Acta Pharmaceutica Turcica
47: 65 – 71 (2005)

Determination of Maprotiline Hydrochloride by Ion- Pair Extraction Using Bromophenol Blue and Bromocresol Purple

Maprotilin Hidroklorürün Bromfenol Mavisi ve Bromkrezol Yeşili Kullanarak İyon Çifti Ekstraksiyonu ile Tayini

Ş. Evrim Kepekçi and Aysel Öztunç*

Istanbul University, Faculty of Pharmacy, Department of Analytical Chemistry 34116, Beyazit, Istanbul – Turkey

Abstract

Two simple, rapid, sensitive and accurate spectrophotometric methods are described for the determination of maprotiline hydrochloride in tablets. The methods are based on the reactions of the drug with bromophenol blue (BPB) and bromocresol purple (BCP) in buffered aqueous solutions at pH 3 and 4, respectively to give coloured ion-pair complexes extractable with chloroform. The coloured products are quantitated spectrophotometrically at 411 nm with BPB and 409 nm with BCP. Beer's law is obeyed in the concentration range 2-12 μg ml^{-1} with both reagents. The proposed methods are applied successfully to the analysis of the drug in its tablet form.

Key Words: Maprotiline Hydrochloride, Ion-pair Complex, Spectrophotometry, Bromophenol Blue, Bromocresol Purple.

Introduction

Maprotiline hydrochloride (MA), 1-(3-methly amino propyl)-dibenzo [b,e] bicyclo [2,2,2] octadien hydrochloride, is a tetracyclic antidepressant although its chemical structure looks like tricyclic antidepressants. It strongly inhibits the uptake of noradrenalin in the brain and peripheral tissues (Martindale, The Extra Pharmacopoeia, 1982). A variety of analytical techniques such as HPLC (Aymard and Livi, 1997; Bakkali *et al.*, 1999), GC (Keller and Zollinger, 1997; Ulrich and Martens, 1997; Hallbach *et al.*, 1999), CE (Buzinkova and Korinkova, 1995; Carkt *et al.*, 2000; Vujic *et al.*, 1999) have been reported for its determination in biological fluids. To determine the drug in tablets, UV- (The United States Pharmacopedia XXII, 1990), visible (Soonhee *et al.*, 1986; Ersoy and Alpertunga, 1998; Öztunç, 1989; Özkul and Öztunç, 2000) spectrophotometric and a high performance liquid chromatographic (The United States Pharmacopedia XXIII, 1995) methods have been published.

The present study describes two visible extractive spectrophotometric methods for the determination of MA through ion pair complex formation using bromophenol blue (BPB) and bromocresol purple (BCP) as the dye reagents. The developed methods have been applied to determine the drug in tablets.

* Corresponding author: e-mail: ayseloztunc@yahoo.com

Materials and Methods

Apparatus: A Shimadzu UV-160 A UV-visible spectrophotometer with 1 cm matched glass cells were used for absorbance measurements. pH Measurements were made with a WTW pH 526 digital pH Meter.

Reagents: All chemicals and reagents were of analytical grade. MA was obtained from Sigma (St.Louis, MO, USA) and Ludiomil tablets were products of Novartis (Turkey). The reagents BPB and BCP were purchased from Merck (Darmstadt, Germany). Distilled water was used to prepare all solutions.

Solutions: The standard solution of MA (100 μg ml^{-1}) was prepared in water. BPB ($2x10^{-3}$ M) and BCP solutions ($1.85x10^{-3}$ M) were prepared in water and ethanol: water (1:10) mixture, respectively.

Phthalate buffer solutions in the pH range 2-4.4 were prepared as follows: To a solution of 1.28 g potassium hydrogen phthalate in water, calculated volume of 0.2 N HCl was added. Required pH was adjusted using a pH meter and then the volume was brought to 250 ml with water.

Procedure For Calibration Curves: For both methods, accurate aliquots containing 10-60 μg of MA were transferred into separate stoppered glass tubes and total volume was brought to 1 ml with water. Then 1 ml of buffer (pH 3 for BPB and pH 4 for BCP method) and 1 ml of dye solutions were added and mixed. Each mixture was extracted with 5 ml of chloroform by shaking with vortex for 2 min. Absorbances of the yellow-coloured organic layers were measured at 411 nm and 409 nm for BPB and BCP methods, respectively against a reagent blank prepared similarly. Calibration curves were constructed using the measured absorbances.

Assay Procedure For Tablets: 10 tablets were weighed and powdered. An accurate amount of the powder equivalent to 25 mg of MA was transferred into a 500 ml calibrated flask and 300 ml of water was added. The mixture was sonicated in an ultrasonic bath for 60 min, then was adjusted to volume with water, mixed and filtered. 2 ml of the filtrate was diluted to 10 ml and a suitable aliquot was subjected to the analysis following the procedure described above. The concentration of MA was calculated from the corresponding regression equation.

Results and Discussion

MA is a tetracyclic antidepressant bearing a secondary aliphatic amino group protonated with hydrochloric acid (Figure 1).

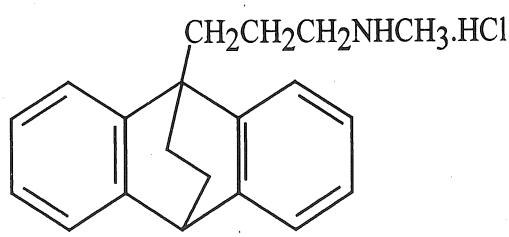

Fig.1. Structure of MA.

Few visible spectrophotometric methods reported for its assay are based on dithiocarbamic acid copper complex formation (Soonhee *et al.*, 1986) and reactions of maprotiline base with π-acceptors, p-chloranile (Ersoy and Alpertunga, 1998) and TCNQ (Öztunç, 1989) . The last two

methods require extraction of the base and heating for the reaction. An extractive spectrophotometric method has also been developed in our laboratory using bromothymol blue (BTB) as the ion-pair forming reagent. Ion-pair extractive spectrophotometry has gained great attention for the determination of many pharmaceutically important compounds (Sane *et al.*, 2000; Gowda *et al.*,2001; Somashekara *et al.*,2001; Mostafa *et al.*, 2002; Reddy *et al.*, 2002). The present study describes two alternative methods for the assay of MA in tablets using BPB and BCP as the dye reagents.

MA as a positively charged amino compound in acidic medium, formed yellow coloured ion-pair complexes with negatively charged counter ions of BPB and BCP. The absorption curves of the complexes extracted into chloroform showed maxima at 411 and 409 nm, respectively (Figures 2 and 3).

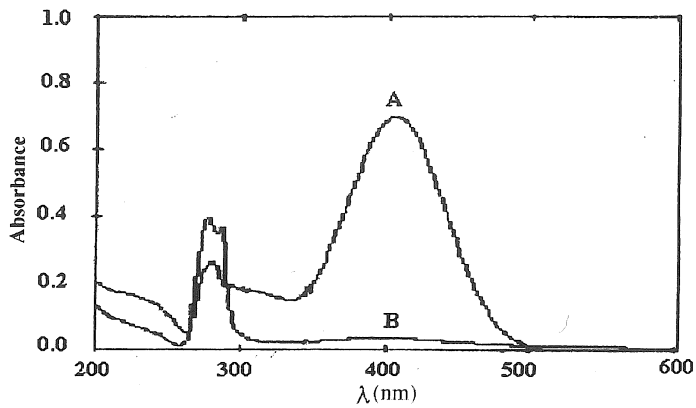

Fig.2. A : Absorption spectrum of the ion-pair complex with BPB in chloroform against the reagent blank.
B: Absorption spectrum of the reagent blank against chloroform.

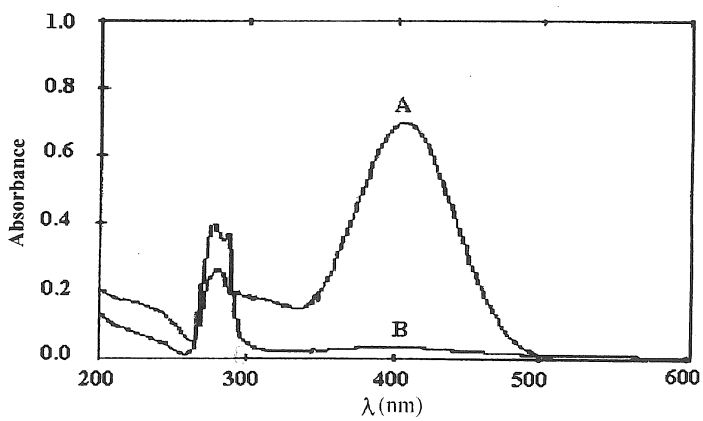

Fig.3. A:Absorption spectrum of the ion-pair complex with BCP in chloroform against the reagent blank.
B: Absorption spectrum of the reagent blank against chloroform.

In the study, optimum experimental conditions were first determined. Since the pH is important for the reactions, different buffer solutions in the pH range 2-4.4 were tested and pH 3 and 4 were found to be the optimum values for BPB and BCP methods, respectively (Figure 4).

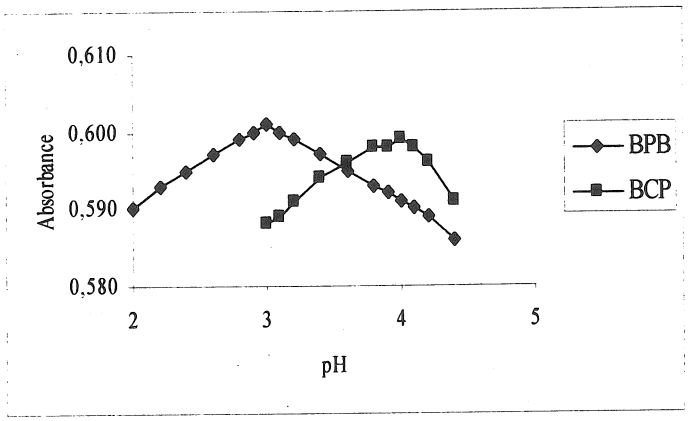

Fig. 4. Effect of pH on the absorbances of the ion-pairs.

A number of immiscible organic solvents were examined to extract the ion-pair complexes from the reaction mixtures. Chloroform was preferred for its effective and selective extraction and a shaking time of 2 min was found optimum to achieve a quantitative recovery of the complexes. The extracted ion-pairs were stable for 24 h at room temperature in the dark.

The amount of the reagents required was examined by changing the mole ratio of BPB and BCP to MA. It was found that a 10 and 6 fold molar excess of BPB and BCP, respectively was sufficient for maximum yield of the reactions.

Under the described experimental conditions, calibration curves for two methods were constructed and Table 1 summarizes the values for Beer's law limits, molar absorptivity, regression equation, correlation coefficients and Sandel's sensitivity for each method.

Table 1. Optical characteristics and statistical data.

Parameters	**BPB**	**BCP**
λ_{max} (nm)	411	409
Beer's law range ($\mu g\ ml^{-1}$)	2-12	2-12
Molar Absorptivity ($L\ mol^{-1}cm^{-1}$)	2.32×10^4	2.41×10^4
Sandel's sensitivity ($mg\ cm^{-2}$ per 0.001 A)	1.37×10^{-5}	1.27×10^{-5}
Regression equation*Y		
Slope (a)	0.0728	0.0756
Intercept (b)	-0.0070	0.0090
Correlation coefficient (r)	0.9997	0.9999

As seen from Table 1, with both reagents linear relationship was found between the absorbances at λ max and the concentrations of the drug in the range 2-12 μg ml^{-1}. The graphs are described by the regression equation, y = ax+b (where y is the absorbance of 1 cm layer, a is the slope, b is the intercept and x is the concentration of the measured solution in the μg ml^{-1}). The correlation coefficients 0.9997 with BPB and 0.9999 with BCP indicate good linearity for the methods. The ε values of the complexes calculated are somewhat higher than the value (1.91×10^4) obtained with the BTB method.
The proposed two methods were applied to the determination of MA in its commercial tablets and satisfactory results were obtained (Table 2).

Table 2. Analysis of MA in tablets (each tablet contains 25 mg of MA).

Statistical values	Proposed Methods		Reference method
	BPB	BCP	
Recovery (%) ± SD	99.45 ± 0.19	99.32 ± 0.21	99.55 ± 0.10
RSD	0.75	0.85	0.11
t-test of significance*	0.22	0.38	
F-test of significance*	2.31	3.92	

* p = 0.05, t = 2.23 and F = 6.39

The standard deviations are found 0.193 and 0.212 for BPB and BCP methods, respectively. The results were compared with those of obtained with the official HPLC method (The United States Pharmacopedia XXIII, 1995). No significant difference has been found in terms of the means and standard deviations using Student's t-test and F-ratio at 95% confidence level.

Conclusion

The proposed extractive spectrophotometric methods are rapid, sensitive, accurate and economic. Therefore they can be recommended in routine analysis of MA in tablets.

Özet

Maprotilin hidroklorürün (MA) tabletlerde analizi için iyon çifti ekstraksiyonuna dayanan basit, hızlı ve duyarlı iki metot geliştirildi. Kloroforma ekstre edilebilen iyon çifti kompleksleri, bromfenol mavisi (BFM) ve bromkrezol moru (BKM) ile sırasıyla pH 3 ve 4 tampon çözeltilerde elde edildi. İyon çiftlerinin maksimum absorbsorbans değerleri BFM ile 411 nm, BKM ile 409 nm de ölçüldü. Her iki metot için de MA konsantrasyonunun doğrusal olduğu aralık 2-12 μg ml^{-1} olarak saptandı. Geliştirilen yöntemler MA içeren tabletlere başarıyla uygulandı.

Acknowledgement

This work was supported by the Research Fund of the University of Istanbul. Project number: T-135/11112002.

References

Aymard, G. Livi, P. (1997). Sensitive and rapid method for the simultaneous quantification of five antidepressants with their respective metabolites in plasma using high-performance liquid chromatography with diode-array detection. *J. Chromatogr. B.,* 183-189 700.

Bakkali A, Corta E, Ciria J.I, Berrueta L.A, Gallo B. and Vicente F. (1999). Solid- phase extraction with liquid chromatograhy and ultraviolet detection for the assay of antidepressant drugs in human plasma. *Talanta* 773-783 49 (4).

Buzinkova T and Korinkova V. (1995).Possible use of capillary isotachophoresis in maprotiline analysis. *Farm. Obz.* 255-259 64 (10).

Cakrt M, Buzinkova T, Polonsky J and Korinkova V. (2000). Spectrofluorimetric and isotachophoretic determination of maprotiline in human blood serum. *Elecrophoresis* 2834-2838 21 (14).

Ersoy L and Alpertunga B. (1998). Spectrophotometric determination of maprotiline hydrochloride. *Analyst* 1745-6 113 (11).

Gowda B.G, Melwanki M.B and Seetharamappa J. (2001). Extractive colorimetric determination of cetirizine hydrochloride in pharmaceutical preparations. *Journal of Pharmaceutical and Biomedical Analysis* 1021-1026 25 (5-6).

Hallbach J, Vogel H, Boogaard P.W and Guder W.G. (1999). Identification and quantification of tricyclic antidepressants in serum by computerized gas chromatography-mass spectrometry. *Clin. Lab* 191-200 45.

Keller T. and Zollinger U. (1997). Gas chromatographic examination of postmortem specimens after maprotiline intoxication. *Forensic Sci. Int.* 117-123 88 (2).

Martindale, The Extra Pharmacopoeia, Twenty-eigth Edition, The Pharmaceutical Press, London (1982).

Mostafa S, El-Sadek M and Alla E.A. (2002). Extractive spectrohotometric determination of antihypertensive agents in pharmaceutical dosage forms. *Journal of Pharmaceutical and Biomedical Analysis* 173-180 28 (1).

Özkul A and Öztunç A. (2000). Determination of maprotiline hydrochloride in tablets by ion-pair extraction using bromthymol blue. *Die Pharmazie* 321-322 55 (4).

Öztunç A. (1989). Spectrophotometric determination of maprotiline hydrochloride with 7,7,8,8-tetracyanoquinodimethane. *Mar. Univ. Ecz. Derg.* 139-43 5 (2).

Reddy M.N, Murthy T.K, Rao Y.S, Sushma K, Sankar D.G. (2002). Extractive spectrophotometric determination of sildenafil citrate in pharmaceutical dosage forms. *Indian Drugs* 39 (2), 106-109.

Sane R.T, Surve V and Francis M. (2000). Extractive colorimetric determination of meloxicam from its pharmaceutical preparation. *Indian Drugs* 390-393 37 (8).

Somashekara Ramappa P.G and Revanasiddappa H.D. (2001). Extractive spectrohotometric determination of antihypertensive agents in pharmaceutical dosage forms. *Indian Drugs* 97-99 38 (2).

Soonhee K.S and James B.S. Edited by Florey, K. Analytical Profiles of Drug Substances., 15, Academic Press, New York, (1986).

The United States Pharmacopedia, Twenty-third Revision (USP XXIII) Board of Trustees. (1995).

The United States Pharmacopedia XXII, United States Pharmacopedial Convention, INC., Rockville (1990).

Ulrich S and Martens J. (1997). Solid-phase micro-extraction with capillary gas-liquid chromatography and nitrogen-phosphorus selective detection for the assay of antidepressant drugs in human plasma. *J. Chromatogr. B Biomed. Sci* 217-234 696(2) (appl.).

Vujic Z, Radulovic D and Manojlovic S. (1999). Determination of maprotiline hydrochloride by capillary zone electrophoresis. *Pharm. Pharmacol. Commun.* 623-624 5 (11).

Received: 27.12.2004
Accepted: 04.04.2005