WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 2.786
Volume 3, Issue 6, 102-112. Research Article ISSN 2278 – 4357

SPECTROPHOTOMETRIC MICRO DETERMINATION OF MECLIZINE HYDROCHLORIDE IN THEIR PHARMACEUTICAL FORMULATIONS AND SPIKED PLASMA

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Article Received on
25 March 2014,

Revised on 17 April 2014,
Accepted on 10May 2014

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ABSTRACT

A simple, accurate and highly sensitive spectrophotometric method is proposed for the rapid determination of meclizine hydrochloride using bromocressol green (BCG) and bromophenol blue (BPB). The method consists of extracting the formed ion- associates into chloroform. The ion -associates exhibit absorption maxima at 417 and 412 nm for BCG and BPB, respectively. Meclizine HCl can be determined up to 2.6-25 and 2.5-17.5 µg/ml, using BCG and BPB, respectively. The effect of acidity, reagent concentration, time, solvent and stoichiometric ratio of the ion- associates were studied. The molar absorptivity and Sandell sensitivity of the reaction products were calculated. The method was applied to the determination of the drugs in their pure form or pharmaceutical preparations.

KEY WORDS: Meclizine hydrochloride; Spectrophotometric; bromocressol green (BCG) and bromophenol blue (BPB); Pharmaceutical analysis.

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], using capillary electrophoresis [4] and determine the solubility of meclizine using nonionic surfactants [5], using spectrophotometric [6, 7]. Bromocressol green is known to yield a charge transfer complex, which is applied in the determination of some drugs [8-11]. The bromophenol blue has also reported for the determination of pharmaceutical compounds [9-17]. Spectrophotometry is considered as the most convenient analytical technique in

pharmaceutical analysis because of its inherent simplicity and availability in most quality control laboratories [18-21]

The present work aims to present a simple, rapid and sensitive method for the determination of meclizine HC1 in pure form and in their pharmaceutical preparations and can be used for the quality control and assurance of these drugs in industry. The method is based on the formation of ion-associate between the cited drug and BCG or BPB. These methods are very simple in application and less expensive in comparison to the above mentioned techniques but at the same time offering a high degree of accuracy and precision when compared to the pharmacopoeial method and could be used simply to determine the shelve stability time of the drug.

EXPERIMENTAL

Apparatus

All the absorption spectral measurements were made using JASCO V-530 (UV-VIS) spectrophotometer (Japan), with scanning speed 400 nm m^{-1} and band width 2.0 nm. Equipped with 10 mm matched quartz cells.

Reagents and materials

- All chemicals used were of analytical or pharmacopoeial grade purity and doubly distilled water were used. Standard meclizine HC1 was obtained from Delta Pharma S. A. E.10^{th} of Ramadan City, Egypt.
- The acid dye reagents BCG and BPB were obtained from E. Merck Darmstdt F. R. Germany.
- Standard solution 100 µg/ml of meclizine HCl was prepared by dissolving pure drug (pharmaceutical grade) in the least amount of warm water and made up to 100 ml in measuring flask with bidistilled water.
- The solution remained stable for two months when kept refrigerated. Stock solution of bromocressol green (BCG) (1 *x* 10^{-3} M) and bromo-phenol blue were prepared by dissolving 0.0698 and 0.0670 g, respectively, in 100 ml acetone.
- The acid dye reagents (BCG and BPB) were stable for several weeks.
- A 1.0 M solution of HC1 was prepared by diluting appropriate volume of AnalaR stock solution to 100 ml measuring flask with bidistilled water and standardized as recommended [22].

General Procedure

Into a 50 ml separating funnel, a volume of meclizine HC1 (100 μg/ml) 0.5 ml (1 *x* 10^{-3} M) of BCG and BPB, 1.0 ml of 1.0 M HC1 or 1.5 ml of 1.0 M HC1 in the case of BCG and BPB, respectively. The volume was made up to 10 ml with bidistilled water. The formed ion-associates were extracted with 4 ml chloroform by shaking for 2 min, then repeating the extraction twice by using two new 4 ml aliquots of chloroform. The reaction mixture was allowed to separate into two phases. The organic layer was collected into a 10 ml calibrated measuring flask and the volume was made up to the mark with chloroform. The absorbance of the extracts was measured at the recommended maximum wavelength (417 and 412 nm for BCG and BPB, respectively) (**Figure 1**), against a reagent blank prepared in the same manner without the addition to the drug. All measurements were carried out at room temperature (25±2 ^{o}C).

Determination of meclizine HC1 in tablets

Twenty tablets were weighted and finely powdered. A portion of the powder corresponding to 25 mg of meclizine HCl was weighed and dissolved in warm water and transferred into 25 ml calibrated measuring flask and then made up to the mark with bidistilled water. One milliliter of this solution was used for color development with each reagent and extracted as reported under general procedure.

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

Several parameters such as acidity, type and amount of acid added, reagent concentration, sequence of addition and effect of extracting solvent were optimized to achieve high sensitivity, stability, low blank reading and reproducible results.

Effect of acidity

In a trial to elucidate the optimum medium for the quantitative determination of meclizine HC1, the effect of sulphuric, acetic and hydrochloric acids was examined. The highest absorbance value was obtained in the presence of 1.0 M HC1. It was found that on using 1.0

ml of 1.0 M HCl in the case of BCG or 1.5 ml of 1.0 M HCl in the case of BPB, maximum absorbance values and high stability were achieved.

Effect of the reagent concentration

The effect of reagent concentration was tested by using amounts (0.3-5 ml) of 1 x 10^{-3} M solution of each reagent with 0.5 ml of 1 x 10^{-3} M of meclizine HCl. The results showed that 1.5 ml of (BCG) and 1.0 ml of (BPB) were sufficient for the production of maximum and reproducible color intensity.

Effect of sequence e of mixing

The most favorable sequence was reagent-drug-acid for the production of highest color intensity and the shortest time for developing maximum absorbance, while the other sequence require longer time and produce lower absorbance values.

Effect of time and temperature

The effect of time on the formation and stability of the ion- associates was studied by measuring the absorbance of the extracted ion- associates at increasing time intervals, the results showed that the ion- associates were formed almost instantaneously in all cases at room temperature (25±2 ^{o}C). The developed color remained stable for 8 and 10 h using BCG and BPB, receptively. After these intervals, a slight decrease in color intensity occurred.

Effect of extracting solvent

The polarity of the solvents affects both extraction efficiency and absorptivity of the ion associates. Several water-immiscible organic solvents including benzene, toluene, carbon tetrachloride, chloroform, methylene chloride, 1,2-dichloroethane and nitrobenzene were tried. The most convenient solvent found to produce, the highest absorbance, extraction power and stability of color of the formed ion- associates were chloroform for both BCG and BPB. The study repealed that a volume ratio of 3:2 (aqueous : organic) was the most suitable for the ion- associate extraction.

The stoichiometric ratio of the ion - associate

The stoichiometry of the ion-associates formed between the drug and the reagents was investigated by applying the continuous variation [23] and the molar ratio [24] methods at the wavelengths of maximum absorbance. The results obtained showed that the stoichiometric ratio of the ion-associates is 1:1 (reagent : drug) in all cases.

Analytical data

Beer's law was verified up to (2.6 - 25) and (2.5 - 17.5) µg/ml of meclizine HCl with BCG and BPB, respectively. The molar absorptivity (Є) calculated and found to be 2.6 *x* 10^4 and 2.94 *x* 10^4 L/ mol.cm, with BCG and BPB, respectively, indicating high sensitivity of the reagents under investigations for the determination of meclizine HCl. The regression equations (A = a+bC) where A = absorbance, a = intercept, b = slope and C = concentration in µg/ml), calculated from the calibration graph, were evaluated and recorded in (**Table 1**). The intercept of the lines were very small indicating that there is no systematic difference between determined and expected concentration within the investigated rang using the present method. For more accurate results, Ringbom concentration range was determined by plotting log [drug] in µg/ml against % transmittance from which the linear portion of the curve gave accurate range for the determination of the drug under investigation (**Table 1**). In order to determine the accuracy and precision of the present method, solutions containing five different concentrations of drug were prepared and six replicate determinations, converting the usable concentration range, were carried out for the pure form and the pharmaceutical of the drugs under investigation. The recovery values almost reach 100 % recovery, revealing a high accuracy of the results (**Table 2**).

The proposed method was successfully applied to determine AMD 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 [25].

The calculated standard deviations are compared with those obtained by the pharmacopoeial method of meclizine HCl [25] based on (potentiometric titration using 0.1 M perchloric acid using calomel electrode system by applying the t- and F- tests (**Table 4**). Such comparison showed that there is no significant difference, at 25 % confidence level, between the values obtained by the proposed and the pharmacopoeial method. This indicates the high accuracy and precision of the present method.

Table (1): Optical and regression characteristics of meclizine HCl with BCG and BPB.

Parameters	BCG	BPB
λ_{max} (nm)	417	412
Bear's law limits (µg/ml)	2.6-25	2.5-17.5
Ringbom limits (µg/ml)	2.8-24	2.7-17
Molar absorptivity (L/mol.cm)	2.6×10^4	2.94×10^4
Sandell sensitivity (ng/cm^2)	18.5	16.4
Detection limits (µg/ml)	0.0175	0.0149
Quantitation limits (µg/ml)	0.0583	0.0496
Regression equation*: Slope (b)	0.054	0.061
Intercept (a)	-0.025	-0.045
Correlation coefficient (r)	0.9998	0.9996
Stoichiometric ratio	1:1	1:1
RSD** %	0.59	0.46

*With respect to A = a + b C 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 procedure.

Reagent	Taken µg/ml	Recovery %	RSD[a] %	RE[b] %	Confidence limits[c]
BCG	5.0	97.0	0.44	0.46	4.85±0.0224
	9.0	99.7	0.21	0.22	8.97±0.0199
	14.0	99.3	0.19	0.19	13.9±0.0273
BPB	4.0	102.3	0.83	0.87	4.09±0.0357
	6.0	98.2	0.80	0.84	5.89±0.0493
	12.0	98.3	0.58	0.61	11.8±0.0724

[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	BCG		BPB	
		Taken 10 µg/ml			
		Found* µg/ml	Recovery %	Found* µg/ml	Recovery %
Vomidoxine 25 mg(1)	0.0	10.09	100.90	09.98	99.80
	1.0	11.01	100.09	10.98	99.82
	2.0	12.02	100.16	11.97	99.75
	3.0	12.98	99.85	12.96	99.69
Navoproxine 25 mg(2)	0.0	09.99	99.90	10.10	101.0
	1.0	10.99	99.91	10.97	99.73
	2.0	12.01	100.08	12.03	100.25
	3.0	12.98	99.85	13.01	100.08
Ezadoxine 25 mg(3)	0.0	10.11	101.10	09.95	99.50
	1.0	10.99	99.91	10.96	99.64
	2.0	11.99	99.92	11.95	99.58
	3.0	13.01	100.08	13.04	100.31
Dizirest B_6 25 mg(4)	0.0	09.97	99.70	10.06	100.6
	1.0	10.99	99.91	10.98	99.82
	2.0	11.98	99.83	11.99	99.91
	3.0	12.99	99.92	13.06	100.46
Spiked plasma pimples	0.0	09.99	99.90	10.04	100.4
	1.0	11.09	100.82	10.95	99.55
	2.0	12.09	100.75	12.09	100.75
	3.0	12.97	100.08	13.08	100.15

* 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						
	BCG			BPB			Official method
	Recovery %	t-value	F-ratio	Recovery %	t-value	F-ratio	Recovery %
Vomidoxine 25 mg[(1)]	99.2	0.29	1.78	99.8	0.58	1.99	98.3
Navoproxine 25 mg[(2)]	100.2	0.88	2.39	100.5	1.29	2.48	98.8
Ezadoxine 25 mg[(3)]	99.4	0.44	1.51	99.6	0.38	1.56	98.9
Dizirest B_6 25 mg[(4)]	98.9	0.29	1.67	100.1	0.35	1.59	98.4
Spiked plasma pimples	100.15	1.09	2.88	99.37	0.77	1.58	98.8

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.

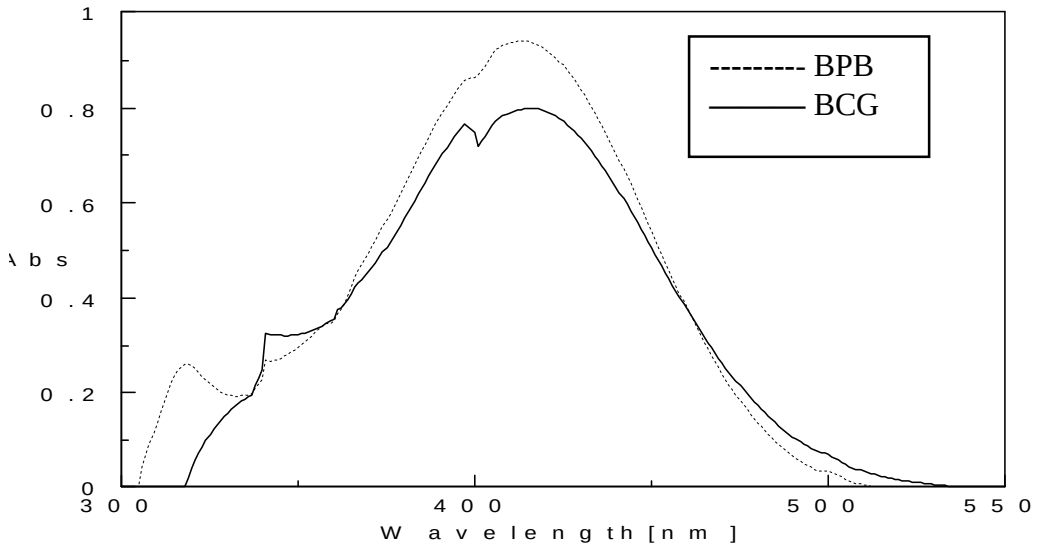

Figure 1: Absorption spectra for 15 µg/ml of meclizine HCl with BCG and BPB.

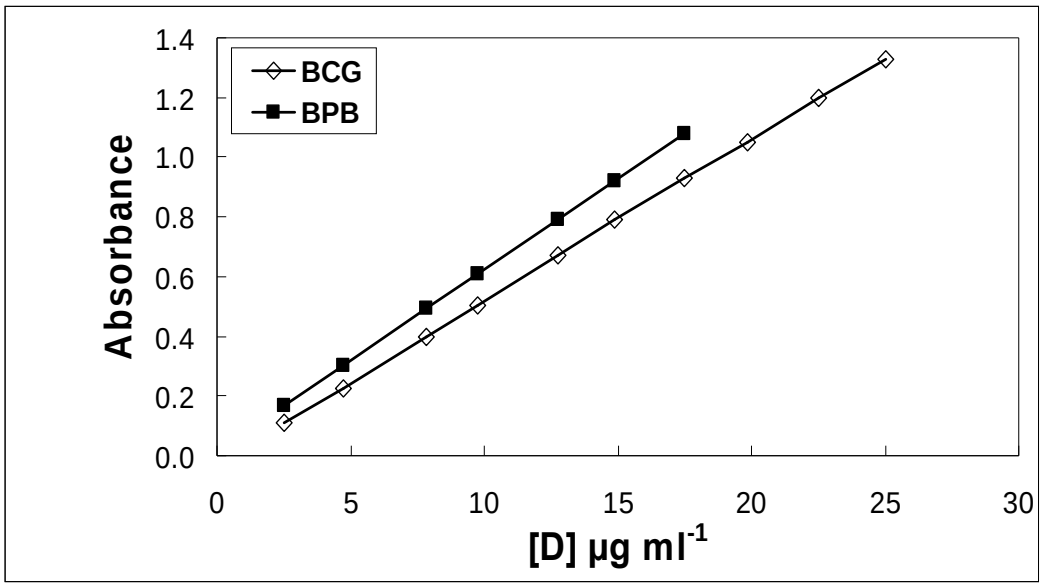

Figure 2: Validity of Beer's law for meclizine HCl with BCG and BPB.

Interference

A systematic qualitative study was under taken by measuring the absorbance of solutions containing 1.0 ml of 100 µg/ml drug together with varying excess of different additives and excipients which may be present in the pharmaceutical preparations using the recommended methods of such reagents for meclizine HCl. No significant interference was observed from the excipients commonly used such as glucose, lactose, fructose, starch and magnesium stereate, this shows that the method is applicable in the case of pharmaceutical preparations of the drug.

CONCLUSIONS

The proposed method for the estimation of meclizine HCl using bromocressol green and bromophenol blue are advantageous over many of the reported methods due to its sensitivity, rapidity and good agreement with the pharmacopoeial methods. The high recovery percentage and lows relative standard deviation reflect the high accuracy and precision of the proposed method. Moreover, the method is easy, applicable to wide ranges of concentration, beside less time consuming and depend on simple reagents which are available. This offering economic and acceptable method for the routine determination of the cited drug (Beer's law up to 2.6 and 2.5 µg/ml) uses BCG and BPB, respectively. So it is recommended for the routine determination in pure samples and in their pharmaceutical formulations.

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