Turk J Chem
25 (2001) , 485 – 490.

Spectrophotometric Determination of *Propranolol* as Cu(II), Ni(II) and Co(II) Dithiocarbamate Complexes*

Ayşegül GÖLCÜ, Mustafa DOLAZ, Selahattin SERİN
KSU, Faculty of Science and Arts, Department of Chemistry,
46100, Kahramanmaraş-TURKEY

Received 06.10.2000

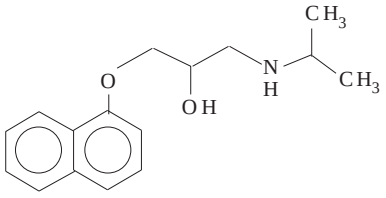
A spectrophotometric method was developed for the determination of the beta adrenergic blocking drug propranolol. The method was based on the formation of Cu(II), Ni(II) and Co(II)-dithiocarbamate complexes from the secondary amine group of propranolol with carbondisulfide (CS_2) and the acetate salts of the metals in ammonia medium.

The method was applied to the analysis of propranolol tablets and the results were statistically compared with those obtained by the official method using t- and F-tests. There was no significant difference between the mean values and the precisions of the two methods at the 95% confidence level.

Key Words: Propranolol, pharmaceutical Formulations, spectrophptpmetry, metal-dithiocarbamate complex, tablets

Introduction

Propranolol, a drug widely used in the treatment of hypertension, angina cardiac arrhythmias and thyrotoxicosis, is almost completely metabolized in man[1].



The major metabolites identified in plasma and urine include conjugates of propranolol and 4-hydroxypropranolol and free α-naphthoxylactic acid[2−7]. The methods presently available for the measurement of these metabolites use either spectrofluorometry[8], thin-layer chromatography[2,9], gas chromatography[10,13], gas chromatography-mass spectrometry [3,14,15] or high performance liquid chromatography[4,16−22]. All these methods require extensive sample work-up.

*This paper has beed presented at MBCAC III (3rd Mediterranean Basin Conference on Analytical Chemistry) 4-9 June, 2000 Antalya-Turkey

The aim of the present work is to develop an easy, rapid method for the determination of propranolol in tablets. The method is based on the reaction of its secondary amino group with CS_2in the presence of ammonia to form the corresponding dithiocarbamate, which forms coloured complexes with Cu (II), Co(II) and Ni(II) ions.

Experimental

Apparatus

A double beam spectrophotometer (Schimadzu 160 A) with a fixed slitwidth was used.

An MP 220 pH meter was used for the pH measurements.

Chemicals

Propranolol was kindly provided by Sanofi-Doğu Drug Inc., İstanbul, Turkey, and was used without prior purification. Metal salts and other chemicals were purchased from Merck. All chemicals used were of analytical reagent grade.

Metal Solutions

9.10^{-3} M metal solutions were prepared in methanol.

Other Solutions

Twenty-five percent ammonia and 5% CS_2 solutions were prepared in ethanol (EtOH).

Stock Solution of Drug

Prepared by weighing accurately 25 mg of the drug into a 50 mL volumetric flask, dissolving in absolute ethanol and diluting to volume with EtOH.

Assay procedure for dosage forms

Tablets

Twenty tablets of propranolol were weighed and pulverized into a fine powder. An aliquot equivalent to about 25 mg of propranolol was transferred to 50 mL flasks. A suspension with 10 mL of ethanol was shaken for 2 min and filtered into a 50 mL volumetric flask. The first flask was rinsed with small amounts of water, which were transferred through the same filter paper to the volumetric flask to obtain a solution of 50 mL.

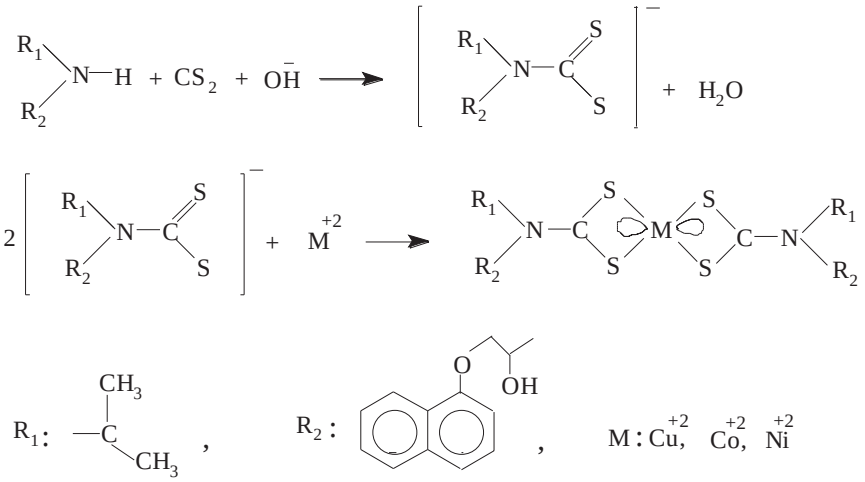
Recommended Procedure for Pure Forms

Calibration Curves

0.1-0.5 $mg.mL^{-1}$ standard solution was transferred to test tubes. 1.0 mL 10% CS_2 solutions, 0.5 mL 25% ammonia solutions were added to each tube. All of the tubes were vortexed for 2 min and 1 mL metal solutions were added to each tube. The absorbance of the resulting solution was measured at 605 nm for Cu(II), 636 nm for Ni(II) and 644 nm for Co(II) against reagent blanks.

Results and Discussion

The reaction between propranolol and metal (Scheme) is a simple condensation reaction with CS_2 in the presence of ammonia to form the corresponding dithiocarbamate, which forms a coloured complex with metal (II) ions[21].



Scheme

Metal-dithiocarbamate complexes have been used in the spectrophotometric and HPLC determination of both secondary amines[22] and metal ions[23]. However, primary amines, for example amlodipine, do not yield the dithiocarbamate reaction. Several previous experiences have shown that the complexes formations rates are rather high. In a series of solutions, the pH was changed from 7 to 11, maintaining the metals concentration of 9.10^{-3} M and ligand concentration of 25 mgL^{-1}. The spectrums were recorded from 200 to 800 nm. The maximum absorbances at 605 nm, 636 nm and 644 nm for Cu(II), Ni(II) and Co(II) respectively (Figs. 1-3). The maximum absorbances showed maximum values with the minimum change in the pH range from 9.0 to 10.0. Hence pH 9.0 was chosen for further studies. Metals and propranolol forms brown (for Cu(II)), orange (for Ni(II)) and green (for Co(II)) complexes.

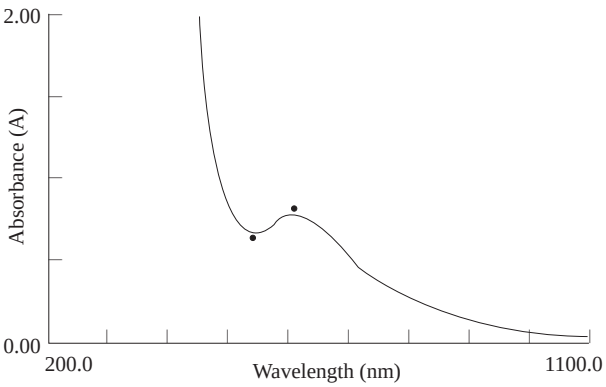


Figure 1. The absorption spectrum of the propranolol-Cu(II) dithiocarbomate complex.

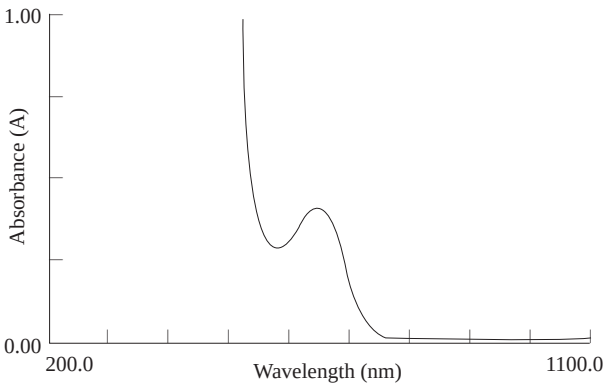


Figure 2. The absorption spectrum of the propranolol-Ni(II) dithiocarbamate complex.

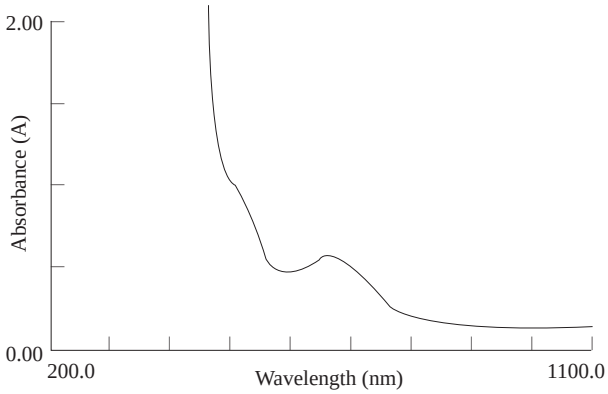


Figure 3. The absorption spectrum of the propranolol-Co(II) dithiocarbamate complex.

Table 1. The effect of the amount of metal on complex formation.

ExpNo		Absorbance			
		0.5	1.0	1.5	2.0
1	Cu	*	0.797	0.824	0.899
	Ni	*	0.419	0.498	0.548
	Co	*	0.498	0.567	0.623
2	Cu	*	0.801	0.819	0.890
	Ni	*	0.417	0.496	0.552
	Co	*	0.490	0.560	0.632
3	Cu	*	0.799	0.820	0.901
	Ni	*	0.421	0.500	0.547
	Co	*	0.498	0.569	0.629
4	Cu	*	0.800	0.821	0.896
	Ni	*	0.419	0.499	0.550
	Co	*	0.496	0.567	0.626
5	Cu	*	0.798	0.822	0.900
	Ni	*	0.418	0.496	0.548
	Co	*	0.498	0.566	0.625
X					
	Cu	*	0.799	0.821	0.897
	Ni	*	0.419	0.498	0.549
	Co	*	0.496	0.566	0.627
SD					
	Cu	*	0.002	0.019	0.018
	Ni	*	0.021	0.022	0.024
	Co	*	0.031	0.030	0.029
%RSD					
	Cu	*	0.350	1.045	4.566
	Ni	*	0.70	2.987	6.908
	Co	*	0.56	1.987	5.879

In order to obtain the exact amount of reactive for optimal complex colour formation, 0.5, 1.0, 1.5, 2.0 mL of metal solutions were added to reaction media and the results were compared (Table 1). The addition of 0.5 mL metal did not yield any complex as this was a low concentration for prporanolol-metal dithiocarbamate complex formation. The addition of 1.0, 1.5, 2.0 mL metal solutions gave high absorbance

values and the relative standard deviations were close to each other. However, the addition of 1.5-2.0 mL of metal solution series yielded high absorbance blank solutions. Therefore it was decided to work with 1.0 mL metal solutions.

The effect of the percentage of CS_2 in ethanol was studied by changing it from 1 to 10% . The maximum absorbance was obtained with EtOH containing 5% of CS_2. A linear relationship was obtained between absorbance (A) and propranolol concentration (c) (0.799-25 mg.mL^{-1} for Cu(II), 0.419-25 mg.mL^{-1} for Ni(II), 0.498-25 mg.mL^{-1} for Co(II)).

Propranolol possesses a secondary amine group. Spectrophotometric assay methods are based on the reaction of the amine group with Cu(II), Ni(II) and Co(II) were developed with CS_2 in the presence of ammonia. Metals react propranolol at room temperature giving a coloured complexes. The calibration equation for 5-25 mg.mL^{-1} propranolol is y= 0.038 x-0.006 (r = 0.9999) (for Cu(II)). Since the coloured complex is stable for 60 min, the method can be applied to large series of samples. The calibration equation for 5-25 mg.mL^{-1} propranolol is y= 0.003 x + 0.008 (r = 0.9987) (for Ni(II)). Since the colour complexes decompose in 15 min, the method is not suitable for large series of samples. The calibration equation for 5-25 mg.mL^{-1} propranolol is y= 0.007 x - 0.019 (r = 0.9997) (for Co(II)). The coloured complex stable 20 min.

The developed method was applied to the assay of propranolol in commercial tablet formulations. The method was compared with the method of BP 98[24]. There was no significant difference between the mean values and precisions of the two methods at the 95% level (Table 2).

Table 2. Analysis of Propranolol Tablets (40 mg/Tablet)

Statistical Value	Described Method	Reference Method
Recovery (%)	$100.33_{Cu(II)}$	100.88
	$99.99_{Ni(II)}$	101.01
	$101.12_{Co(II)}$	102.23
SD	0.002	0.004
	0.021	0.040
	0.031	0.029
SD%	0.350	0.670
	0.700	0.850
	0.560	0.790
t-test of significance*	1.090	1.090
	1.810	1.810
	1.170	1.170
F-test of significance*	3.430	3.430
	2.980	2.980
	3.050	3.050

T= 2.23, F= 5.05 for p= 0.05, N=5

Acknowledgements

The authors are grateful to Dr A. Sibel Özkan (Univ. of Ankara, Fac. of Pharmacy, Dept. of Analytical Chem.) for her help.

References

1. J. W. Paterson, M. E. Conolly, C. T. Dollery, A. Hayes and R. G. Coopper, **Pharmacol. Clin., 2,** 127, (1970).
2. Y. Garceau, I. Davis and J. Hasegawa, **J. Pharm. Sci., 67,** 826, (1978).
3. V. T. Vu and F. P. Abramson, **Biomed. Mass Spectrom., 5**, 686, (1978).
4. J.F. Pritchard, D. W. Schneck and A. H. Hayes, Jr., **J. Chromatogr., 162**, 47, (1979).
5. T. Walle, T. C. Fagan, E. C. Conradi, U. K. Walle and T. E. Gaffney, **Clin. Pharmacol. Ther., 26**, 167, (1979).
6. T. Walle, E. C. Conradi, U. K. Walle, T. C. Fagan and T. E. Gaffney **Clin. Pharmacol. Ther., 26**, 548, (1979).
7. T. Walle, E. C. Conradi, U. K. Walle, T. C. Fagan and T. E. Gaffney **Clin. Pharmacol. Ther., 26**, 686, (1979).
8. P. S. Rao, L. C. Quesada and H. S. Mueller, **Clin. Chim. Acta, 88**, 355, (1978).
9. M. Schafer, H. E. Geissler and E. Mutscher, **J. Chromatogr., 143**, 607, (1977).
10. T. Walle, **J. Pharm. Sci., 63**,1885, (1974).
11. D. S. Saelens, T. Walle and P. J. Privitera, **J. Chromatogr.,** 123, 185, (1976).
12. J. F. Prichard. D. W. Schneck, W. J. Racz and A. H. Hayes, Jr., **Clin. Biochem., 11**, 121, (1978).
13. D. E. Easterling, T. Walle, E. C. Conradi and T. E. Gaffney, **J. Chromatogr.,162**, 439, (1979).
14. T. Walle, J. Morrison, K. Walle and E. C. Conradi, **J. Chromatogr., 114**, 351, (1975).
15. T. Walle, U.K Walle, D.R. Bridges, E.C. Conradi and T.E. Gaffney, **Clin. Chem., 24,** 991, (1978).
16. W.D. Mason, E.N. Amick and O.H. Weddle, **Anal. Lett., 10,** 515, (1977).
17. R.L. Nation, G.W. Peng and W.L. Chiou, **J. Chromatogr., 145,** 429, (1978).
18. A.M. Taburet, A.A. Taylor, J.R. Mitchell, D.E. Rollins and J.L. Pool, **Life Sci., 24,** 991, (1979).
19. F. Pritchard, D. Schneck and A. Hayes, Jr., **Res. Commun. Chem. Pathol. Pharmacol., 23,** 279, (1979).
20. M. Lo and S. Riegelman, **Journ. of Chromatog., 183,** 231-220,1980.
21. G. Alpdoğan and S. Sungur, **Analytical Letters, 30(7)**, 1359-1368, 1997.
22. T. Mitsui, Y. Fujimura, **Nippon Kagaku Kaishi., 10,** 1908-1911, 1974; **C.A., 81,** 181012 w (1974).
23. A. M. Bond, G.G. Wallace, **Anal. Chem.,** 54, 1706-1712, 1982.
24. The British Pharmacopoeia 1998, Version 2.0, (CD-ROM), The Stationary Office Ltd., March 1998.