Spectrophotometric determination of meclozine HCl and papaverine HCl in their pharmaceutical formulations

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Abstract

A simple, accurate and highly sensitive spectrophotometric method is proposed for the rapid determination of meclozine and papaverine hydrochlorides using chromotrope 2B (C2B) and chromotrope 2R (C2R). The method consists of extracting the formed ion-associates into chloroform in the case of meclozine HCl and into methylene chloride in case of papaverine HCl. The ion-associates exhibit absorption maxima at 536 and 524 nm for C2B and C2R with meclozine HCl and at 540 and 528 nm with papaverine HCl, respectively. Meclozine can be determined up to 4.0 and 2.6 mg ml^{-1}, using C2B and C2R, respectively, while papaverine can be determined up to 1.68 and 1.37 mg ml^{-1}, 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 state or pharmaceutical preparations with mean recovery values of 99.63–100.80 and 99.75–100.08% and coefficient of variation 0.945–2.210 and 1.020–1.268 for meclozine HCl and papaverine HCl, respectively. © 2002 Published by Elsevier Science B.V.

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1. Introduction

Meclozine hydrochloride is an antiemetic agent used in post-operative vomiting. Several methods have been reported for the determination of meclozine HCl including spectrophotometry [1–3] and HPLC [4,5].

Papavarine hydrochloride, relaxes the various smooth muscles, also it relaxes the smooth musculature of the larger blood vessels, especially coronary, systemic peripheral and pulmonary arteries and it increases cerebral blood flow. Some methods have been reported for the determination of papaverine HCl including HPLC [6], TLC [7], spectrophotometry [8–10] and iodometry [11].

Chromotropic acid (4,5-dihydroxynaphthalene-2,7-disulphonic acid), is used for the preparation of azo dyes which are very famous indicators

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for the spectrophotometric and chelatometric determination of metal ions [12,13]. Recently, some chromotropic acid azo dyes have been used for the extraction-spectrophotometric determination of Cephalosporins [14], betamethazone [15] and terfenadine [16].

Chromotrope 2B (C2B), is 3-(*p*-nitrophenylazo)-chromotropic acid (acid red 176, C. I. 16575). Chromotrope 2R (C2R), is 3-(phenylazo)-chromotropic acid, disodium salt (acid red 29, C. I. 16570).

The present work aims to present a simple, rapid and sensitive method for the determination of meclozine and papaverine hydrochlorides 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 drugs and some chromotropic acid mono azo dyes. 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 studied drugs.

2. Experimental

2.1. Apparatus

Spectral measurements were carried out by using a Uincam UV–vis spectrophotometer (Helios Alpha) with 1 cm matched quartz cells.

2.2. Reagents and materials

Analytical grade reagents and doubly distilled water were used to prepare all solutions.

Pure grade meclozine HCl and its pharmaceutical preparation (Navidoxine tablets, 25 mg/tablet) were provided by UCBS.A. Pharmasector, Braine-L'alleud, Belguim, while papaverine HCl (Vasorin ampoules, 60 mg/2 ml) were provided by Memphis Co. for pharmaceutical and chemical industries, Cairo, Egypt.

Chromotrope 2B (C2B) and chromotrope 2R (C2R) were obtained from Aldrich (USA).

Standard solution $(2 \times 10^{-3}–10^{-2}$ M of meclozine HCl $(M_w = 463.9)$ or papaverine HCl $(M_w = 375.9)$ were prepared by dissolving pure drug(pharmaceutical grade) in 100 ml methanol for meclozine HCl or in the least amount of warm water for papaverine HCl and made up to 100 ml with bidistilled water. The solutions remained stable for two months when kept refrigerated. Stock solutions of chromotrope 2B $(5 \times 10^{-3}$ M) $(M_w = 513.37)$ and chromotrope 2R $(M_w = 468.37)$ were prepared by dissolving 0.2566 and 0.2341 g, respectively, in 100 ml bidistilled water. The chromotropic acid azo dyes aqueous solutions were stable for several months.

2.3. General procedure

Into a 50-ml separating funnel, a volume of meclozine HCl containing up to 4.5 mg or papaverine HCl solution containing up to 3 mg was transferred, 5 ml of 5×10^{-3} M C2B or C2R, 3 ml of 1 M HCl in the case of meclozine HCl or 4 and 1 ml in the case of papaverine HCl using C2B and C2R, respectively, were added and the volume was made up to 10 ml with distilled water. The formed ion associates were extracted with 5 ml chloroform in the case of meclozine HCl or 5 ml methylene chloride in the case of papaverine HCl by shaking for 2 min, then repeating the extraction twice by using two new 5 ml aliquots of the extractant. The reaction mixture was allowed to separate into two phases. The organic layer was collected into 25-ml calibrated measuring flask and the volume was made up to the mark with chloroform or methylene chloride for meclozine HCl and papaverine HCl, respectively. The absorbance of the extracts was measured at the recommended maximum wavelength (Table 1), against a reagent blank prepared in the same manner without the addition of the drug. All measurements were carried out at room temperature (25 ± 2 °C).

2.4. Determination of meclozine hydrochloride in Navidoxine tablets

Twenty tablets were weighed and finely powdered.

A portion of the powder corresponding to 25 mg of meclozine hydrochloride was weighed and dissolved in methanol and transferred into 25-ml calibrated measuring flask and then made up to the mark with methanol. One milliliter of this solution was used for colour development with each reagent and extracted as reported under general procedure.

2.5. Determination of papaverine hydrochloride in Vasorin ampoules

The contents of ten ampoules were mixed and the average volume for one ampoule was determined. An aliquot of the solution equivalent to 60 mg papaverine hydrochloride was quantitavely transferred to 50-ml calibrated measuring flask and made up to the mark with bidistilled water. One milliliter of this solution was used

Table 1
Characteristics and analytical data of meclozine hydrochloride and papaverine hydrochloride ion-associates

Parameters	C2B	C2R
Meclozine HCL		
λ_{max} (nm)	536	524
Beer's law up to (mg/ml)	4.0	2.6
Ringbom (mg/ml)	0.49–3.46	0.43–2.43
Molar absorptivity (ε) (l mol^{-1} cm^{-1})	4.45×10^3	9.75×10^3
Sandell sensitivity [ng cm^{-2}]	0.104	0.048
Regression equations		
Intercept	0.009	0.0001
Slope	0.379	0.475
Correlation coefficient	0.998	0.999
Papaverine HCl		
λ_{max} (nm)	540	528
Beer's law up to (mg/ml)	1.60	1.37
Ringbom (mg/ml)	0.27–1.46	0.25–1.40
Molar absorptivity (ε) (l mol^{-1} cm^{-1})	1.17×10^4	2.14×10^4
Sandell sensitivity (ng cm^{-2})	0.033	0.018
Regression equations		
Intercept	0.002	0.030
Slope	0.560	0.570
Correlation coefficient	0.9993	0.9998

for colour development with each reagent and extracted as reported under general procedure.

3. 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.

3.1. Effect of acidity

In a trial to elucidate the optimum medium for the quantitative determination of meclozine HCl and papaverine HCl, the effect of sulphuric, acetic and hydrochloric acids was examined. The highest absorbance value was obtained in the presence of 1.0 M HCl. It was found that on using 3 ml of 1.0 M HCl in the case of meclozine HCl or 4 and 1 ml in the case of papaverine HCl using C2B and C2R, respectively, maximum absorbance values and high stability were achieved.

3.2. Effect of the reagent concentration

The effect of reagent concentration was tested by using varying amounts (1–6) ml of 5×10^{-3} M solution of each reagent with 1 ml of 2×10^{-3} M of meclozine HCl and papaverine HCl. The results showed that 5 ml of 5×10^{-3} M of C2B and C2R were sufficient for the production of maximum and reproducible colour intensity.

3.3. Effect of sequence of mixing

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

3.4. Effect of time and temperature

The effect of time on the formation and stability of the ion-associates was studied by measuring the absorbances 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 °C).

In the case of meclozine HCl the developed colour remained stable for 10 and 8 h using C2B and C2R, respectively. In the case of papaverine HCl, the developed colour remained stable for 16 and 18 h using C2B and C2R, respectively. After these intervals, a slight decrease in colour intensity occurred.

3.5. 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, ether and nitrobenzene were tried. The most convenient solvent found to produce the highest absorbance, extraction power and stability of colour of the formed ion-associates were chloroform in the case of meclozine HCl and methylene chloride in the case of papaverine HCl. The study revealed that a volume ratio of 2:3 (aqueous:organic) was the most suitable for the ion-associate extraction.

3.6. The stoichiometric ratio of the ion-associate

The stoichiometry of the ion-associates formed between the drugs under investigation and the reagents was investigated by applying the continuous variation [17] and the molar ratio [18] methods at the wavelengths of maximum absorbance. The results obtained showed that the stoichiometric ratio of the ion-associates is 1:2 (reagent:drug) in all cases.

3.7. Analytical data

Beer's law was verified up to 4.0 and 2.6 mg

ml^{-1} of meclozine HCl or 1.6 and 1.37 mg ml^{-1} of papaverine HCl with C2B and C2R, respectively. The molar absorptivity (ε) calculated and found to be 4.45×10^3, 9.75×10^3, 1.17×10^4 and 2.14×10^4 for meclozine HCl and papaverine HCl with C2B and C2R, respectively, indicating high sensitivity of the reagents under investigations for the determination of the above cited drugs. The regression equations ($A = a + bc$ where A = absorbance, a = intercept, b = slope and c = concentration in mg/ml), calculated from the calibration graph according to the Kaleidagraph, 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 range using the present methods. For more accurate results, Ringbom concentration range was determined by plotting log [drug] in µg ml^{-1} against % transmittance from which the linear portion of the curve gave accurate range of the determination of the drugs under investigation (Table 1). In order to determine the accuracy and precision of the present methods, solutions containing five different concentrations of each drug were prepared and six replicate determinations, covering the usable concentration range, were carried out for the pure form and the pharmaceutical preparation of the drugs under investigation. The recovery values almost reach 100% recovery, revealing a high accuracy of the results (Table 2). The mean values obtained and the calculated standard deviations are compared with those obtained by the pharmacopoeial methods of meclozine HCl [19] (based on potentiometric titration using 0.1 M sodium hydroxide) and papaverine HCl [20] (based on titration with 0.1 M perchloric acid using crystal violet solution as indicator) by applying the t- and F-tests (Table 3). Such comparison showed that there is no significant difference, at 95% confidence level, between the mean values or variances obtained by the proposed and the pharmacopoeial methods. This indicates the high accuracy and precision of the present methods.

Table 2
Spectrophotometric determination of meclozine and papaverine hydrochlorides

Method	Pure solution mg		% Recovery	Navidoxine tablets mg		% Recovery
	Taken	Found		Taken	Found	
Meclozine-Ic	0.40	0.403	100.87	0.40	0.395	98.70
	0.60	0.605	100.90	0.60	0.587	97.90
	2.00	2.015	100.75	2.00	1.970	98.50
	4.00	4.06	100.82	4.00	3.88	97.00
Mean recovery ± RSD[a]		100.80 ± 2.210		Mean recovery ± RSD[a]		98.20 ± 0.655
Meclozine-Id	0.40	0.405	101.00	0.40	0.395	99.00
	0.60	0.591	99.50	0.60	0.597	98.50
	1.00	0.990	99.00	1.00	1.00	100.00
	2.00	1.98	99.00	2.00	2.02	101.00
Mean recovery ± RSD[a]		99.63 ± 0.945		Mean recovery ± RSD[a]		99.50 ± 1.00
				Vasorin ampoule		
Papaverine-Ic	0.20	0.199	99.50	0.20	0.20	100.00
	0.40	0.401	101.80	0.40	0.399	99.00
	1.00	0.994	99.40	1.00	1.016	101.60
	1.50	1.485	99.00	1.50	1.508	100.50
Mean recovery ± RSD[a]		100.08 ± 1.268		Mean recovery ± RSD[a]		100.28 ± 1.080
Papaverine-Id	0.20	0.199	99.50	0.20	0.198	99.00
	0.40	0.40	100.00	0.40	0.40	100.00
	1.00	1.00	100.00	1.00	0.988	98.80
	1.30	1.285	99.00	1.30	1.30	100.00
Mean recovery ± RSD[a]		99.75 ± 1.020		Mean recovery ± RSD[a]		98.70 ± 1.313

[a] Relative standard deviation (average of six determinations).

3.8. Interference

A systematic quantitative study was undertaken by measuring the absorbance of solutions containing 1 ml of 2×10^{-3} M 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 meclozine HCl and papaverine HCl. No significant interference was observed from the excipients commonly used such as glucose, lactose, fructose, starch and magnesium stereate up to 20-fold in the case of meclozine HCl and up to 30-fold in the case of papaverine HCl. This shows that the method is applicable in the case of pharmaceutical preparations of the investigsted drugs.

4. Conclusions

The proposed method for the estimation of meclozine HCl and papaverine HCl using chromotrope 2B and chromotrope 2R 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 low relative standard deviation reflect the high accuracy and precision of the proposed methods, moreover, the methods are easy, applicable to a wide range of concentration, beside being less time consuming and depend on simple reagents which are available, thus offering economic and acceptable methods for the routine determination of the cited drugs. In the case of meclozine HCl and papaverine

Table 3
Statistical treatment of data obtained for meclozine and papaverine hydrochlorides applying the proposed methods in comparison with the pharmacopoeial methods

	Official method	C2B	C2R
Meclozine HCl			
Pure solution			
$X \pm$ S.D.	100.18 ± 1.28	99.83 ± 0.92	99.70 ± 1.01
N	6	6	6
t-value (2.57)*		0.960	0.790
F-value (5.05)*		1.390	1.135
Tablets			
$X \pm$ S.D.	100.30 ± 1.03	100.08 ± 1.26	100.28 ± 1.08
N	6	6	6
t-value (2.57)*		0.81	0.25
F-value (5.05)*		1.17	1.03
Papaverine HCl			
Pure solution			
$X \pm$ S.D.	99.90 ± 1.52	100.03 ± 1.16	99.63 ± 1.30
N	6	6	6
t-value (2.57)*		0.31	0.82
F-value (5.05)*		1.31	1.17
Tablets			
$X \pm$ S.D.	99.50 ± 1.471	99.68 ± 1.25	99.88 ± 1.50
N	6	6	6
t-value (2.57)*		0.39	0.77
F-value (5.05)*		1.11	1.72

N = number of replicates.
 * Theoretical value at 95% confidence level.

HCl, chromotrope 2B showed larger usable range (Beer's law up to 4.0 and 1.6 mg ml^{-1}, respectively than chromotrope 2R so it is recommended for the routine determination in pure samples and in their pharmaceutical formulations.

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