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Short Communication

Colorimetric methods for the assay of carbimazole in drug formulations using dichromate and molybdate*

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Keywords: *Colorimetric method; carbimazole oxidation; dichromate; molybdate.*

Introduction

Carbimazole is ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate. It is an antithyroid substance commonly used in the treatment of hyperthyroidism. It reduces the uptake and concentration of inorganic iodine by the thyroid gland, but its main effect is to reduce the formation of dio-iodotyrosine and hence of thyroxine [1–3]. Methods for the determination of carbimazole and the structurally related methimazole include titrimetry [4–8], chromatography [2], electrochemistry [9, 10] and spectrophotometry [11, 12]. The British Pharmacopoeia [12] described a spectrophotometric method for the determination of carbimazole by dissolving the sample in water in a calibrated flask and measuring the absorbance of the resulting solution at λ_{max} of 291 nm.

The present paper describes two kinetic methods for the determination of carbimazole by its oxidation in sulphuric acid media using potassium dichromate in one method and sodium molybdate in the other.

Experimental

Reagents and samples

Stock solutions of 80 mg ml^{-1} potassium dichromate were prepared in 2.5 M sulphuric acid and stock solutions of 100 mg ml^{-1} sodium molybdate solution were prepared in 2 M sulphuric acid. Carbimazole reference standard (1 mg ml^{-1}) was prepared in water. Carbimazole test solution (1 mg ml^{-1}) was prepared from Neo-Mercazole tablets (Nicholas Ltd, England) by taking an amount equivalent to 0.100 g of carbimazole dissolved in 30 ml chloroform, warming, stirring, filtering and washing with warm chloroform. The combination was evaporated to dryness and the residue was dissolved in 50 ml warm water. It was stirred, cooled and made up to 100 ml.

Apparatus

A Beckman model 35 spectrophotometer was used.

Method

Ten millilitres of the potassium dichromate stock solution or 25 ml of the molybdate stock solution were placed in a 50 ml calibrated flask; 5 to 25 ml of carbimazole solution was added and diluted to the mark with distilled water. The flask with its contents was swirled, the stop-watch turned on and the flask was immediately placed in a water bath thermostatted at 90°C. At a fixed time of 25 min in case of dichromate and 12 min in case of molybdate, the absorbance was measured directly (at λ_{max} 585 nm in case of dichromate and at λ_{max} 650 nm in case of molybdate) after cooling under a tap for 2 min, against a reagent blank treated similarly. The amount of carbimazole was calculated from the corresponding calibration equation.

Results and Discussion

Theory of the kinetic method [13]

In high excess of the oxidant concentration a

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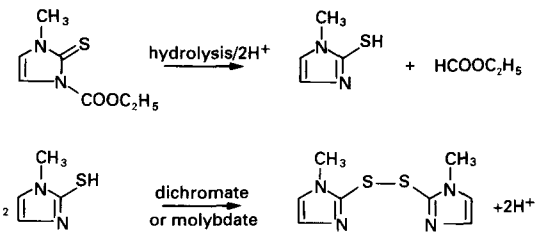
pseudo-reaction rate of the following form could be attained: rate = $\Delta A/\Delta t = k'$ [carbimazole]$_0$; where ΔA is the change of absorbance of the oxidant at λ_{max} over a preselected time interval. At this fixed constant time the above equation becomes: $\Delta A = k''$ [carbimazole]^n, where n is the order of the reaction with respect to carbimazole. This was found to be 1 and k'' is a rate constant at the preselected fixed time and equals $k'\Delta t$. Therefore, a plot of absorbance versus carbimazole initial concentration gives a straight line from which unknown concentrations can be calculated.

Reaction mechanism and optimization

This method is based on the oxidation of carbimazole with potassium dichromate or sodium molybdate, both in sulphuric acid media, thus producing the green chromium(III) species absorbing at λ_{max} 585 nm and molybdenum blue absorbing at λ_{max} 650 nm, respectively. The oxidation of carbimazole with potassium dichromate or sodium molybdate is suggested to proceed to the disulphide compound through the formation of methimazole [2, 3, 8] according to the following scheme:



In both cases the oxidation reaction of carbimazole was found to be taking place under specific conditions and only on heating. The reaction proceeds slowly to final products in several hours and the rate is found to increase with an increase in temperature and concentrations of carbimazole, oxidant and sulphuric acid. The fixed time was chosen on the basis of correlation coefficients of the calibration graph, slope and intercept. Sixteen mg ml^{-1} dichromate in 0.5 M sulphuric acid and 50 mg ml^{-1} sodium molybdate in 1 M sulphuric acid were adequate concentrations for a moderate reaction rate at 90°C. The effect of an increase in carbimazole concentration on the reaction rate is positive as represented in Figs 1 and 2. The limiting range of carbimazole determination was between 40 and 300 μg ml^{-1}

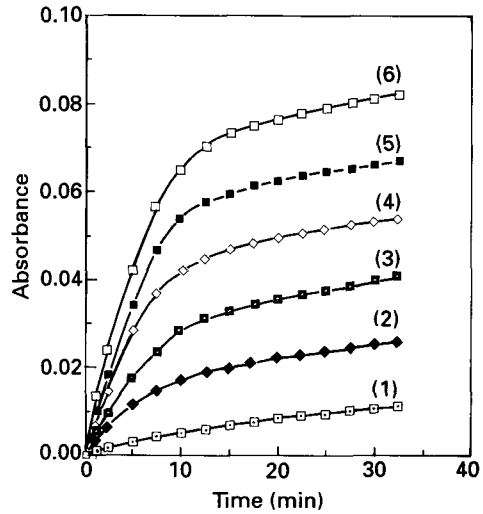


Figure 1
Absorbance–time graphs for the reaction between carbimazole and potassium dichromate taking constant concentrations of 0.5 M sulphuric acid and 16 mg ml^{-1} potassium dichromate at different concentrations of carbimazole 1, 40; 2, 100; 3, 150; 4, 200; 5, 250; 6, 300 μg ml^{-1}.

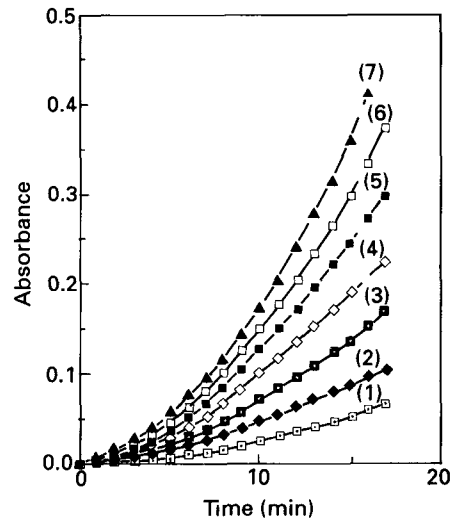


Figure 2
Absorbance–time graphs for the reaction between carbimazole and sodium molybdate taking constant concentrations of 1 M sulphuric acid and 50 mg ml^{-1} sodium molybdate at different concentrations of carbimazole: 1, 20; 2, 30; 3, 40; 4, 50; 5, 60; 6, 70; 7, 80 μg ml^{-1}.

when dichromate was used and between 0 and 80 μg ml^{-1} when molybdate was used. The dependence of the reaction rate on carbimazole concentration is illustrated in Figs 1 and 2, which show an increase in rate as carbimazole concentration is increased. In the dichromate method, the reaction slows after sampling to give a rate of change of absorbance of 0.0001 a.u. per 5 min (see Fig. 1). This is

Table 1
Results of determination of carbimazole (five replicates) in Neo-Mercazole* proprietary drug by the two described methods as compared with those obtained by the B.P. method

Amount of carbimazole taken ($\mu g\ ml^{-1}$)	Potassium dichromate method			Sodium molybdate method			B.P. method			Calculated†	
	Found ($\mu g\ ml^{-1}$)	Relative error (%)	SD	Found ($\mu g\ ml^{-1}$)	Relative error (%)	SD	Found ($\mu g\ ml^{-1}$)	Relative error (%)	SD	‡	§
10				10.04	0.4	0.2	10.06	0.6	0.0	2.2	
20				19.94	−0.3	0.3	19.98	−0.1	0.9	1.5	
30				30.24	0.8	0.3	30.21	0.7	0.3	0.7	
40	39.72	−0.7	0.2	39.40	−1.5	0.7	39.64	−0.9	0.4	1.9	2.2
50	49.70	−0.6	0.6	49.40	−1.2	0.3	49.45	−1.1	0.3	0.7	1.8
60	60.06	0.1	0.7	59.28	−1.2	0.7	59.76	−0.4	0.2	2.5	1.6
70	70.21	0.3	0.4	70.14	0.2	0.3	70.28	0.4	0.6	1.5	0.6
80	79.76	−0.3	0.2	79.92	−0.1	0.0					
120	118.68	−1.1	0.3								
150	151.05	0.7	0.3								
200	198.69	−1.3	0.4								
250	252.25	0.9	0.7								
300	297.60	−0.8	0.3								
Average error (%)		0.7			0.7			0.6			

*Neo-Mercazole is commercially available in tablet form, a product of Nicholas Lab. Ltd, and each tablet is claimed to contain 5 mg carbimazole.
†Limit value = 2.78 ($P = 0.05$).
‡Sodium molybdate method vs B.P. method.
§Potassium dichromate method vs B.P. method.

sufficiently constant to allow transferrence from water bath, mounting in the photocell and recording measurements without fear of changes or errors in readings. It is therefore, not necessary to stop the reaction by any of the common previous techniques [14] as temperature jump or changing pH or changing pressure, etc. and hence avoid errors encountered with those methods. This allows easy application of the fixed time method for the determination of carbimazole.

For obtaining a calibration equation, rates of the reaction were measured at different times versus initial carbimazole concentrations, and all gave good straight lines. At the fixed times of 25 and 12 min better correlation coefficients were obtained when dichromate and molybdate were used, respectively, with the following calibration equations for calculating unknown concentrations of carbimazole: $A = -0.002337 + 0.0002677\ C$ and $A = -0.03968 + 0.003482\ C$ for the methods, respectively. C refers to carbimazole concentration in $\mu g\ ml^{-1}$.

Analytical appraisal

The results obtained by the two methods and the B.P. method [12] for the determination of carbimazole in one batch of Neo-Mercazole proprietary drug are given in Table 1. From the results obtained by the three methods and from the student *t*-test values it is clear that there is no significant difference between the proposed methods and the B.P. method. The advantage of the two new methods over the B.P. method is that they are more selective and specific. The results also reveal that excipients in the dosage form encountered, did not interfere with carbimazole determination.

Conclusion

The molybdate method was found to be more sensitive than the dichromate and the B.P. methods. The advantage of the dichromate over the two other methods was the fact that it could be applied in a wider and higher concentration range of carbimazole if required. Our present methods suffer lower sampling frequency compared with the B.P. method.

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