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N-2, 6- DIMETHYLPHENYL-2,3-DICHLOROMALIMIDE AS ANALYTICAL REAGENT FOR DETERMINATION OF ISONIAZID IN THE PRESENCE OF OTHER INGREDIENTS

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ABSTRACT

A synthetic reagent, N-2,6-dimethylphenyl-2,3-dichloromalimide was used in the spectrophotometric estimation of isoniazid in the presence of its expected degradation isonicotinic acid, other antitubercular components such as ethionamide and ethambutol hydrochloride which are present in its formulations. The molar ratio and the optimum complexation condition have been studied and the orange colour formed was measured at λ 515nm. The method was used for the determination of isoniazid in bulk powder with mean percentage accuracy 100.27±0.84, then applied on Isocid, prepared Trecaplix and Etibi INH tablets.

A comparative study with the official method showed no significant difference, furthermore the proposed procedure has the advantage of determination of isoniazid in the prence of other components which may be present in its formulations.

INTRODUCTION

Different methods were reported for the determination of isoniazid , the official methods of analysis in the USP[1], B.P[2] and European pharmacopoeia[3], are titrimetry. Polarographic methods with electrochemically generated chlorine or bromine were reported[4-9]. Isoniazid was determined gravimetry as its Cu (II), Hg (II)

or picrate salts[8]. The most colourimetric method based on hydrazone formation with p-dimethylaminobenzaldehide, benzaldehyde and vanillin[9-13]. Also it gave blue colour with naphthoquinone derivatives[14,15] and colour complex with metals[16]. A number of fluorimetric methods have been reported[17,18].

In the present work the reaction of malimide derivative as (π acceptor) and isoniazid as (n donor) gives an orange colour which can be measured at 515nm. Other ingredients which may be present doesn't interfere.

EXPERIMENTAL

Apparatus : Shimadzu 260 u.v. self recording spectrophotometer.

MATERIALS AND REAGENTS

All the reagents were of the analytical grade quality .
Isoniazid powder from CID Co., Egypt.
N-2,6-Dimethylphenyl-2,3-dichloromalimide was synthesized according to procedure[19], the identity and purity of the substance were verified by melting point, IR, UV, TLC and solubility.
Ethambutol hydrochloride from Memphis Co., Egypt.
Ethionamide from Alexandria Co., Egypt.
Prepared Trecaplix tablets; labelled to contain isoniazid 250 mg and ethionamide 250 mg.
Prepared Etibi INH tablets; labelled to contained 200 mg ethambutol hydrochloride and 100 mg isoniazid.
Isoniazid stock solution; 1mg.ml^{-1} in ethanol.
N-2,6-Dimethylphenyl-2,3-dichloromalimide stock solution; 1mg.ml^{-1} in ethanol.

PROCEDURE

a) FOR BULK POWDER

A known volume of ethanolic solution containing 0.5-3 mg of isoniazid was treated with 5 ml of the reagent, heated on water bath

for 40 min. at 60°C, cooled and transferred quantitatively to a 10 ml volumetric flask, then diluted to volume with ethanol and the absorbance was measured at 515nm against the corresponding reagent blank .

b) FOR TABLET FORM

Twenty tablets were powdered and mixed. A quantity equivalent to 100 mg of isoniazid was quantitatively extracted with ethanol, filtered in a 100 ml volumetric flask and the flask completed to volume with ethanol and the method was continued as under bulk powder .

RESULTS AND DISCUSSION

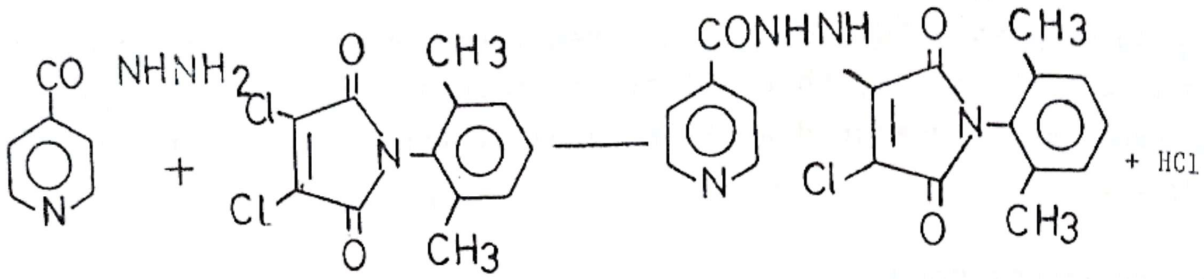
Isoniazid contains a primary amino group in its molecule and attempts were made to use N-2,6-dimethylphenyl-2,3-dichloromalimide as π acceptor for its determination . An orange coloured products were formed after heating on water bath at 60° for 40 min. the absorption spectra of the reaction product show high absorption band at 515 nm as shown in fig. (1) .

Linear relationship were obtained for the absorbance of the reaction product versus concentration in the range of 5-30 mg % in the final measured solutions and the graph can be represented by the following regression equation :

$A_{515} = - 0.009 + 0.014\ C \qquad t = 0.996$

where (A) is the absorbance and (C) is the concentration in mg % in the final measured solution .

Sass et al [20] suggested a replacement reaction between chloranil and amino compounds with the liberation of chloride and we favour this suggestion and the reaction can be represented as shown in the following scheme :



This was confirmid by the appearance of white opalescece on addition of HNO_3 and silver nitrate and by IR spectra where the NH group appear at 3350 cm^{-1} and the two carbonyl groups at 1660 and 1710 cm^{-1} .

The molar ratio of the reaction was performed by the continous variation method [21] and the maximum absorbance was found near 0.5 which confirm the ratio 1:1 as expected because isoniazid contains only one available primary amine and the other amide or tertiary nitrogen in the pyridine does not interact Fig. (II) .

Ethionamide which contains amidic nitrogen does not interact and also ethambutol which present as hydrochloride salt does not interfere. Isonicotinic acid the expected impurty during preparation not react also with the reagent as shown in Fig. (I) .

The proposed procedure was applied for the determination of isoniazid bulk powder which also determined by the official method and statistical analysis of the results showed no significant difference between the two methods, table (I,III) . The validity of the proposed procedure was assessed by applying to pharmaceutical gosage form; isocid tablets, prepared Trecaplix and Etibi I.N.H. and the results obtained are shown in table (II) which show good result and the proposed procedure has the advantage of analysing compounds in dosage form without interference from other excipients or from other components in the formulation, in addition to simplicity of the procedure and wide application for primary amino compounds .

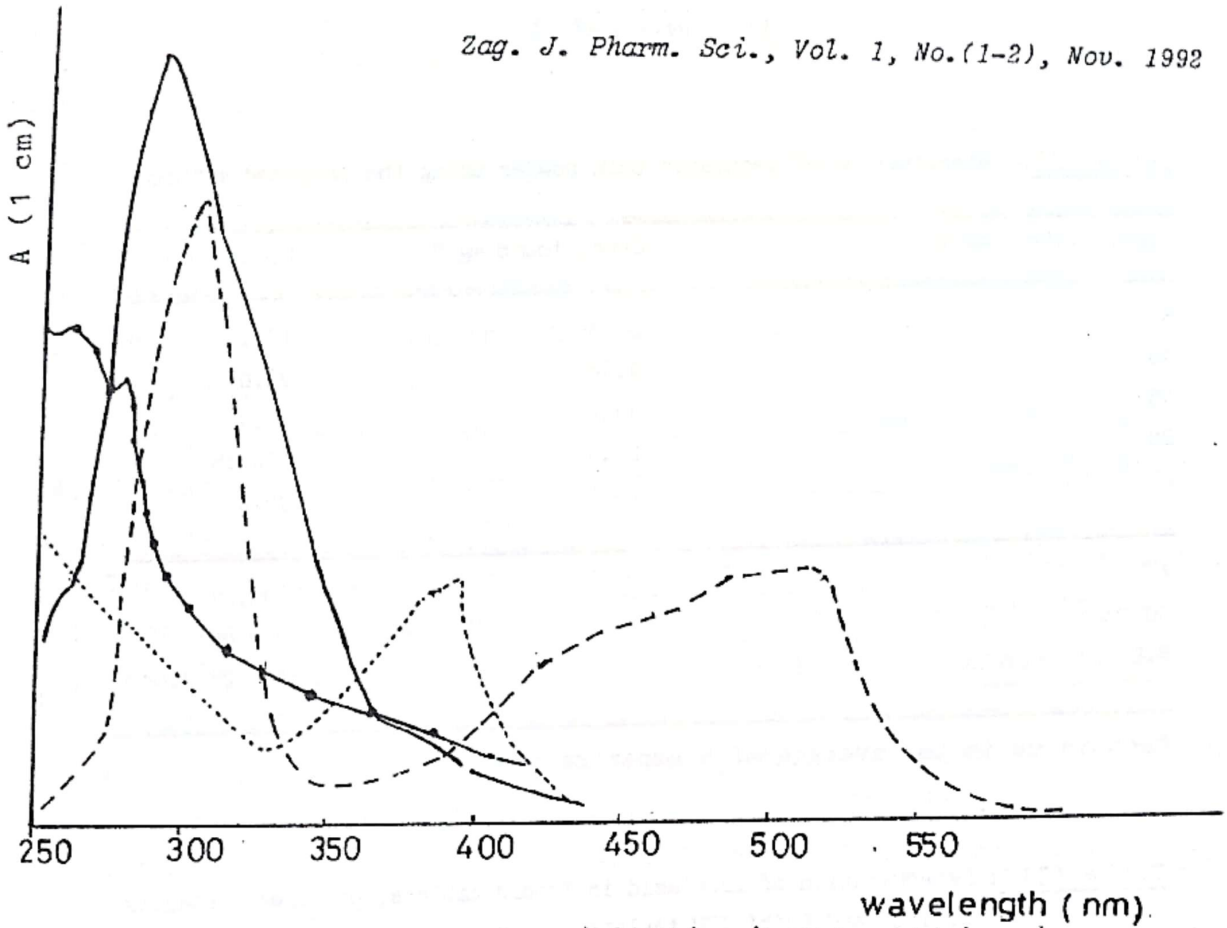


Fig.(I) Absorption spectra of INH (---), Ethionamide(——), Ethambutol (—•—•—) and Isonicotinic acid (.....) with the reagent.

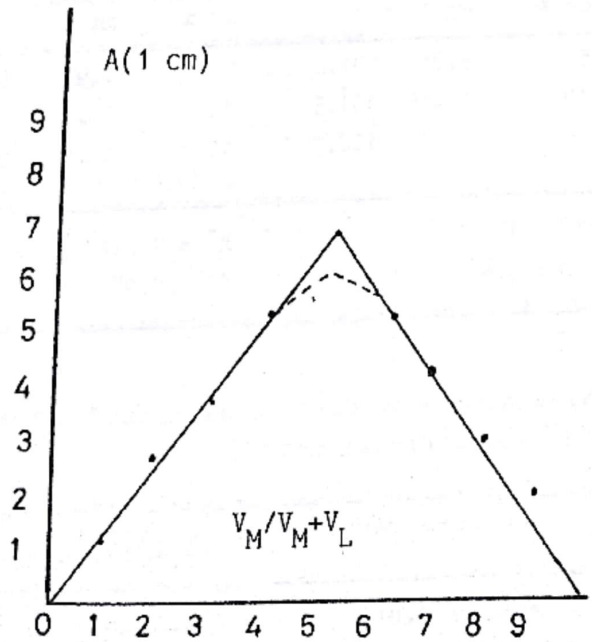


Figure (II) Continous variation plott of Isoniazid(V_M) : Reagent (V_L) complex.

Table (I): Determination of isoniazid bulk powder using the proposed method

Conc. Claimed mg %	Conc. found mg %	Recovery %
5	5.18	101.6
10	9.98	99.8
15	14.91	99.4
20	20.13	100.65
25	24.95	99.8
$\bar{X}$		100.27
SD		0.89
F.L		100.27 ± 0.84

Each value is the average of 5 experiments

Table (II): Determination of isoniazid in Isocid tablets, prepared Trecaplix tablets and Etibi INH tablets.

Isocid			Trecaplix			Etibi INH		
Conc. claimed mg %	Conc. found mg %	Recovery %	Conc. claimed mg %	Conc. found mg %	Recovery %	Conc. claimed mg %	Conc. fonnd mg %	Recovery %
5	5.1	102.0	5	5.06	101.2	5	4.95	99.0
10	10.09	100.9	10	10.15	101.5	10	10.1	101.0
15	15.1	100.7	15	15.1	100.7	15	14.9	99.3
$\bar{X}$ = 101.2			$\bar{X}$ = 101.13			$\bar{X}$ = 99.97		
SD = 0.7			SD = 0.4			SD = 0.9		

Table (III): Statistical analysis of data of isoniazid obtained by the proposed and official method

	Proposed method	Official method B.P (1988)
Confidance limit	100.29 ± 0.84	101.08 ± 1.31
N	5	5
Student t test	1-65 (2.306)	
F ratio	2.46 (5.05)	

Fig. in parenthesis are the theoretical value.

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إستخدام المركب ن -٢،٦ - داى مثيل فينيل - ٢،٣ - داى كلور الماميد ككاشف تحليلى لتقدير الأيزونيازيد فى وجود المركبات الأخرى

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إستخدم الكاشف المخلق ن -٢ ، ٦ داى مثيل فينيل -٢ ، ٣ -داى كلور الماليميد فى التقدير الطيفى للأيزونيازيد فى وجود نواتج التكسير المتوقعة مثل حمض أيزونيكوتنيك فى وجود المركبات الأخرى التى تستخدم فى علاج الدرن مثل الأثيون أميد والأثيامبيوتول هيدروكلوريد التى توجد معه فى المستحضرات الصيدلية مثل أقراص أيتبى أرى أن أتش والتريكابلكس .

وقد تم دراسة أنسب الظروف للتفاعل . وتم مقارنة الطريقة المقترحة بالطريقة الدستورية ووجد عدم وجود فرق جوهرى إلا أن الطريقة المقترحة أكثر دقة وحساسية علاوة على أنها بسيطة وبواسطتها يمكن تقدير الأيزونيازيد فى وجود المركبات الأخرى .