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Colorimetric Determination of Methimazole

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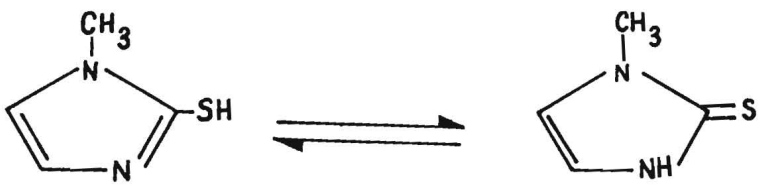
Methimazole (1-methylimidazole-2-thiol) reacts with sodium nitroprusside in presence of sodium hydroxide, and on treatment with acetic acid it gives a navy blue color measurable at 580 nm. The effects of pH, time, concentrations of sodium nitroprusside and hydroxide, and type and concentration of acid used have been studied. This color is used as a basis for a colorimetric method for the determination of pure methimazole and in pharmaceutical preparations. The method can be adopted for concentrations ranging from 15 to 45 mc g/ml with 100%±2.3 accuracy.

Methimazole (1-methylimidazole-2-thiol) is clinically used as anti-thyroid drug. Kossakowski (1972), Blazek *et al.* (1957), Zoellner and Vastagh (1970), Varga and Zoellner (1958), Zoellner and Varga (1957), Posagay (1961) and Bayer and Posagay (1961) analysed methimazole by adopting titrimetric methods. However, Hyyden and Braunon (1967) recommended an infra-red spectrophotometric method of determination for methimazole tablets. This method was studied collaboratively by several analysts, (Horwitz, 1970) and average recoveries from tablet mixtures were found to range from 96.6%±1.0 to 101.1%±0.9. Berg (1971) studied the color developed by the reaction of methimazole with diphenyl picrylhydrazine. Szabe *et al.* (1974) described a method for the identification and determination of



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methimazole by conversion into its colored 1:1 Cu^{2+} complex which has maximum absorption at 614 nm. Recently Aboul-Enein (1979) analysed methimazole in pure form and tablet formulations by nuclear magnetic resonance (NMR) spectrometry. In this procedure benzoic acid is used as an internal standard and the $N\text{-}CH_3$ protons of methimazole at 3.56 δ and the aromatic protons of benzoic acid at 7.5 and 8.13 δ are taken as criteria for analysis.

The pharmacopoeial method (1975) of assay of methimazole tablets involves extraction with distilled water and alkalimetric titration with 0.1N–NaOH in presence of silver nitrate using bromothymol blue as an indicator.

In this paper, the authors tried to propose a simple, feasible and accurate method for the quantitative determination of methimazole in pure form and in pharmaceutical formulations.

Experimental

(i) Reagents

Methimazole standard solution

Dissolve 500 mg of authentic methimazole (Eli Lilly & Co., Indianapolis, U.S.A.) in 100 ml of distilled water. This solution is quantitatively diluted before use to give a solution of 500 mcg per ml.

Sodium nitroprusside solution

A freshly prepared 2.0% w/v aqueous solution of sodium nitroprusside (M & B).

Sodium hydroxide 2N

Acetic acid 2N

Test Samples: Tablet $(R)_I$ and Tablet $(R)_{II}$ each tablet is labelled to contain 5 mg and 10 mg of methimazole respectively.

(ii) Apparatus

Varian Techtron 635 UV visible spectrophotometer was used for measurement.

(iii) Procedure

(a) Preparation of sample solution: Shake, for 30 minutes, an accurately known quantity of powdered tablets containing about 62.5 mg of methimazole with 500 ml of distilled water; centrifuge an aliquot of this suspension for 10 minutes, decant and keep clear supernatent for further use.

(b) Development of color: Insert an aliquot equivalence of the test solution or the standard methimazole solution ranging from 250 to 350 mcg of methimazole in a 10 ml volumetric flask, add 2 ml of sodium hydroxide followed by 0.8 ml of sodium nitroprusside, mix and leave for 10 min. Add 3 ml of acetic acid solution and keep in ice-bath for further 10 min. Adjust to volume at room temperature and measure absorbance of the blue color of the standard and the test solutions at 580 nm against a blank carried out simultaneously.

(R) Eli Lilly & Co., Indianapolis, U.S.A.

Table 1. Colorimetric determination of methimazole by nitroprusside proposed method.

Pharmaceutical compound	Methimazole			
	Stated (mg)	Added (mg)	% Recovery.*	S.D.
Tablet I	5	–	98.2	± 2.3
		10	98.6	–
Tablet II	10	–	98.4	± 2.0
		10	97.8	–

* The figure stands for a mean of six runs.

Discussion

Methimazole is an active antithyroid drug possessing a thiol group in addition to the imidazole ring in its structure, this suggested the possibility of a color reaction with nitroprusside in an analogous manner to other compounds with similar chemical structures. The blue color produced by treating methimazole in alkaline medium with sodium nitroprusside, was investigated and the factors affecting the intensity, sensitivity and stability of this color were studied and controlled, so that the method was rendered quantitative. Experimental studies showed that λ_{max} was 580 nm. The optimum amounts of sodium hydroxide and sodium nitroprusside are 2 ml and 0.8 ml respectively. Lower quantities gave less intense and less stable color. The study of the developed blue color showed that the use of 3 ml 2N acetic acid gave the most stable and intense color; lower concentrations gave lower results whereas higher ones did not affect the results. Although acids other than acetic acid gave the same color, a lower intensity was obtained. The color reaches its maximum intensity after 10 minutes of mixing with acetic acid and lasts for more than two hours.

The calibration curve for methimazole, was prepared under the established experimental conditions. According to this curve, Lambert-Beer's Law is obeyed in concentrations ranging from 15 to 45 mcg per ml. The calculated $E^{1\%}_{1cm}$ by the proposed method is 151. The blank solution containing sodium nitroprusside, sodium hydroxide and acetic acid gave 98% transmission against distilled water indicating that the blank had negligible absorbance with respect to the sample solution. The standard deviations (S.D.) are ±2.3 and 2 for the 5 mg and 10 mg tablets respectively. It should be pointed out that for extraction of methimazole from pulverized tablets, high dilution followed by centrifugation proved to be necessary; since filtration procedure resulted in lower results. The method is simple, quick as well as sensitive compared to the U.S.P. method.

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تعيين لوني لعقار الميثيمازول

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يتفاعل عقار الميثيمازول مع نيتروبروسيد الصوديوم في وجود هيدروكسيد الصوديوم وبإضافة حمض الخل ينتج لون أزرق يقاس عند طول موجة ٥٨٠ متر$^{-٩}$ ولقد تمت دراسة متغيرات الأس الهيدروجيني وتراكيز نيتروبروسيد الصوديوم والهيدروكسيد وكذلك نوع وتركيز الحمض. واستخدم اللون الأزرق كأساس للطريقة اللونية لتعيين الميثيمازول النقي وفي المستحضرات الصيدلانية ويمكن استخدام الطريقة للتراكيز من ١٥ إلى ٤٥ ميكروجرام في الملل بدقة تصل إلى ١٠٠٪±٢,٣.