

Spectrophotometric Determination of Mexiletine Hydrochloride in Capsules Using Bromothymol Blue

Zeynep AYDOĞMUŞ, S. Müge ÇETİN, Sedat TOSUNOĞLU

*University of İstanbul, Faculty of Pharmacy, Department of Analytical Chemistry,
34452, İstanbul-TURKEY
e-mail: smugecetin@yahoo.com*

Received 26.06.2001

A new spectrophotometric method based on the formation of an ion-pair using bromothymol blue as ion-pair complexing reagent was developed for the determination of mexiletine hydrochloride in capsules. The ion-pair formed was highly coloured and easily extracted with dichloromethane. The calibration curve was linear over the concentration range 1.08–10.8 $\mu\text{g}\cdot\text{ml}^{-1}$ at $\lambda_{max} = 408 \text{ nm}$ ($r = 0.9999$). The results obtained from the developed method were compared statistically with those obtained by the British Pharmacopeia method.

Key Words: Spectrophotometry, Mexiletine hydrochloride, Bromothymol blue, Ion-pair.

Introduction

Mexiletine hydrochloride (MH), [1-(2,6-(dimethylphenoxy)-2-aminopropane hydrochloride], is an antiarrhythmic drug used for treatment of ventricular arrhythmias^{1–3}. Although a variety of UV-spectrophotometry⁴, fluorimetry⁵, gas^{6,7} and high performance liquid chromatography^{8,9} techniques for assaying mexiletine in both capsules and biological materials have been described, only a derivative spectrophotometric method¹⁰ has been reported. More recently, a spectrophotometric method based on the formation of ion-pair complexes with methyl orange was reported¹¹. Since there are serious side effects of MH, namely tachycardia, arterial fibrillation, hypotension and need to follow the patient during treatment, rapid and sensitive methods for the determination of MH are still required. In this study, our aim was to develop a new more sensitive spectrophotometric determination method for the analysis of mexiletine hydrochloride and its capsules based on the formation of an ion-pair with bromothymol blue (BTB) as an ion-pair complexing reagent.

Experimental

Materials and methods

Apparatus

A Shimadzu UV-160 A UV-visible spectrophotometer with 1 cm path length glass and quartz cells and WTW pH 526 pH meter with a combined glass electrode were used.

Chemicals

Mexiletine hydrochloride and capsules of it (Mexital[®]) were kindly supplied by Eczacıbaşı Pharmaceuticals (İstanbul, Turkey). The other chemicals and solvents used were analytical reagent grade. Bidistilled water was used throughout the work.

Stock solution of MH

About 10.8 mg of MH was dissolved in 50 ml of water (1×10^{-3} M).

Reagent solution

About 187.2 mg of BTB was dissolved in 50 ml of 5% alcohol (5.99×10^{-3} M).

Procedures

Preparation of Calibration Graph

Suitable aliquots of the stock solution of MH (0.25–2.5 ml) were transferred to stoppered glass tubes and 2.5 ml of the stock solution of BTB (5.99×10^{-3} M) was added to each of them. Then the mixture was extracted with 5 ml dichloromethane by vortex mixer for 2 min; 1 ml of the organic phases was put into a calibrated flask, and diluted to 10 ml with dichloromethane. Absorbance values were measured at 408 nm against a blank solution which was prepared in a similar way. The calibration graph of MH was plotted and the regression equation was calculated.

Assay Procedure for Capsules

Capsule powder equivalent to about 200 mg of MH was accurately weighed and transferred into a 250 ml calibrated flask. Then 100 ml of water was added, and the mixture was shaken mechanically for 1 h and diluted to volume with water, and mixed and filtered. Then 0.25 ml of filtrate was taken from this solution, and the same procedure was applied as described above for the calibration graph. The amount of MH in capsules was calculated from the regression equation of the calibration graph.

Results and Discussion

Optimum ion-pair formation conditions with respect to solvent, pH, time and amount of the reagent were investigated. The ion-pair formed was highly coloured and easily extracted with dichloromethane. The absorption spectrum in CH_2Cl_2 showed a maximum at 408 nm. Buffer solutions (phosphate buffer pH = 5–8) were tried, but the ion-pair showed the highest absorbance in the nonbuffer solution. The final solution was stable for 18 h at room temperature in darkness. The stoichiometric ratio of MH / BTB was found to be 1:1 by Job's curve. The optimum molar ratio of reagent to MH was found to be 6 by the molar ratio method (Figure 1). Under these conditions, a linear correlation was observed between absorbance and concentration of MH over the range $1.08\text{--}10.8 \mu\text{g}\cdot\text{ml}^{-1}$ (Figure 2). The regression equation was $A = 0.0906 c + 0.0137$ with a the correlation coefficient $r = 0.9999$.

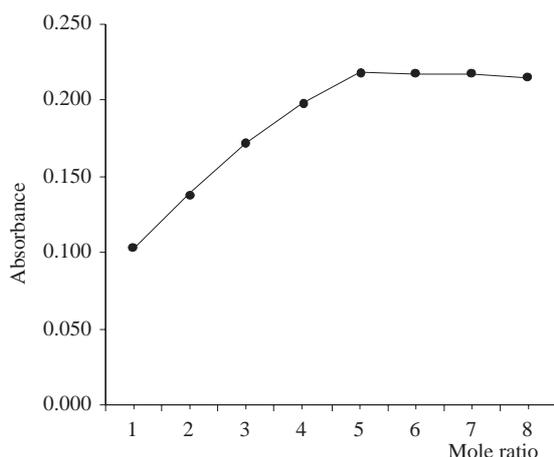


Figure 1. Effect of mole ratio of BTB to mexiletine hydrochloride.

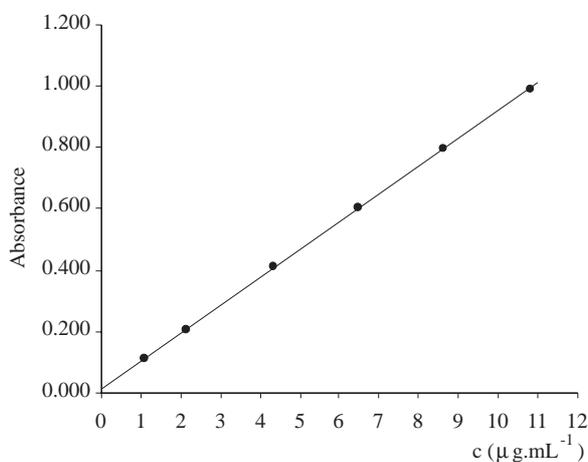


Figure 2. Calibration curve.

The proposed method was applied to commercially available capsules. The results were compared with those obtained by the official method⁴. Statistical comparisons in terms of t- and F-tests for these methods given in the Table. There are no significant differences between the proposed method and the official method with respect to the mean values and standard deviations at a 95% confidence level.

Table. Comparison of the results obtained by spectrophotometric and UV- spectrophotometric methods for the assay of **MH** in capsules.

Statistical values	Proposed method	UV-spectrophotometric method (BP 1993)
Mean (mg)	200.13	200.19
Recovery \mp standard deviation, [%]	100.06 \mp 1.02	100.09 \mp 0.76
Confidence limits	200.13 \mp 0.93	200.19 \mp 0.69
t-test*		0.12
F-test*		1.79

* n = 6 p = 0.05 t = 2.23 F = 5.05 (each capsule contains 200 mg of **MH**)

The proposed method was also compared with a reported method¹¹ with respect of the linear ranges and statistically values. The linear range in the reported method was 1.1-7.6 $\mu\text{g.ml}^{-1}$. The proposed

method was more accurate and precise in terms of t- and F-tests. Moreover, maximum absorbance occurred in phthalate buffer in the reported work, whereas the highest absorbance was obtained in the nonbuffer solution in this work. The stability of the colour of ion-pair formation has also not been investigated¹¹.

The results show that this method is simple, accurate and precise and it can be recommended for the routine pharmaceutical analysis of mexiletine hydrochloride.

Acknowledgement

This work was supported by the Research Fund of University of Istanbul. Project number 1402 / 05052000.

References

1. P.J. Pentikainen, **Eur. J. Clin. Pharmacol.**, **25**, 773-777 (1983).
2. J.P. Monk and R.N. Brogden, **Drugs**, **40**, 374-411 (1990).
3. M.A. Abounassif, M.S. Mian and N.A.A. Mian, "Analytical Profiles of Drug Substances", Vol. 20, pp 433-75, Academic Press, New York, 1989.
4. **British Pharmacopeia**, Vol. II, pp. 1012-1013, Her Majesty's Stationery Office, London, 1993.
5. W. Scheja, J.W. Scheja and H. Bruester, **GIT Labor. Med.**, **6 (1)**, 14-15, 18-20, 22-23, 26-28, 31-32 (1983). -Ref., C.A. 100, 96023s (1983).
6. A.F. El-Walily, **Alexandria J. Pharm. Sci.**, **5 (1)**, 57-60 (1991).
7. S. Willox and B.N. Singh, **J. Chromatogr.**, **128 (1)**, 196-198 (1976).
8. O.H. Drummer, S. Horodimis, S. Kourtis, M.L. Syrjanen and P. Tippet, **J. Anal. Toxicol.**, **18 (3)**, 134-138 (1994).
9. V.L. Lanchote, B.P. Sueli, E.J. Cesarino, Y.A. Mere, S.R. Cavani, J. Santos and C. Bertucci, **Chirality**, **9 (8)**, 738-782 (1997).
10. V.L. Lanchote, V.J. Santos, E.J. Cesarino, E. Jose, D.S.A. Carvalho, Y.Jr. Mere and S.R.C.J. Santos, **Chirality**, **11 (2)**, 85-90 (1999).
11. C. Önal, A. Önal and S. Tosunoğlu, **J. Fac. Pharm. İstanbul**, **34 (1)**, 1-6 (2001).