxidation of the drug by potassium dichromate in acidic medium, and measurement of the absorbance of the chromium(III) formed at 580 nm. Regression analysis of Beer's law plots showed good correlation in the concentration ranges (0.2-11.4 µg/ml). The apparent molar absorptivity, Sandell sensitivity, detection and quantitation limits were calculated for two methods. Statistical treatment of the results reflects that the proposed procedures are precise, accurate and easily applicable for the determination of meclizine HCl in pure form and in pharmaceutical preparations.

KEYWORDS: Meclizine HCl; Spectrophotometric; Redox reaction; Potassium permanganate; Potassium dichromate; Pharmaceutical analysis; Spiked human plasma.

INTRODUCTION

Meclizine HCl is piperazine 1-[(4-chlorophenyl) phenylmethyl]-4-[(3-methylphenyl) methyl]-dihydrochloride monohydrate is an antiemetic agent used in post-operative vomiting [1, 2]. Several methods have been reported for the determination of meclizine HC1 inducing HPLC [3-5], using capillary electrophoresis [6] and determine the solubility of meclizine using nonionic surfactants [7], using spectrophotometric (direct and indirect) [8-12] and using simultaneous analysis [13-15].

The oxidation reaction between $KMnO_4$ and meclizine HCl in alkaline medium or potassium dichromate in acidic medium have not been investigated yet, which is applied in the determination of some drugs [16, 22]. Therefore, the present study was devoted to explore $KMnO_4$ and $K_2Cr_2O_7$ as an oxidizing reagents in the development of direct selective and sensitive spectrophotometric methods for the determination of meclizine HCl in Tablets and plasma. The present work describes two spectrophotometric methods which are superior to the reported ones, for rapidity, reproducibility, time consuming and high sensitivity. The proposed methods which used are well known for their high absorptivity and they will have been utilized for estimation of oxidant (potassium permanganate in alkaline or potassium dichromate in acidic medium). Where modern and expensive apparatus such as GLC, HPLC and HPTLC are not available.

EXPERIMENTAL

Apparatus

All the spectral measurement were made using double-beam UV/Vis spectrophotometer (Biotech Engineering Ltd., UK), with wavelength range 190 – 1100 nm, spectral bandwidth 2.0 nm, with scanning speed 400 nm/min, equipped with 10 mm matched quartz cells. A thermostat water bath, Buchi 461

water bath, Schwiz (France) was used to carry out the temperature studies and Magnetic Mix. 100, Thermo Scientific, UK.

Material and reagents

All chemicals used were of analytical grade and all solutions were freshly prepared in doubly distilled water.

- Pure meclizine HCl bulk powder was obtained from Egyptian Organization for Control and Pharmaceutical Research-Egypt. meclizine HCl working solution was prepared by dissolving 0.01 g of pure meclizine HCl in 50 ml of bidistilled water and complete to 100 ml with bidistilled water to obtain the working standard solution of 100 µg/ml, store the prepared solution at room temperature.
- A stock (5.0×10^{-4} M) solution of $KMnO_4$ (Aldrich), was freshly prepared by dissolving an accurate weight in bidistilled water, and standardized [23].
- A solution of 7.0 M H_2SO_4, was prepared by adding exact volume from stock (98%) concentrated acid to bidistilled water in 500 ml measuring flask, and standardized as recorded [24].
- Solutions of 0.05 M carbonate free NaOH, in 500 ml measuring flask, and standardized as recorded [25].

General procedure

The method depends on oxidation of meclizine HCl by addition of 0.01-0.71 ml meclizine (100 µg/ml) to 1.0 ml of 5.0×10^{-4} M $KMnO_4$ containing 2.0 ml of 0.05 M NaOH (for first method) was heated in a thermostat water bath at 45±1 °C for 2.0 min), to produce a water-soluble bluish-green colored species which measurable at λ_{max} 610 nm, against $KMnO_4$ similarly prepared as a blank. For the second method, depends on oxidation of meclizine HCl by addition of 0.02-1.14 ml meclizine (100 µg/ml) to 2.0 ml (1.0×10^{-2} M) $K_2Cr_2O_7$ containing 2.0 ml of 6.0 M H_2SO_4. The solution was heated in a water bath at 80±1 °C for 15.0 min, and measurement of the absorbance of the chromium(III) formed at 580 nm. The concentration range was determined in each case by plotting the concentration of meclizine HCl against absorbance at the corresponding maximum wavelengths.

Procedure for tablets forms

Twenty tablets were carefully evacuated; their contents were weighed and finely powdered. An accurately weighed quantity of the tablet contents equivalent to 10 mg of meclizine HCl was transferred into a 100 ml calibrated flask, and dissolved in about 40 ml of distilled water. The contents of the flask were swirled, sonicated for 5 min, and then completed to volume with water. The contents were mixed well and filtered rejecting the first portion of the filtrate. The prepared solution was diluted quantitatively with distilled water to obtain a suitable concentration for the analysis.

Procedure for spiked plasma samples

Aliquots of 1.0 ml of plasma were spiked with different concentration levels of meclizine HCl. The spiked plasma samples were treated with 0.1 ml of 70% perchloric acid and vortexed for 1.0 min. The samples were centrifuged for 20 min at 13000 rpm. The supernatants were transferred into test tubes and neutralized with 1.0 M NaOH solution.

RESULTS AND DISCUSSION

First method

The first method is based on the reaction of the drug with potassium permanganate in the presence of sodium hydroxide. The reaction takes place completely after 10 min at room temperature 25±1 °C. To accelerate the full color developments, the reaction mixture was heated in a thermostat water bath at 45±1 °C for 2.0 min. The produced water-soluble bluish-green colored species was measured at λ_{max} 610 nm. The color remains constant for at least 48 h.

$Mn^{+7}O_4^-$ (Violet) + OH^- + meclizine HCl →

$Mn^{+6}O_4^{2-} + H_2O + O_2$ + Oxidation products
(Bluish–green colored λ_{max} 610 nm)

Second method

- The second method, depends on oxidation of meclizine HCl by potassium dichromate in the presence of 6.0 M H_2SO_4. The solution was heated in a water bath at 80±1 °C for 15.0 min, and measurement of the absorbance of the chromium(III) formed at 580 nm.

$Cr_2^{(+6)}O_7^{2-}$ + acid + meclizine HCl →
(Orange)

$Cr^{+3} + H_2O$
(green, λ_{max} = 580 nm)

The influence of each of the following variables on the reaction was tested.

Effect of permanganate concentration

The influence of potassium permanganate concentration was studied in the range from 10^{-5} - 10^{-4} M, as final concentration. The optimum results were obtained with 1.0 ml of 5.0×10^{-4} M; higher

concentration of $KMnO_4$ caused the color to disturbed.

Effect of medium

For first method, different concentrations of NaOH were examined. The most suitable concentration to achieve maximum yield of redox reaction was found to be 2.0 ml of 0.05 M NaOH. For the second method, different types of acid were examined (HCl, $HClO_4$, H_2SO_4, H_3PO_4, CH_3COOH and HNO_3). The most suitable acid to achieve maximum yield of redox reaction was found to be sulphoric acid. Moreover, various volumes of 6.0 M H_2SO_4 were tested and found to be 2.0 ml (Figure 1).

Effect of temperature and time

For first method A, the reaction takes place completely after 10 min at room temperature 25±1 ^oC. The oxidation process of meclizine HCl with NaOH is catalyzed by heating in a thermostat water bath at 45±1 ^oC for 2 min, to produce a water-soluble bluish-green colored species. The oxidation process of meclizine HCl for the second method in acidic medium was catalyzed by heating in water bath of 80±1 ^oC. The time required to complete the reaction was 2 min. After oxidation process. The color resulted remains constant for at least 72 h..

Effect of sequence of additions

The effect of sequence of additions on the oxidation process of meclizine HCl was studied by measuring the absorbance of solution prepared by different sequence of additions against a blank solution prepared in the same manner. Experiments showed that (Oxidant-NaOH/(or)Acid-Drug) gave the best results.

Analytical data

Beer's law limits (Figure 2), molar absorptivities, Sandell sensitivities, regression equations and correlation coefficients were calculated and recorded. The limits of detection (K=3) and quantitation (K=10) were established according to IUPAC definitions [26] are recorded in Table 1. In order to determine the accuracy and precision of the methods, solution containing three different concentrations of meclizine HCl were prepared and analyzed in six replicates. The analytical results obtained from this investigation were summarized in Table 2.

Interference

A systematic quantitative study was undertaken by measuring the absorbance of solutions containing 5.0, 8.0 µg/ml of meclizine HCl (for method A, B respectively) with varying concentration of the additives and excipients such as cellulose, talc powder, lactose, calcium hydrogen phosphate, magnesium stearate, micro-crystalline cellulose and starch. Under the experimental conditions, the effect of excipients frequently found in formulations was evaluated using the proposed method; the excipients in all tablets are not interfere.

Method validation

The proposed method was successfully applied to determine meclizine HCl in its dosage forms and in spiked serum plasma. The accuracy of the proposed methods is evaluated by applying standard addition technique, in which variable amounts of the drug were added to the previously analyzed portion of pharmaceutical preparations and in spiked serum plasma. The results recorded in Table 3, were compared statistically with the official method [27] by Student's t-test (for accuracy), and variance ratio F-test (for precision) [28], at 95% confidence level as recorded in Table 4. The results showed that the t- and F- values were lower than the critical values indicating that there was no significant difference between the proposed and official methods. The proposed method was more accurate with high recoveries compared to the official method. So the proposed method can be recommended for routine analysis of meclizine HCl in pure and dosage forms in the majority of drug quality control laboratories.

CONCLUSIONS

The proposed method was advantageous over other reported visible spectrophotometric and colorimetric methods, related to their high reproducibility, high sensitivity, less time consuming and using simple and inexpensive reagents. Moreover, these methods allowed the determination of meclizine HCl up to 0.1 µg/ml, in addition to simplicity, rapidity, precision and stability of colored species for more than 72 h. The proposed method may be applied for routine analysis and in quality control laboratories for the quantitative determination of the meclizine HCl in raw materials and in pharmaceutical formulations.

Table 1
Optical and regression characteristics of meclizine HCl for the proposed methods.

Parameters	$KMnO_4$ in basic medium	$K_2Cr_2O_7$ in acidic medium
λ_{max} nm	610	580
Stability / h	36	72
Beer's law limits (µg/ml)	0.1 - 7.1	0.2 - 11.4
Ringbom limits (µg/ml)	0.3 - 6.8	0.4 - 10.9
Molar absorptivity (l mo/l. cm)	9.44×10^4	4.43×10^4
Sandell sensitivity (ng/cm)	7.87	10.87
Detection limits (µg/ml)	0.055	0.038
Quantitation limits (µg/ml)	0.183	0.127
Regression equation*: Slope (b)	0.127	0.092
Intercept (a)	0.0057	0.0089
Correlation coefficient (r)	0.9999	0.9998
RSD** %	0.71	0.68

* A = a + bC where C is concentration of drug in µg/ml and A is absorbance.
** Relative standard deviation for six determinations.

Table 2
Evaluation of the accuracy and precision of the proposed methods for meclizine HCl.

Reagents	Taken µg/ml	Recovery %	RSD [a] %	RE [b] %	Confidence limits [c]
$KMnO_4$ in basic medium	2.0	99.00	089	0.68	1.98 ± 0.0135
	4.0	100.50	0.67	0.57	4.02 ± 0.0228
	6.0	99.83	0.53	0.52	5.99 ± 0.0311
$K_2Cr_2O_7$ in acidic medium	3.0	99.00	0.70	0.91	2.97 ± 0.0269
	6.0	100.33	0.68	0.64	6.02 ± 0.0387
	10.0	99.60	0.52	0.29	9.96 ± 0.0290

[a] Relative standard deviation for six determinations.
[b] Relative error.
[c] 95 % confidence limits and five degrees of freedom.

Table 3
Determination of meclizine HCl in capsules using standard addition technique.

Samples	Added µg/ml	$KMnO_4$ in basic medium Taken 5.0 µg/ml		$K_2Cr_2O_7$ in acidic medium Taken 8.0 µg/ml	
		Found* µg/ml	Recovery %	Found* µg/ml	Recovery %
Vomidoxine 25 mg(1)	0.0	5.09	101.8	8.08	101.00
	1.0	6.01	100.16	8.98	99.77
	2.0	7.02	100.29	9.97	99.70
Navoproxine 25 mg(2)	0.0	4.99	99.8	8.06	100.75
	1.0	6.02	100.33	8.97	99.66
	2.0	7.01	100.14	9.95	99. 5
Ezadoxine 25 mg(3)	0.0	4.88	97.6	8.08	101.00
	1.0	6.02	100.33	9.03	100.33
	2.0	7.01	100.14	9.95	99.50
Dizirest B_6 25 mg(4)	0.0	5.06	101.2	7.95	99.38
	1.0	6.05	100.83	8.93	99.22
	2.0	7.06	100.86	9.91	99.10
Spiked plasma pimples	0.0	5.05	101.00	7.91	98.87
	1.0	6.05	100.83	8.98	99.77
	2.0	6.88	98.29	9.94	99.40

* Average of six determinations.
(1) Pharaonia Pharmaceutical, Pharo-pharma Company, Cairo, Egypt.
(2) Delta Phama S A. E. 10th of Ramadan City, Egypt.
(3) Multipharma for Pharmaceuticals and Chemicals Company, S. A. E., Egypt.
(4) Sigma Pharmaceutical Industries Company, S. A. E., Egypt.

Table (4): Determination of meclizine HCl in pharmaceutical formulations (Tablets).

Pharmaceutical formulations	Proposed methods						
	$KMnO_4$ in basic medium			$K_2Cr_2O_7$ in acidic medium			Official method
	Recovery %	t- value	F- ratio	Recovery %	t- value	F- ratio	Recovery %
Vomidoxine 25 mg[1]	99.6	0.28	1.98	100.02	0.74	1.79	98.7
Navoproxine 25 mg[2]	99.5	0.87	2.48	99.6	1.09	2.40	99.1
Ezadoxine 25 mg[3]	100.1	0.57	1.22	98.8	0.48	1.51	98.7
Dizirest B_6 25 mg[4]	99.1	0.38	1.79	100.2	0.65	0.89	98.3
Spiked plasma pimples	100.01	1.01	2.08	99.77	0.87	1.72	98.9

Theoretical value for t- and F- values for five degrees of freedom and 95 % confidence limits are 2.57 and 5.05, respectively.

(1) Pharaonia Pharmaceutical, Pharo-pharma Company, Cairo, Egypt.

(2) Delta Phama S A. E. 10th of Ramadan City, Egypt.

(3) Multipharma for Pharmaceuticals and Chemicals Company, S. A. E., Egypt.

(4) Sigma Pharmaceutical Industries Company, S. A. E., Egypt.

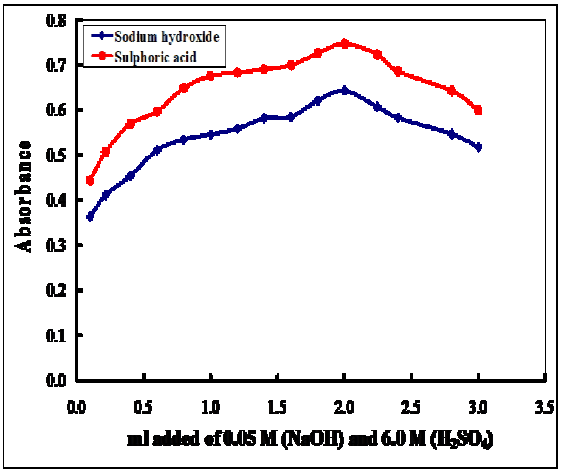

Figure 1: Effect of ml added of 0.05 M (NaOH) and 6.0 M (H_2SO_4).

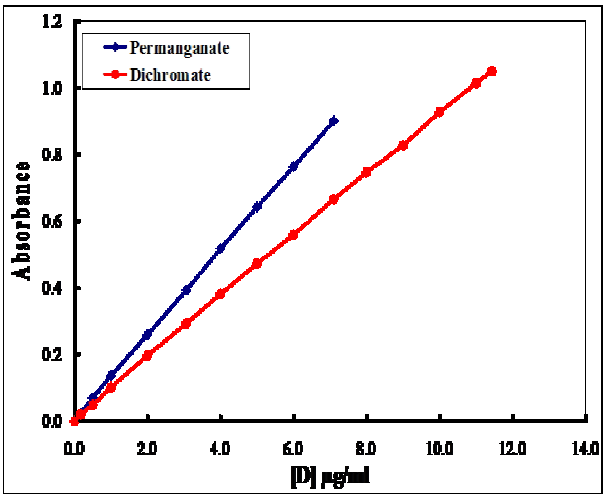

Figure 2: Validity of Beer's law for reaction product of meclizine HCl with $KMnO_4$ (5.0×10^{-3} M) in alkaline medium, $K_2Cr_2O_7$ (1.0×10^{-2} M) in acidic medium (method B).

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