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Determination of ethionamide in pharmaceutical by spectrophotometry through oxidation reaction with potassium iodate

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ABSTRACT

Objective: To described two new spectrophotometric methods for the determination of ethionamide (ETM) in pure and tablet forms. **Methods:** The developed first method is based on the oxidation of ETM by KIO₃ in H₂SO₄ medium, and the in situ generated iodine is extracted into chloroform and measured at 520 nm, While in the second method, the same iodine is complexed with starch and the intense blue colored complex is measured at 580 nm. Different variables affecting the reactions were carefully studied and optimized. **Results:** Beer's law is obeyed in the concentration ranges of 20–400 and 5–125 μg/mL with Methods A and B, respectively, with the respective molar absorptivity (ε) values of 4.04 × 10² and 1.39 × 10³ L/mol/cm. The Sandell sensitivity values were calculated to be 0.4113 and 0.1193 μg/mL. The limits detection and quantification were calculated to be 0.85 and 2.56 μg/mL for Method A and 0.27 and 0.81 μg/mL for Method B. The intraday and interday precisions expressed as relative standard deviation (%RSD) were found to be in the range 1.46–2.32%. The accuracy expressed as relative error (%RE) was better than 2.35%. The methods were also found to be robust and rugged as found from low values of RSD. **Conclusion:** The two developed methods were applied to the determination of ETM in tablets and no interference was observed from common tablet excipients.

INTRODUCTION

Ethionamide (ETM), chemically called 2-ethylthioisonicotinamide, is a second line agent with activity against various mycobacteria, including *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and *Mycobacterium avium-intracellulare* [1,2]. Ethionamide is the official in the United States Pharmacopoeia [3] which describes an ultraviolet-spectrophotometric method for its assay. In British Pharmacopoeia [4], the drug is determined by titration with HClO₄ in anhydrous acetic acid medium with potentiometric endpoint detection.

A survey of the literature reveals that a few chromatographic methods have been reported for its determination in biological fluids [5-11], various methods for the determination of ETM in pharmaceuticals have been proposed and include fluorimetry [12], visual titrimetry [13] and potentiometric titrimetry [14,15], and spectrophotometry [16-27]. The

spectrophotometric methods are based on the reaction of ETM with several organic or inorganic reagents such as osmic acid [16], sodium nitroprusside, [17,18] iron (III), [19] iron (III)-p-phenylenediamine, [20] pyridylazoresorcinolvanadium, [21] alizarin violet 3B and alizarin brilliant violet R [22], dichlone, [23,24] and N-bromosuccinimide celestine blue [25]. Using permanganate [26] and iodine [27] as oxidants, two kinetic methods have also been described.

The methods based on redox reactions [25-27] are complicated since the concentrations of the reagents employed are to be known accurately and the kinetic methods require careful and meticulous control of all experimental variables.

The aim of this work was to develop easy, rapid, and reliable methods based on oxidation reaction employing potassium iodate which finds extensive application in spectrophotometric assay of pharmaceuticals [28-35]. The methods are based on the oxidation of ETM by KIO₃ in H₂SO₄

medium, and determination of *in situ* the generated iodine either by extracting into chloroform for measurement at 520 nm (Method A) or by complexing with starch followed by the measurement of the resultant blue species at 580 nm (Method B). In both the methods, the amount of iodine, thus determined is related to the amount of ETM.

METHODS

Apparatus

A Systronics model 166 digital spectrophotometer (Systronics, Ahmedabad, Gujarat, India) with matched 1-cm quartz cells was used for absorbance measurements.

Materials and Reagents

Doubly distilled water and analytical reagent grade chemicals were used. A 0.5% aqueous solution of KIO_3 (Merck, Mumbai, India), 0.1M HCl (Merck, Mumbai, India sp. gr. 1.18) were prepared in the usual manner. Spectroscopic grade organic solvents (Merck, Mumbai, India) were used in the study. Starch indicator was prepared by adding a paste of 1 g starch in water to 100 mL boiling water, boiled for 1 min, and cooled.

Pure ethionamide (ETM) sample certified to be 99.86% pure was provided from Panacea Biotic Ltd. as gift and used as received.

A 500 $\mu\text{g}/\text{mL}$ standard solution of ETM was prepared by dissolving 250 mg of pure drug in 0.1M HCl and diluted with the same solvent in a 500 mL calibrated flask. ETM containing tablets: Ethide (Lupin Ltd., Mumbai, India), Ethiokox (Radicura Private Ltd., New Delhi, India), and Myobid (Panacea Biotic, New Delhi, India) each labeled contain 250 mg of ETM were purchased from local commercial sources.

General Procedures

Preparation of calibration graph

- Method A. Aliquots of standard ETM solution (0.5–8.0 mL; 500 $\mu\text{g}/\text{mL}$) were placed in a series separating funnels, and the volume in each was brought to 10 mL with 0.1 HCl. Then, 2 mL of KIO_3 solution was added and the contents mixed well. 10 mL of chloroform was added from a burette to each funnel and shaken for 1 min, and the layers were allowed to separate. The chloroform layer was dried by passing over anhydrous Na_2SO_4 and the absorbance measured at 520 nm against the reagent blank.
- Method B. Varying aliquots (0.1–2.5 mL) of standard 500 $\mu\text{g}/\text{mL}$ ETM solution were accurately transferred into a series of 10 mL calibrated flasks, and the volume was diluted to 3 mL with 0.1 HCl. To each flask, 2 mL of KIO_3 and 1 mL of starch were added successively, the volume was then made up to the mark with water, mixed well, and absorbance measured at 580 nm versus the reagent blank.

A calibration graph was prepared in both methods, and the unknown concentration was computed from the regression equation derived from the absorbance concentration data.

Procedure for Tablets

Twenty tablets were weighed accurately and ground into a fine powder. A portion of the powder equivalent to 50 mg of ETM was weighed accurately and transferred into a 100 mL calibrated flask, 60 mL of 0.1 M HCl was added, and the content was shaken for 20 min. The volume was diluted to the mark with 0.1 M HCl, mixed well, and filtered using Whatman 42 filter paper. The filtrate (500 $\mu\text{g}/\text{mL}$ in ETM) was subjected to assay using 4 mL in Method A and 1 mL in Method B, in five replicates.

Procedure for Placebo and Synthetic Mixture Analyses

A placebo blank of the composition: 20 mg talc, 30 mg starch, 20 mg sucrose, 20 mg lactose, 10 mg gelatin, 20 mg sodium alginate, 30 mg magnesium stearate, and 20 mg methylcellulose was prepared by homogeneous mixing in a mortar. 25 mg of placebo was placed in a 50 mL calibration flask and its extract was prepared as described under "Procedure for Tablet." 2 mL of the extract was subject to analysis following the general procedures. To 20 mg of the placebo blank prepared above, 25 mg of pure ETM was added, mixed thoroughly and the mixture was quantitatively transferred into a 100 mL calibrated flask; and then, steps described under "procedure for tablets" were followed.

RESULTS AND DISCUSSION

The proposed methods are direct and essentially based on the determination of iodine released *in situ* upon reacting ETM with KIO_3 in acid medium. The concentration of the iodine thus determined is related to the concentration of the drug responsible for the iodine released. In Method A, the iodine released is extracted into chloroform and measured at 520 nm, whereas Method B entails complexation of iodine with starch and subsequent measurement of absorbance of the colored species at 580 nm [Figure 1]. Possible reaction pathway is shown in [Figure 2].

Method Development

Preliminary experiments were performed to determine the optimum concentration of KIO_3 and starch to give the maximum response. 2 mL of 5% KIO_3 was found optimum in both the methods, and 1 mL of 1% starch was found sufficient to complex the iodine released in Method B. Hydrochloric acid (0.1 M) was found ideally suited to prepare the drug solution and no additional acid was required to cause the redox reaction that facilitated the assay. The redox reaction between ETM and KIO_3 , subsequent release of iodine, and also the complexation reaction between I_2 and starch were instantaneous. The extracted colored species measured was stable for 24 h and 60 min in Methods A and B, respectively. Of the several organic solvents tried to extract the iodine in Method A, chloroform was most suitable because of high sensitivity and stability of the colored species. A shaking time for 1 min was necessary to quantitatively extract the iodine to the chloroform layer and the two layers got clearly separated within 1 min (Method A).

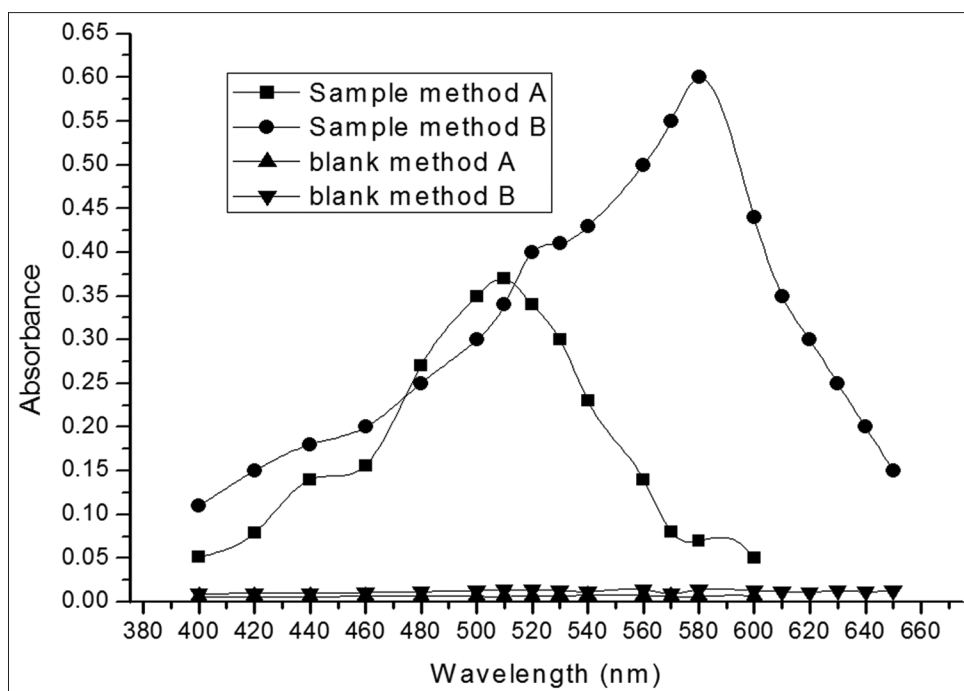


Figure 1: Absorption spectra colored species (150 $\mu\text{g}/\text{mL}$ ETM for Method A, and 70 $\mu\text{g}/\text{mL}$ ETM for Method B)

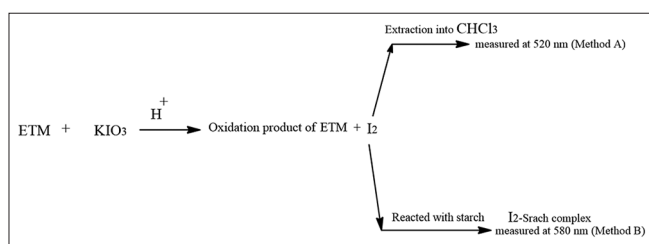


Figure 2: Possible reaction pathway

Method Validated

Linearity and sensitivity

The calibration graphs obtained follow Beer's law up to 400 and 125 $\mu\text{g}/\text{mL}$ ETM for Methods A and B, respectively as shown in Figure 3. Regression parameters along with the respective dynamic linear ranges, molar absorptivity, and Sandell sensitivity values, and the detection and quantification limits are given in Table 1.

Precision and Accuracy

Precision and accuracy of the methods were evaluated by replicate analyses of the pure drug solution at three concentration levels within the linear range. The analyses were performed on the same day (intraday) and on five consecutive days (interday) using the solutions prepared afresh each day. The precision expressed as relative standard deviation (%RSD) was satisfactory with the RSD values <2.5%. The accuracy of the methods expressed as relative error (%RE) was better than 2.5% revealing fair precision and accuracy of the methods [Table 2].

Table 1: Sensitivity and regression parameters

Parameter	Method A	Method B
λ_{max} , nm	520	580
Color stability	24 h	60 min
Linear range, $\mu\text{g}/\text{mL}$	20–400	5.0–125
Molar absorptivity (ϵ), L/mol/cm	4.04×10^2	1.39×10^3
Sandell sensitivity*, $\mu\text{g}/\text{cm}$	0.4113	0.1193
Limit of detection (LOD), $\mu\text{g}/\text{mL}$	0.85	0.27
Limit of quantification (LOQ), $\mu\text{g}/\text{mL}$	2.56	0.81
Regression equation, y^{**}		
Intercept (a)	-0.003	0.0063
Slope (b)	0.0025	0.0078
Standard deviation of a (S_a)	9.98×10^{-2}	9.98×10^{-2}
Standard deviation of b (S_b)	2.8×10^{-4}	8.9×10^{-4}
Regression coefficient (r)	0.9964	0.9994

*Limit of determination as the weight in $\mu\text{g}/\text{mL}$ of solution, which corresponds to an absorbance of $A=0.001$ measured in a cuvette of cross-sectional area 1 cm^2 and $l=1 \text{ cm}$. ** $y=a+bx$, where y is the absorbance, x concentration in $\mu\text{g}/\text{mL}$, a intercept, and b slope

Robustness and Ruggedness

Robustness was examined by evaluating the influence of a small variation of the method variables on the performance of the methods. In these experiments, one parameter was changed whereas the others were kept unchanged, and the %RSD was calculated each time. It was revealed from the values of %RSD that small alterations in the experimental variables did not affect the methods significantly. Ruggedness was tested by applying the proposed methods to the determination of ETM using the same optimum conditions

but using three different instruments in three different laboratories, and also using the single instrument but by three different analysts. Results obtained from instrument-to-instrument as well as analyst-to-analyst variations did not affect the performance of the methods. The results of this study are presented in Table 3.

Selectivity

The placebo blank when subjected to analysis by the proposed methods yielded absorbance values close to those of the reagent blanks. On analyzing the synthesis mixture using the two methods, the percent recoveries recorded were 98.46 ± 0.85 ($n = 5$) (Method A), 101.3 ± 1.42 ($n = 5$)

(Method B) ensuring that the methods are selective for the determination of ETM in tablets.

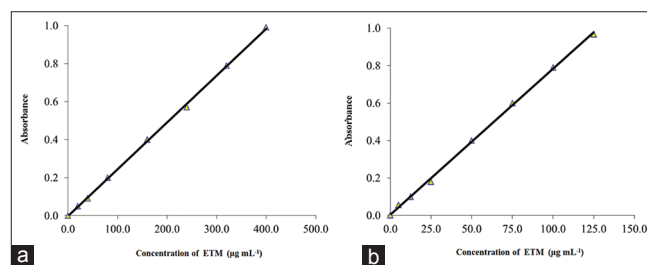


Figure 3: (a) Standard graph (Method A), (b) standard graph (Method B)

Table 2: Evaluation of intraday and interday accuracy and precision

Method	ETM taken ($\mu\text{g/mL}$)	Intraday accuracy and precision ($n=7$)			Interday accuracy and precision ($n=5$)		
		ETM found ^a ($\mu\text{g/mL}$)	RSD ^b %	RE ^c %	ETM found ($\mu\text{g/mL}$)	RSD ^b %	RE ^c %
A	100	100.77	1.88	0.77	100.85	1.84	0.85
	200	203.81	1.66	1.91	204.11	2.32	2.01
	300	305.43	1.97	1.81	304.44	2.11	1.48
B	40	40.44	1.59	1.10	40.67	1.89	1.68
	80	80.95	1.46	1.19	81.88	1.77	2.35
	120	122.04	1.65	1.70	121.89	2.19	1.58

^aMean value of seven determinations, ^brelative standard deviation (%), ^crelative error (%), RSD: Relative standard deviation

Table 3: Method robustness and ruggedness expressed as intermediate precision (% RSD)

Method	ETM taken ($\mu\text{g/mL}$)	Robustness (%RSD)	Ruggedness (%RSD)	
		Parameters altered	Interanalysts ($n=3$)	Interlaboratories ($n=3$)
		Volume of KIO_3^*		
A	100	1.86	1.44	1.57
	200	1.88	1.63	1.78
	300	2.34	1.06	2.43
B	40	1.98	1.85	1.79
	80	2.23	1.73	2.31
	120	2.44	1.68	1.97

*1.8, 2.0 and 2.2 mL in both methods. RSD: Relative standard deviation

Table 4: Results of analysis of tablets by the proposed methods and statistical comparison of the results with the official method

Tablet brand name	Nominal amount	Found* (% of nominal amount \pm SD)		
		Official method	Proposed methods	
			Method A	Method B
Ethide	250	99.66 \pm 1.09	99.92 \pm 0.79	97.88 \pm 1.23
			t=2.10	t=1.08
			F=1.90	F=1.25
Ethiokox	250	100.10 \pm 0.75	101.36 \pm 1.36	101.45 \pm 1.64
			t=1.81	t=1.67
			F=3.29	F=4.78
Myobid	250	99.59 \pm 1.64	98.97 \pm 1.51	100.3 \pm 1.21
			t=0.59	t=0.81
			F=1.18	F=1.84

*Mean value of five determinations. Tabulated t-value at the 95% confidence level and for four degrees of freedom is 2.77. Tabulated F-value at the 95% confidence level and for four degrees of freedom is 6.39

Application to tablets

Results of determination of ETM in three brands of commercial tablets by the proposed methods are presented in Table 4 and are in agreement with the label claim as well as those obtained by the reference method [4], in which the drug is determined by titration with HClO_4 in anhydrous acetic acid medium with potentiometric endpoint detection.

Statistical comparison of the results by applying the Student's *t*-test for accuracy and variance ratio *F*-test for precision indicate no significant difference between the proposed methods and the reference method with respect to accuracy and precision when the calculated *t*- and *F*-values did not exceed the tabulated values at the 95% confidence level for four degrees of freedom.

Table 5: Results of recovery experiment through standard-addition method

Method	Tablet studied	ETM in tablet, $\mu\text{g/mL}$	Pure ETM added, $\mu\text{g/mL}$	Total found, $\mu\text{g/mL}$	Pure ETM recovered Percent \pm SD*
A	Ethide 250	149.58	75	225.23	102.40 \pm 1.87
		149.58	150	302.15	101.01 \pm 1.74
		149.58	225	384.55	103.80 \pm 1.77
B	Ethide 250	44.02	22.5	67.33	101.90 \pm 1.44
		44.02	67.5	113.22	101.91 \pm 1.55
		44.02	112.5	157.98	101.90 \pm 1.76

*Mean value of three determinations

Table 6: Comparison of the proposed and the existing methods

Reagents	Methodology	Linear rang $\mu\text{g/mL}$	LOD/LOQ ($\mu\text{g/mL}$)	Remark	Reference number
Sodium nitroprusside	Orange colored product in basic medium measured at 510 nm	-	-	-	20
Sodium nitroprusside	Orange-red complex measured at 510 nm	5–32	-	-	21
DCNQ	Orange colored product in ethanol measured at 440 nm	-	-	-	16
DCNQ	Red colored product formed in the presence of ammonia in alcohol medium measured at 530 nm	-	-	-	17
PAR-V (V)	Ternary complex (1:1:1) extracted into chloroform and measured at 560 nm	0.2–20	-	30 min contact time, extraction step	22
Iron (III)	Purple-violet colored complex in acid medium measured at 510 nm	0–36	-	Longer contact time	18
Iron (III)-PPD	Thionine compound measured at 600 nm	-	-	Multiple step reaction involved	19
Osmic acid	Light yellow colored formed at pH 4 measured at 375 nm	0.25–40	-	60 min contact time, pH adjustment required	23
NBS-CB	Unbleached dye color measured in acid medium at 540 nm	0.2–5.0	-	Critical acid concentration; unstable reagent used; concentrations of both reagents to be known	25
KMnO_4	Blue colored manganite in alkaline medium measured at 610 nm (direct method)	1–10	-	Critical NaOH concentration reaction rate precariously dependent on experimental variables	26
	Absorbance at a fixed time of 20 min measured (kinetic method)	1–10	-		
Sodium azide-iodine	Decreases in absorbance at the 5 th min measured at 348 nm (kinetic method)	10–100	0.7/-	Reaction rate precariously dependent on experimental condition	27
KIO_3	I_2 in chloroform measured at 520 nm	20–400	0.85/2.56 0.27/0.81	No drastic experimental conditions, instantaneous reaction, more sensitive	Present methods
KIO_3 -starch	I_2 -starch complex measured at 580 nm	5–125	-		

DCNQ: Dichloronaphthoquinone, PAR: Pyridylazoresorcinol, PPD: P-phenylenediamine, NBS: N-bromosuccinimide, CB: Celestine blue

Accuracy by Recovery Experiment

To further establish the accuracy and reliability of the proposed methods, recovery experiment through standard-addition procedure was performed. To the preanalyzed tablet powder, pure ETM was added at three levels and the total found by the proposed methods. Each determination was performed in triplicate. From the percent recovery values of pure drug, added to the tablet powder, summarized in Table 5, it is clear that coformulated substances in the tablets did not interfere in the determination, and thereby complementing the results of the selectivity study.

CONCLUSION

The results demonstrated the usefulness of potassium iodate as a reagent for the spectrophotometric assay of ethionamide in pharmaceuticals. The proposed methods offer the advantages of simplicity selectivity and applicability over wide linear dynamic ranges compared to the previously reported methods [Table 6]. The methods were demonstrated to accurate and precise besides being robust and rugged, since small deliberate alterations in the operating conditions, instruments, and personal were not found to significantly affect their performance.

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