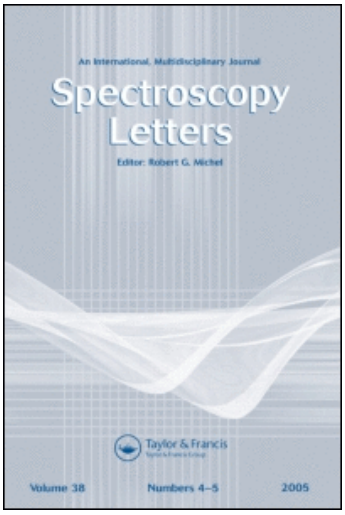

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SPECTROPHOTOMETRIC AND SPECTRODENSITOMETRIC DETERMINATION OF CARBIMAZOLE

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SPECTROPHOTOMETRIC AND SPECTRODENSITOMETRIC DETERMINATION OF CARBIMAZOLE

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ABSTRACT

Two selective, sensitive and reproducible methods for the determination of carbimazole are described. The spectrophotometric determination of carbimazole was achieved through its reaction with a known excess of potassium bromate in bromide solution, then residual reagent was treated with sodium fluorescein in buffered medium at pH 5.5, where equivalent eosin is produced, which absorbed maximally at 517 nm. Stoichiometric study of the reaction showed that, carbimazole reacts with potassium bromate in the ratio of 1:1. The spectrophotometric method is linear over a range of 30–110 μg%.

The spectrodensitometric analysis provides a rapid and precise method for the separation and quantitation of carbimazole. The method depends on the quantitative densitometric evaluation of thin layer chromatogram of carbimazole at 291 nm. It determines the drug in concentration range of 5–22.5 μg per spot.

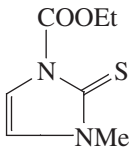
The two methods retained their accuracy and precision when applying the standard addition technique. The results obtained by

applying the proposed methods were statistically analysed and compared with those obtained by the official B.P. method.

Key Words: Carbimazole; Spectrophotometry; Spectrodensitometry; Determination.

INTRODUCTION

Carbimazole, ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate, is used in the treatment of human hyperthyroidism, an illness caused by thyroid gland hyperfunction (1,2). It has the following structural formula:



Carbimazole, mol. wt. = 186.2

This antithyroid drug has also been used to increase growth and weight in animals for human consumption, with harmful consequences for human health. The determination of carbimazole is important in different areas such as clinical chemistry, nutrition and pharmaceutical formulations.

Methods for analysing carbimazole include titrimetric (3–5), spectrophotometric (6–9), derivative spectrophotometric (10), fluorimetric (11), flow injection (12), electroanalytical (13–15), infra-red (16), nuclear magnetic resonance (17), gas chromatographic (18,19), high performance liquid chromatographic (20–22) and radioimmunoassay (23).

The present work reports two simple, sensitive and accurate methods for the determination of carbimazole. The first method based on the reaction between potassium bromate and the drug, as well as the reaction between residual bromine and sodium fluroscein to produce eosin, which was used for the determination of carbimazole spectrophotometrically. The spectrodensitometric method determined carbimazole in the presence of its metabolite, or degradation product, methimazole. The proposed procedures have been applied successfully to the determination of carbimazole in pharmaceutical preparation.

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EXPERIMENTAL

Apparatus

- UV/Vis spectrophotometer: Shimadzu UV-1601 PC. Uv-visible double beam spectrophotometer with 1 cm quartz cuvets, Shimadzu Corporation Kyoto-Japan.
- Densitometer: dual wavelength Shimadzu flying CS-9000 with video display and high-speed, high-quality, parallel-head printer/plotter.
- Hamilton micro-syringe, 25 μl, calibrated at 0.2 μl per unit.
- Thin-layer chromatography (TLC) plates: pre-coated with Silica Gel GF, 0.25 mm thickness, fluorescent at 254 nm (E. Merck, Darmstadt, Germany).

Samples

1- Carbimazole authentic sample was kindly supplied by CID Co., Cairo, Egypt (A.R.E.). The purity was found to be 99.87 ± 0.611 by the official B.P. method (6).
2- The pharmaceutical formulation "Carbimazole" tablet claimed to contain 5 mg batch no. 1099113, 1099114 and 1089114 (expired), were offered by CID Co., Cairo, Egypt.
3- Carbimazole stock solution is prepared to contain 0.02 mg.ml^{-1} of carbimazole in distilled water.
4- Carbimazole stock solution is prepared to contain 1 mg.ml^{-1} of carbimazole in dichloromethane.

Reagents

All chemicals and reagents are of pure analytical grade.

- Standard potassium bromate reagent (0.0025 N); dilute 25 ml 0.1 N potassium bromate in 5% potassium bromide to one liter.
- 20% Hydrochloric acid (v/v); dilute 200 ml concentrated hydrochloric acid to one liter with distilled water.
- Sodium hydroxide solution: aqueous solution (0.5 N).
- Acetate buffer (pH 5.5) prepared by addition of 100 ml (0.2 M) acetic acid to 900 ml (0.2 M) sodium acetate (24).

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- Sodium fluorescein: aqueous solution was prepared in concentration of 0.38 mg.ml^{-1} by dissolving 0.38 g sodium fluorescein (BDH) in distilled water and complete the volume to one liter.
- Acetone and dichloromethane, Merck, Germany.

Procedures

Spectrophotometric Determination of Carbimazole by Indirect Method

For Calibration Curve: Into 100 ml measuring flask, transfer 5 ml $KBrO_3$ /KBr (0.0025 N) reagent. Acidify with 5 ml 20 % (v/v) hydrochloric acid. Add aliquots of carbimazole stock solution (0.02 mg.ml^{-1}) equivalent to 0.03 – 0.11 mg of the drug. Allow to stand for 15 minutes. Neutralize the acidity using 0.5 N sodium hydroxide solution. Add 5 ml acetate buffer followed by 1.6 ml sodium fluorescein reagent, and leave to stand for 20 minutes. Measure the absorbance of the resulting solution at 517 nm (25). Blank is measured against experiments where absorbance is related to potassium bromate consumed by carbimazole.

Assay of Carbimazole Tablet

Accurately weigh and powder 20 tablets. Take the calculated needed weight of the powdered tablets containing 80 mg of carbimazole, add 400 ml of water, warm to a temperature not exceeding 35°C, shake for 5 minutes, add 200 ml of distilled water, shake again and add sufficient water to produce 1000 ml. Filter, dilute 50 ml of the filtrate to 100. Take aliquots equivalent to 0.03 – 0.11 mg.ml^{-1} of carbimazole and apply the suggested procedure as given before.

Authentic Powder

Apply volumes ranging from 5 – 22.5 μl of carbimazole stock solution (1mg. ml^{-1} in dichloromethane) into a TLC plate (20 × 20 cm), 2 cm from the edge of the plate using a 25 μl microsyringe as successive fractions at 1.5-2 cm intervals and 2.5 cm from the sides and the bottom of the plate. Dry with a stream of air after each addition. Allow the chromatogram to develop with the selected mobile phase; dichloromethane-acetone (80:20) in a horizontal glass jar to a height of about 15 cm. Dry in a stream of cold air and scan to investigate the optimum wavelength and determine the intensity of each spot separately.

All the necessary precautions were taken to guard against the possible degradation of carbimazole to methimazole. These precautions included the use of

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freshly prepared solution at low temperature and protected from light. Moreover, all precautions were taken to avoid possible evaporation of volatile solvents leading to more concentrated solutions.

Pharmaceutical Formulation

Accurately weigh and powder 20 tablets. Take the calculated needed weight of the powdered tablets containing 25 mg of carbimazole into a small beaker, enough to prepare stock solution (1mg.ml^{-1}) of carbimazole. Macerate in 5 ml of dichloromethane and filter into a 25 ml measuring flask. Wash the beaker and the residue three times each with 5 ml and complete to the mark with same solvent. 1 ml of this solution is claimed to contain 1 mg of carbimazole. Apply the prementioned procedures as given before.

RESULTS AND DISCUSSION

Previous work (5) has demonstrated that carbimazole was successfully determined in hydrochloric acid medium by indirect titration using potassium bromate. It was found that 15–20 minutes in contact with the reagent is sufficient for bromination of carbimazole at room temperature.

It was reported that, bromine reacts with fluorescein producing eosin (25). The quantitative determination of carbimazole by applying the suggested procedure is valid in concentration from 30-110 μg%. A (1%, cm) was calculated from different authentic samples containing from 0.03 – 0.11 mg/100 ml of the drug.

Table 1. Determination of Pure Samples of Cabimazole by the Proposed Spectrophotometric Method

Taken μg.ml^{-1}	Found μg.ml^{-1}	Accuracy %
40	39.94	99.85
50	50.11	100.22
60	60.35	100.58
70	70.49	100.70
80	79.89	99.86
90	90.37	100.41
Mean ± S.D.		100.27 ± 0.805

*Average of three determinations.

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Table 2. Determination of Carbimazole Tablet by the Proposed Spectrophotometric Method

Carbimazole Tablet			Standard Addition		
Claimed 5 mg/Tablet	Spectro Method	B.P. Method	Pure (μg) Added	Found mg	Recovery %
Batch No. 1099113	100.38 ± 0.521	99.41 ± 0.066	30	30.02	100.07
Batch No. 1099114	100.30 ± 0.587	100.19 ± 0.552	40	40.42	101.05
Batch No. 1089114 (expired)	97.35 ± 0.425	88.25± 0.231	50	50.53	101.06
Mean ± S.D.				100.73 ± 0.569	

A (1%, cm) was found to be 7178.39 ± 187.63. The proposed method is used for the assay of the authentic carbimazole, Table 1. The results demonstrated good precision, with average recoveries 100.27 ± 0.805.

Under the experimental conditions used, the molar ratio relating carbimazole to bromate was found to be 1:1, which was in agreement with the reported method (5). The method was successfully applied for the analysis of carbimazole tablet. The percentage recoveries obtained by this method comply with the requirements cited by the B.P. 1998 (6) for carbimazole powder, and for its tablets and comparable to those obtained by the B.P. official method, Table 2. The validity of the method was further ascertained by applying the standard addition technique, where the mean percentage recoveries was found to be 100.73 ± 0.569.

It was of interest to note that bromate reacts with both carbimazole and its hydrolytic product (methimazole), which could explain the higher results of the suggested procedure than the B.P. official method in analysing the expired tablet, Table 2.

Spectrodensitometric Method

Thin layer chromatography is used for both qualitative and quantitative analysis. Quantitative methods depend on both measuring spot size and intensity or determination after elution of compounds from TLC plates (26). Densitometry offers a simple way of quantifying directly on a TLC plate by measuring the optical density of the separated spots. The amounts of compounds are determined by comparing them to a standard curve from reference materials chromatographed simultaneously under the same conditions. Quantitative evaluations of thin layer

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Table 3. Determination of Authentic Samples of Carbimazole by the Suggested Spectrodensitometric Method

Taken μg.spot^{-1}	Found* μg per Spot	Accuracy %
5	5.06	101.20
7.5	7.54	100.53
10	10.02	100.20
12.5	12.47	99.76
15	15.09	100.60
17.5	17.44	99.66
Mean ± S.D.		100.33 ± 0.576

*Average of three determinations.

chromatograms by densitometry is based on differential measurement of a beam emerging from the sample-free and sample containing zones of the plate. Beer's law can not strictly be applied because the evaluation takes place in a light scattering medium in contrast to the photometry of solutions. So far there is no simple and generally applicable mathematical equation that can express the relationship between detector response and sample concentration (27,28).

Quantitation was achieved in this procedure by TLC scanning densitometer. The investigated compound was separated on pre-coated silica gel plates with fluorescent phosphor. Absorbance measurement (reflection mode) was performed in situ at 291 nm. The R_f value was found to be 0.76. The quantitative determination

Table 4. Statistical Comparison of the Results Obtained by the Suggested Spectrophotometric, Spectrodensitometric, and the B.P. Method (6) on the Analysis of Pure Carbimazole

Data	Spectrometric Method	B.P. (1998) Method	Densitometric Method
Concentration range	0.3–1.1 μg.ml^{-1}	2–14 μg.ml^{-1}	5–22.5 μg per spot
Mean	100.27	99.87	100.33
S.D.	0.805	0.611	0.576
N	6	6	6
Variance	0.648	0.373	0.332
F (4.3)*	1.737	—	1.123
T (1.86)	0.413	—	0.343

*Numbers in parentheses are the corresponding theoretical values of F and t (p = 0.05).

Table 5. Determination of Carbimazole Tablet by the Suggested Spectrodensitometric Method

Carbimazole Tablet			Standard Addition		
Claimed 5 mg/Tablet	Densitometric Method	B.P. Method	Pure Added μg per Spot	Found μg per Spot	Recovery %
Batch No. 1099113	99.89 ± 0.393	99.55 ± 0.211	2.5	2.514	100.56
			5	5.021	100.42
Batch No. 1099114	99.99 ± 0.179	100.19 ± 551	7.5	7.490	99.87
			10	10.049	100.49
Batch No. 1089114 (expired)	86.15 ± 0.567	88.25 ± 0.231	12.5	12.467	99.47
Mean ± S.D.				100.22 ± 0.381	

of carbimazole by applying the suggested procedure is valid in concentration range from 5-22.5 μg per spot. The linear regression equation was found to be

$$Y = 0.1799x - 0.9321$$

Where "y" is the area x 1000 at 291 nm and "x" is the concentration of the drug in μg per spot, with a coefficient of variation 0.9969. The proposed method was applied for the determination of pure carbimazole, the results demonstrate a good precessions, as shown in Table 3, Where average recoveries was 100.33 ± 0.576.

T-test shows also that, there is no significant difference between the results obtained by the suggested procedures and the B.P. official method, Table 4.

Carbimazole tablets were analysed for their content of carbimazole by the proposed procedure, and the validity of the method was further checked by applying the standard addition technique, the results obtained are presented in Table 5. Further comparative determination of carbimazole in its pharmaceutical preparation by the B.P. official method has been done, the results are illustrated in Table 5.

The zero order absorption spectra of carbimazole and methimazole show certain overlapping (10), which could explain the lower results of the suggested procedure than the B.P. official method in analysing the expired tablet, Table 2.

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