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Short communication

Potentiometric and voltammetric determination of methimazole

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Abstract

The determination of methimazole was investigated by potentiometric titration in an alkaline medium involving its reaction with iodine and square wave voltammetry (SWV) in 0.1 mol/l Tris–HCl buffer at pH 7.2. In potentiometric titration, the range of determination was 10–500 μmol. A stoichiometric reaction was obtained within the concentration range 0.75–1.25 mol/l of sodium hydroxide by potentiometric titration. A linear calibration graph was obtained over the concentration range 1–700 μmol/l by SWV. The lowest concentration of methimazole detected was 0.5 μmol/l. The relative standard deviations (R.S.D.) were 0.81% in potentiometric titration and 2.89% in square wave voltammetric analysis of thyromazol tablets. The data showed that potentiometric titration using iodine in sodium hydroxide can be used for the determination of methimazole in drug samples without prior separation.

Keywords: Methimazole; Potentiometric titration; Voltammetry; Determination; Thyromazol tablets

1. Introduction

Methimazole (2-mercapto-1-methylimidazole) used in the treatment of hyperthyroid by the production of thyroxin, a hormone excreted by the thyroid gland, inhibits the formation of thyroid hormones [1]. Methimazole is adsorbed by the gastrointestinal tract and concentrated in the thyroid gland [2,3]. It has been reported that methimazole may also cause side effects such as nephritis, liver cirosis, irritation of the skin, allergies and pharyngitis with fever [4].

The determination of methimazole is important in many areas including clinical chemistry and pharmaceutical formulations. Several analytical procedures have been described for the determination of methimazole including thin layer chromatography [1], coulometry [5], conductometry [6], high-performance liquid chromatography with ultraviolet detection [7], spectroscopy [8–10], electrochemistry with a silver–silver sulphide solid-state electrode [11], liquid chromatography with amperometric detection at a nafion/indium hexacyanoferrate film modified electrode [12] and capillary zone electrophoresis with amperometric detection at a carbon electrode [13]. Iodimetric methods have been useful for the determination of

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drugs [14]. However, no studies have been reported on the determination of methimazole using potentiometric titration with iodine in an alkaline medium and square wave voltammetry (SWV). Here the determination of methimazole by potentiometric titration with iodine in sodium hydroxide and SWV is reported. Both methods were successfully applied to the determination of methimazole in thyromazol tablets.

2. Experimental

2.1. Materials and instrumentation

Unless otherwise stated all chemicals were of analytical reagent-grade and purchased from Merck (Darmstat, Germany) or Sigma (Taufkirchen, Germany). The solutions were prepared with doubly distilled water. A standard solution of methimazole (Sigma) was prepared by dissolving a weighed amount of the reagent in 1 mol/l sodium hydroxide solution for potentiometric measurements. Iodine standard solutions of 0.1 mol/l were prepared in doubly distilled water. Solutions of methimazole were prepared in 0.1 mol/l Tris–HCl buffer at pH 7.2 for voltammetric studies. Thyromazol tablets were obtained from a local pharmacy. A Metrohm (Herisau, Switzerland) pH meter with a combined platinum ring electrode was used for the potentiometric measurements. A mechanical stirrer was employed. Voltammetric experiments were performed using an EcoChemie Autolab PGSTAT 12 potentiostat/galvanostat (Utrecht, The Netherlands) with an electrochemical software package GPES 4.9. A three electrode system was used: a 2 mm sized Pt disc working electrode, an Ag/AgCl reference electrode and a Pt wire counter electrode.

2.2. Procedures

2.2.1. Potentiometric titration

A sample of methimazole (10–500 μmol) was dissolved in 25 ml of 1 mol/l NaOH solution and titrated with iodine solution using potentiometric titration with a combined platinum ring electrode. The inflection point of the curve corresponded to the equivalence point of the reaction.

2.2.2. Potentiometric determination of methimazole in thyromazol tablets

Ten tablets were weighed and crushed to a fine powder in a mortar. A mass of powder equivalent to the average mass of one tablet was dissolved in 25 ml of 1 mol/l NaOH. It was then titrated with iodine solution in the same way as the pure substance. The content of methimazole in one tablet was calculated using the following equation.

$$m = \frac{CV}{z} M \quad (1)$$

where m is the content of methimazole in one tablet; C(I), concentration of iodine; V, volume of iodine in the end-point; M, molecular weight of methimazole and z, number of electrons transferred in the reaction of 1 mol.

2.2.3. Voltammetric procedure

A stock solution of methimazole was prepared in 0.1 mol/l Tris–HCl buffer at pH 7.2. A calibration graph was obtained using various concentrations of methimazole scanned between 0.4 and 1.0 V. The Pt working electrode was polished with 0.05 μm alumina prior to each experiment, then rinsed with doubly distilled water. Throughout the experiment oxygen-free nitrogen was bubbled through the solution for 10 min. All experiments were performed at room temperature.

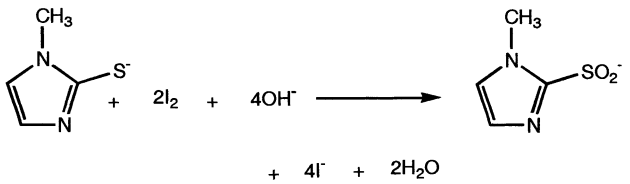
2.2.4. Voltammetric assay of methimazole in thyromazol tablets

Ten tablets were weighed and crushed to a fine powder in a mortar. A mass of powder equivalent to the average mass of one tablet was dissolved in 50 ml of 0.1 mol/l Tris–HCl buffer at pH 7.2. It was then introduced to an ultrasonic bath for 5 min, filtered and diluted with Tris–HCl buffer in a calibrated 100 ml flask. Appropriate dilutions were made from the supernatant solution with Tris–HCl buffer. Then the tablet solution was subjected to SWV. The content of drug was determined referring to the regression equation.

3. Results and discussion

3.1. Potentiometric titration

The results of the potentiometric determination of methimazole with iodine in sodium hydroxide are given in Table 1. It has been demonstrated that the determination of methimazole with iodine in sodium hydroxide is based on the following stoichiometry.



It is known that iodine disproportionates in alkaline medium to produce iodide and hypoiodite ions. The actual oxidising agent here is hypoiodite. The concentration of sodium hydroxide greatly affected the course of the reaction. Potentiometric titration curves of methimazole with iodine in 1 mol/l sodium hydroxide are shown in Fig. 1. It was found experimentally that the concentration of sodium hydroxide must vary within the range of 0.75–1.25 mol/l for the reaction to proceed stoichiometrically. Higher and lower concentration of sodium hydroxide caused a non-stoichiometric reaction between methimazole and iodine. The number of electrons transferred in the reaction between methimazole and iodine was four when the concentration of sodium hydroxide was varied within the range of 0.75–1.25 mol/l. An increase in pH of the reaction solution beyond the range given increases the number of electrons transferred between methimazole and iodine. The determination range for methimazole was within the range of 10–500 μmol. The data recorded in Table 1 reveal that this simple method is highly precise. The precision expressed by relative standard deviation (R.S.D.%) was less than 1%. In acidic or neutral media, the potentiometric titration of methimazole with iodine was impossible due to a lower reaction rate.

Table 1
Results of the potentiometric determination of methimazole

Amount taken (μmol)	Found[a] (μmol)	R.S.D. (%)
10	9.95±0.08	0.82
100	99.3±0.7	0.73
250	249.5±0.7	0.31
500	498.9±0.9	0.19

[a] Mean and standard deviation of five determinations.

3.2. Voltammetric studies

A cyclic voltammogram of 0.15 mmol/l methimazole in 0.1 mol/l Tris–HCl buffer at pH 7.2 is shown in Fig. 2. Methimazole has an anodic peak at ca. 0.8 V. No peaks are observed in the cathodic branch indicating that the methimazole oxidation is an irreversible process. The anodic peak can be attributed to the thiol moiety of methimazole. The peak potential shifted to more positive values on increasing the scan rate, which confirms the irreversibility of the oxidation process. The αn value was 0.885 determined from sampled direct current voltammetry. Square wave voltammograms of various concentrations of methimazole are given in Fig. 3. The dependence of the peak current on the concentration of methimazole was investigated by SWV. There was a linear relationship between the peak current and the concentration of methimazole over the range 1–700 μmol/l, which fitted the equation $I(nA) = 2364.82C$

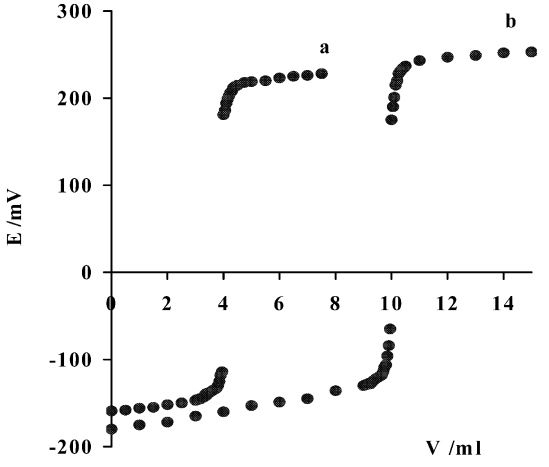


Fig. 1. Potentiometric titration curves for (a) 100 μmol and (b) 250 μmol of methimazole with 0.1 mol/l iodine in 1 mol/l sodium hydroxide solution.

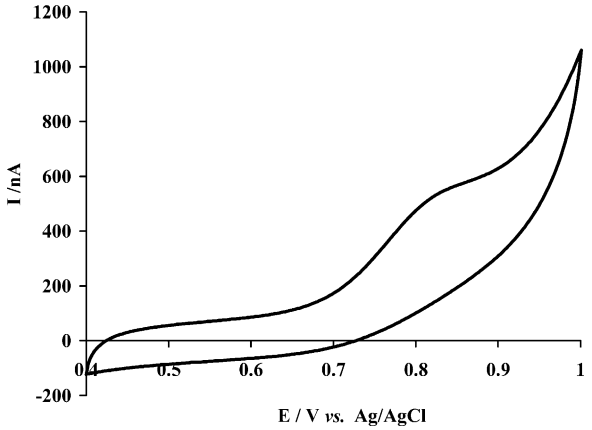


Fig. 2. A cyclic voltammogram of 0.15 mmol/l methimazole in 0.1 mol/l Tris–HCl buffer at pH 7.2. Scan rate, 50 mV/s. Equilibrium time, 10 s.

(mmol/l)+0.465 with a correlation coefficient $r = 0.9993$. The lowest concentration of methimazole detected was 0.5 μmol/l. The detection limit was evaluated on a basis of S/N ratio of 3.

3.3. Determination methimazole in thyromazol tablets

The content of the drug determined by potentiometric titration was calculated using Eq. (1). Square wave voltammetric determination of methimazole in thyromazol tablets was referred to the regression equation. The analysis of thyromazol tablets using both methods is summarised in Table 2. The R.S.D. were 0.81% in potentiometric titration and 2.89% in square wave voltammetric analysis of thyromazol tablets. The validity of the proposed procedures applied to thyromazol tablets was also assured by the recovery of standard additions. The mean recoveries were 99.0% with R.S.D. of 0.62 for potentiometric titration and 97.4% with R.S.D. of 3.02 for SWV. The results of the drug analysis obtained from both methods are in close agreement with the claimed value. At the same time, the results obtained from both methods are also consistent with the results obtained from liquid chromatography and capillary zone electrophoresis [12,13]. However, the results obtained from the potentiometric titration of the drug with iodine in sodium hydroxide indicate that this simple method is more precise and accurate for the determination of methimazole in drug samples. It is also clear that this simple method can be applied to quantify methimazole samples without any separation.

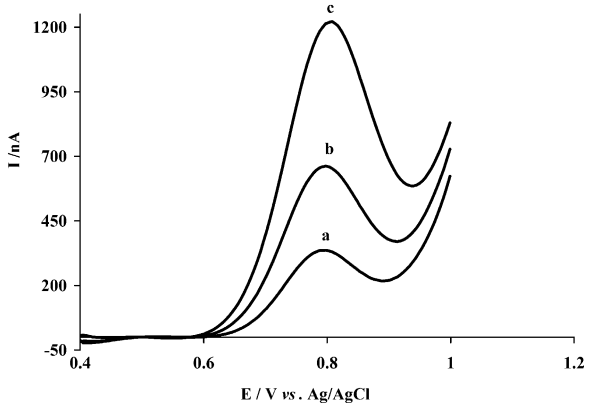


Fig. 3. Square wave voltammograms of (a) 0.15 mmol/l (b) 0.275 mmol/l and (c) 0.5 mmol/l methimazole in 0.1 mol/l Tris–HCl buffer at pH 7.2. Equilibrium time, 10 s; frequency, 10 Hz; step potential, 5 mV; amplitude, 25 mV.

Table 2
Results of the determination of methimazole in thyromazol tablets[a]

	Potentiometry	SWV[c]	[12]	[13]
Found[b] (mg)	4.96±0.04	4.84±0.14	4.82	4.86
Percent (%)	99.2	96.8	96.4	97.2
R.S.D. (%)	0.81	2.89	3.6	2.87

[a] Label claim (5 mg).
[b] Mean and standard deviation of five determinations.
[c] SWV conditions as in Fig. 2.

4. Conclusions

The results of methimazole analysis in thyromazol tablets using both potentiometric titration and SWV are in close agreement with the claimed values. The successful determination of methimazole with iodine in sodium hydroxide using potentiometric titration has been shown to provide an accurate and precise method for the drug in tablet formulations.

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References

[1] M. Aletrari, P. Kanari, D. Partassides, E. Loizou, J. Pharm. Biomed. Anal. 16 (1998) 785–792.
[2] Antithyroid agents,J.E.F. Reynolds (Ed.), Martindale, The Extra Pharmacopoeia, 29th ed, The Pharmaceutical Press, London, 1989, pp. 682–688.
[3] H.Y. Aboul-Enein, A.A. Methimazol Al-Badr, in: K. Forey (Ed.), Analytical Profiles of Drug Substance, vol. 18, Academic Press, New York, 1979, pp. 351–371.
[4] A.C. Edward, Thyroid hormones and drugs that affect the thyroid, in: C.M. Smith, A.M. Reynard (Eds.), Text-Book of Pharmacology, W.B. Saunders Company, Philadelphia, PA, 1992, pp. 652–656.
[5] K. Nikolic, K. Velasevic, Pharmazie 42 (1987) 698–698.
[6] A. Berka, K. Velasevic, K. Nikolic, Pharmazie 44 (1989) 499–499.
[7] G. Moretti, P. Betto, P. Cammarata, F. Fracassi, M. Giambenedetti, A. Borghese, J. Chromatogr. Biomed. 616 (1993) 291–296.
[8] M.G. Elbardicy, Y.S. Elsaharty, M.S. Tawakkol, Spectrosc. Lett. 24 (1991) 1079–1095.
[9] C. Sanchezpedreno, M.I. Albero, M.S. Garcia, V. Rodenas, Anal. Chim. Acta 308 (1995) 457–461.
[10] M.S. Garcia, M.I. Albero, C. Sanchezpedreno, L. Tobal, Analyst 120 (1995) 129–133.
[11] S. Pinzanti, G. Papeschi, E. LaPorta, J. Pharm. Biomed. Anal. 1 (1983) 47–53.
[12] S. Zhang, W. Sun, W. Zhang, W. Qi, L. Jin, K. Yamamoto, S. Tao, J. Jin, Anal. Chim. Acta 386 (1999) 21–30.
[13] A. Wang, L. Zhang, S. Zhang, Y. Fang, J. Pharm. Biomed. Anal. 23 (2000) 429–436.
[14] W. Ciesielski, R. Zakrzewski, A. Krenc, J. Zielinska, Talanta 47 (1998) 745–752.