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SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF TERBUTALINE IN PURE AND IN DOSAGE FORMS

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ABSTRACT

Two simple, sensitive, rapid methods for the determination of terbutaline in pure and in dosage forms are developed. The first one (A) is based on condensation with sodium cobaltinltrite in aqueous acetic acid solution the colour of the complex product is measured at λ_{max} 422nm against reagent blank.

The second method (B) is based on the reaction of the drug with 4-amino antipyrine (4-AAP) in presence of buffer solution of potassium dihydrogen phosphate and oxidising agent potassium ferricyanide. The produced colour is measured at λ_{max} 490nm against reagent blank. Appropriate conditions were established to obtain maximum sensitivity.

The two proposed methods obey Beer's law over concentration ranges of 4-40μg ml^{-1} and 10- 50μg ml^{-1} for A and B respectively. The apparent molar absorptivity and sandel sensitivity for method A is 4.070×10^3 $Lmol^{-1}$ cm^{-1} and 1.348×10^{-2} μg cm^{-2}, while for method B is 0.6×10^4 L mol^{-1} cm^{-1} and 9.14×10^{-2}μg cm^{-2}.

The detection and quantification limits are calculated. The developed methods are applied successfully for the determination of terbutaline in pure and in pharmaceutical formulation without interference from common excepients.

INTRODUCTION

Terbutaline bis[(1RS)-1-(3,5-dihydroxyphenyl)-2-[(1,1-dimethylethylamino) ethanol] sulphate is a selective beta-adrenoreceptor stimulant, with selective bronchodilator action. It is more selectively acting on the β_2-receptors of the trachial and bronchial smooth muscles but its effect is relatively weak on the β_1-receptors of the heart; therefore palpitations seldom occurs[1].

The official method for determination in British pharmacopoeia[2] is a non-aqueous assay the end point is detected potentiometrically. Several analytical methods are available in the literature for its determination, these methods include spectrophotometric,[3-10] ion pair HPLC[11] liquid chromatography[12] capillary eltecrtrophoresis[13] and flow-injection analysis[14]. However, all these methods are costly, tedious time consuming. Two spectrophotometric methods for determination of terbutaline in pure and in their pharmaceutical preparations without prior extraction by simple, rapid and selective assays are described. The methods based on formation of colour complex either with sodium cobaltinitrite or with 4-AAP.

EXPERIMENTAL

1. Apparatus:

Shimadzu 260-UV recording spectrophotometer with 10 mm matched quartz cells was used for all absorbance measurements.

2. Materials and reagents :

All the chemicals were of analytical grade and all solvents were of spectroscopic grade :

a) Pure terbutaline sulphate was supplied kindly by (CID Co., Giza, Egypt).
b) Sodium cobaltinitrite solution (Sigma USA); 1% and, 3×10^{-3}M (0.121gm%) solutions in distilled water were freshly prepared.
c) Acetic acid (Adwic); 6% v/v solution in distilled water.
d) 4-aminoantipyrine (4-AAP) solution, 0.1% w/v and 3×10^{-3} M (0.0203% w/v) in distilled water was freshly prepared from material obtained from Aldrich (USA).
e) Potassium dihydrogen phosphate solution, 0.1% w/v aqueous solution.
f) Potassium ferricyanide solution, 0.1% w/v was freshly prepared in distilled water and supplied by Aldrich (USA).

3. Standard drug solution :

Stock solution of 1mg ml^{-1} were prepared by dissolving 100mg of the drug substance completed to 100 ml bidistilled water. The solution was stable for at least 72 h if stored in a cool and dark place.

4. Pharmaceutical Formulations :

The following commercial formulations were subjected to the analytical procedure (a) Bricanyl tablets®(CID Co., Giza Egypt), each tablet labelled to contain 2.5mg terbutaline sulphate. (b) Aironyl tablet® (SEDICO pharmaceutical Co. 6 October-City Egypt each tablet labelled to contain 2.5 mg terbutaline sulphate.

5. Procedures

5.1 Procedure using sodium cobaltinitrite:

Accurately measured aliquots containing from 4 to 40 μg ml^{-1} terbutaline sulphate were transferred into a series of test tubes, then 1.5ml of 1% sodium cobaltinitrite solution and 0.3 ml of 6% acetic acid solution were added, mixed well, heated in a water bath for 10 min at 60°C. The mixtures were then transferred into a 10-ml calibrated flasks, cooled, completed to 10ml with distilled water and the absorbance was measured at 422nm against a reagent blank (Table 1, Fig. 1).

5.2 Procedure using 4-AAP:

10-50 μg ml^{-1} of terbutaline sulphate were transferred into a 10-ml calibrated flask, then 2ml of 0.1% potassium dihydrogen phosphate solution 2ml of 0.1% 4-AAP solution and 2 ml 0.1% potassium

ferricyanide solution were added. Mixed well, allowed to stand for 10 min at room temperature, then diluted to 10ml with distilled water. The absorbance was measured at 490nm against a reagent blank (Table 1 Fig. 1).

5.3 Procedure for pharmaceutical formulation:

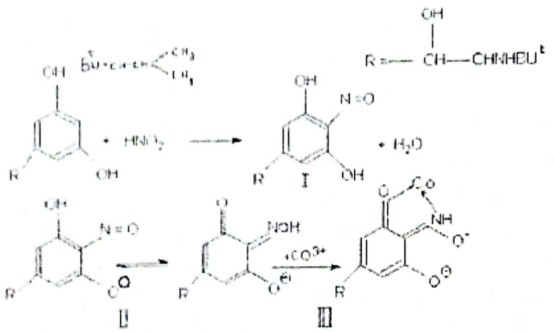
Twenty tablets were weighed, finely powdered and a portion of the powder equivalent to 10 mg of the drug was weighed, extracted with distilled water and filtered. The residue was washed twice with distilled water. The filtrate and the washings were collected in a 100 ml calibrated flask, and completed to volume with distilled water. Aliquots of the solution were transferred into a series of test tubes and proceed as directed in the general procedure.

RESULTS AND DISCUSSION

1. For procedure using sodium cobaltinitrite:

Terbutaline is a phenolic compound that can readily react with sodium cobaltinitrite producing coloured product measured at 422nm (Fig. 1).

This reaction reported by Feigl[15,16] involved heating the phenolic drug with sodium cobaltinitrite in an aqueous acetic acid solution. The resulting 0-Nitroso-phenol (I) in its tautomeric oxime form (II) yields a colored chelate with cobalt III as described in scheme 1.



$$[CO(NO_2)_6]^{-3} + 6H^+ \rightarrow Co^{+3} + 6HNO_2$$

Different parameters affecting the color development and its stability were studied. The effect of different volumes of sodium cobaltinirite on the color development was studied .(Fig. 2) shows that the optimal volume of 0.1% sodium cobaltinitrite is 1.5ml solution giving the highest absorbance.

Figure (3) shows that 0.3ml of acetic acid is appropriate, a larger volume would decrease the absorbance reading. The time required for complete coupling of sodium cobaltinitrite was found to be 10 minutes, longer times caused the absorbance reading to be unstable as shown in Fig. 5. In order to examine the effect of temperature the above mentioned procedure was carried out at different temperatures (room temperature, 30, 40, 50, 60, 70 ... to 100°C using thermostatic waterbath. (Fig.4) shows that maximum and constant absorbance was obtained at 60°C for 10min time of heating. The reaction sequence must be through addition of drug solution, sodium cobaltinitrite solution then the acetic acid is the proper sequence for the determination of the drug.

The reaction between sodium cobaltinitrite and terbutaline was linear at 4-40 µg ml^{-1} concentration range with the following regression equation.

$A_{422} = 0.00433 + 0.00739\ C$

$r = 0.99991$

C = µg ml^{-1} terbutaline

The molar ratio was studied using the continuous variation method[17] (Fig. 6) shows that the reaction proceeds in ratio of 1:1. Therefore that the reaction may proceeds as shown in Scheme (1).

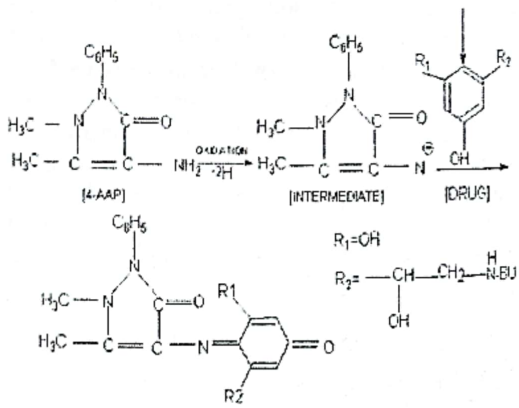
Under the mentioned reaction condition, linear correlation were found between A at 422nm and concentration of the studied drugs. Linearity range molar absorptivity sandels sensitivity and regression, equation analytical parameters are shown in table (1).

2. For procedure using 4 - Amino Antipyrine:

The oxidation of 4-AAP with alkaline potassium ferricyanide, loses 2 protons forming a neucleophilic intermediate which undergoes condensation with the phenolic moieties of the drugs to give coloured product (Scheme 2), **Gasparic et al**[18] used 4-AAP for the spectrophotometric determination of phenols. The coloured product was measured at 490 nm (Fig. 1).

For optimization the reaction condition of 4-AAP with the studied drug, several factors have been carefully studied.

Scheme 2 :



Found maximum colour intensity was produced using 2 ml of 0.1% 4-AAP (Fig. 7) increasing the reagent concentration slightly affected the color intensity. The addition of 2 ml of 0.1% potassium dihydrogen phosphate leads to maximum absorption (Fig. 9). A volume of 2 ml of potassium ferricyanide solution was found to give maximum colour formation (Fig. 8). Measurement of colour was done after 10 min at room temperature (Fig. 10). The molar ratio shows that the reaction proceeds in ratio of 1:1 (Fig.11)

Common additives and excepients did not interfere, so the examined drug can be assayed directly in their dosage form by the proposed method without

prior extraction or separation. The effect of temperature and heating time on the formation of the coloured complex were studied. The reaction of terbutaline proceeds slowly at room temperature, higher temperatures cause fading of the colour, maximum absorbance was obtained after 10min.

The reaction between terbutaline sulphate and 4-AAP was linear at 10 to 50 µg ml^{-1} concentration range with the following regression equation :

$A_{490} = 0.00932 + 0.01089\ C$

$r = 0.99996$

$C = \mu g\ ml^{-1}$ terbutaline

The colour obtained was found to be stable for at least 24 hours at room temperature.

Quantification, sensitivity, accuracy and precision:

A linear correlation was found between absorbance and concentration at specific λ_{max} for each methods [Table. 1]. Intercepts, slopes for the calibration data, molar absorptivities, coefficient of variation and Sandel's sensitivity for the proposed methods were shown in [Table. 1-3]. The proposed methods were applied for the analysis of terbutaline ,and its pharmacautical preparation Bricanyl and Aironyl tablets [Tables 4-7]. Statistical analysis of the results obtained by the proposed methods and the official BP reference method[2] were done using student's (t-est) and the variance ratio (F-test). The calculated values didn't exceed the theoretical one, indicating no significant difference between the compared methods (table 8,9). The proposed sodium Cobaltinitrite and

4-AAP methods are reproducible, accurate and precise need no special apparatus, determines low concentrations in comparison to the nonaqueous method. The recovery of the drugs were also tested by the standard addition method to pharmaceutical preparation and were found to be satisfactory

CONCLUSION

The proposed methods are advantageous when compared to many of the reported spectrophotometric methods because of their higher sensitivity which permits the determination of up 4 µg ml^{-1}. The data given reveal that the proposed methods are simple and sensitive with good accuracy and precision. It can be used directly to determine terbutaline sulphate without prior extraction, the common additives do not interfere.

Tabel 1 : Analytical parameters and statistical data of regression equation for the determination of terbutaline sulphate using sodium cobaltinitrite method (1) and 4-AAP method (2)

Analytical parameters and statistical data	Method (1) using sod. cobaltinitrite	Method (2) using 4-AAP
Linear rang Beer' s Law ug ml^{-1}	4 - 40	10 - 50
λ_{max} nm	422	490
Reagent used	1.5 ml 1% sodium cobaltinitrite	2 ml 0.1% 4-AAP
Other Reagent	0.3 ml 6% acetic acid	2 ml 0.1% $K_3 Fe(CN)_6$ 2 ml 0.1 % $KH_2 PO4$
Temperature C°	60°C in water bath	Ambient 25 C°
Diluting solvent	Distilled water	Distilled water
Time For complete reaction (min)	10	10
a b r	0.000433 0.00739 0.99991	0.000932 0.01089 0.99996
Molar absorptivity $L.mol^{-1}cm^{-1}$	$4.0\ 70\times10^3$	0.6×10^4
Sandel' s sensitivity µg cm^{-2}	1.348×10^{-2}	$9.14\ 10^{-2}$

Abs = b x C + a; where C is the unknown concentration in ug/ml

Table 2: Determination of terbutaline using sodium cobaltinitrite method (1)

Taken µg ml^{-1}	Found µg ml^{-1}	Recovery %
04	4.01	100.25
10	9.99	99.90
15	14.98	99.86
20	20.02	100.10
25	25.01	100.04
30	30.18	100.6
36	35.98	99.94
40	39.98	99.95
Mean	--	100.08 ±0.228
N	--	8
S.D	--	0.228
R.S.D	--	0.228
S.E	--	0.080
V	--	0.052

Table 3: Determination of terbutaline using 4-AAP method (2):

Taken µg ml^{-1}	Found µg ml^{-1}	Recovery %
10	9.95	99.5
15	14.98	99.86
25	25.01	100.04
35	35.02	100.05
40	39.95	99.87
45	44.90	99.77
50	50.10	100.2
Mean	--	99.898± 0.211
N	--	7
S.D	--	0.211
R.S.D	--	0.211
V	--	0.044
S.E	--	0.080

Table 4: Determination of terbutaline in Bricanyl® tablets using suggested sodium cobaltinitrite method (1)

Taken µg ml^{-1}	Added µg ml^{-1}	Found µg ml^{-1}	Recovery %
4	----	3.90	97.50
4	6	9.85	99.16
4	11	14.95	100.45
4	16	20.10	100.93
4	21	25.2	101.42
4	26	30.1	100.76
4	32	35.95	100.15
4	36	40.2	100.83
Mean %	--	--	100.15 ±1.18
N	--	--	8
V	--	--	1.393
S.D	--	--	1.180
R.S.D	--	--	1.178
S.E.	--	--	0.417

Table 5: Determination of terbutaline in Bricanyl® tablets using 4-AAP method (2)

Taken µg ml^{-1}	Added µg ml^{-1}	Found µg ml^{-1}	Recovery %
10	--	9.98	99.80
10	5	14.95	99.40
10	15	24.85	99.13
10	25	35.10	100.48
10	30	39.9	99.73
10	35	45.2	100.62
10	40	50.1	100.30
Mean %	--	--	99.92±0.520
N	--	--	7
V	--	--	0.270
S.D	--	--	0.520
R.S.D	--	--	0.520
S.E.	--	--	0.196

Table 6: Determination of terbutaline in Aironyl® tablets using sodium cobaltinitrite method (1).

Taken µg ml^{-1}	Added µg ml^{-1}	Found µg ml^{-1}	Recovery %
4	--	3.98	99.5
4	10	13.90	99.20
4	15	19.1	100.80
4	20	23.98	100
4	25	29.2	100.88
4	30	33.98	100
4	36	40.2	100.61
Mean %	--	--	100.14 ± 0.601
N	--	--	7
V	--	--	0.362
S.D	--	--	0.601
R.S.D	--	--	0.601
S.E.	--	--	0.227

Table 7: Determination of terbutaline in Aironyl® tablets using 4-AAP method (2).

Taken µg ml^{-1}	Added µg ml^{-1}	Found µg ml^{-1}	Recovery %
5	5	9.95	99.5
5	10	14.95	99.67
5	15	20.1	100.55
5	20	25.2	100.8
5	30	34.97	99.91
5	40	45.1	100.2
5	45	50.2	100.4
Mean %	--	--	100.147± 0.440
N	--	--	7
V	--	--	0.193
S.D	--	--	0.440
R.S.D	--	--	0.439
S.E.	--	--	0.166

Table 8: Determination of terbutaline using suggested method (1) sodium cobaltinitrite and method (2) using 4-AAP compared with reference B.P method[2].

Item	Method (1) using sodium cobaltinitrite	Method (2) using 4-AAP	Official B.P method[2]
Mean%	100.08	99.898	100.215
N	8	7	9
V	0.052	0.044	0.192
S.D	0.228	0.211	0.438
R.S.D	0.228	0.211	0.438
S.E	0.080	0.080	0.146
t	1.705 (4.77	3.98 (4.77)	--
F	3.69 (3.73)	4.36 (5.05)	--

Table 9: Comparison between suggested method (1) and (2) and B.P official method in determination of pharmaceutical formulation Aironyl tablet and Bricanyl® tablets.

	tem	Sodium cobaltinitrite method(1)	4-AAP method (2)	Offical B.P method[2]
Aironyl tablet	Mean	100.14	100.147	100.05
	N	7	7	10
	SD	0.601	0.440	0.327
	V	0.362	0.194	0.107
	R.SD	0.601	0.439	0.327
	S.E	0.227	0.166	0.103
	t	0.407 (3.29)	0.595 (3.29)	--
	F	3.380 (3.37)	1.813 (3.37)	--
Bricanyl® tablets	Mean	100.15	99.93	99.83
	N	8	7	10
	SD	1.180	0.520	0.570
	V	1.393	0.270	0.325
	R.SD	1.178	0.520	0.570
	S.E	0.417	0.196	0.180
	t	0.799 (3.285)	0.491 (3.29)	
	F	4.280 (5.050)	1.203 (4.10)	

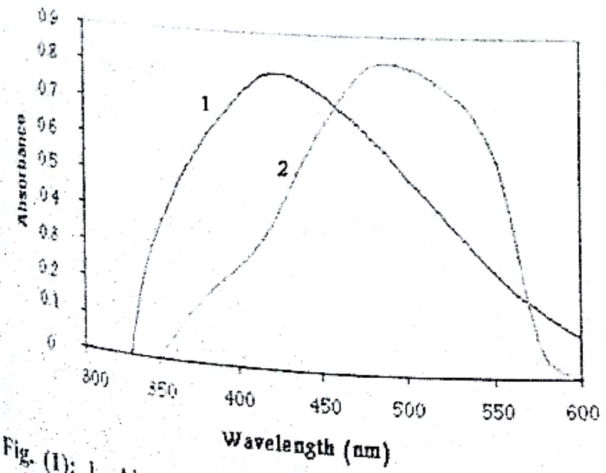


Fig. (1): 1- Absorption spectrum of terbutaline sulphate with sodium cobaltinitrite λmax 422 nm.
2- Absorption spectrum of terbutaline sulphate with 4-AAP λmax 490 nm .

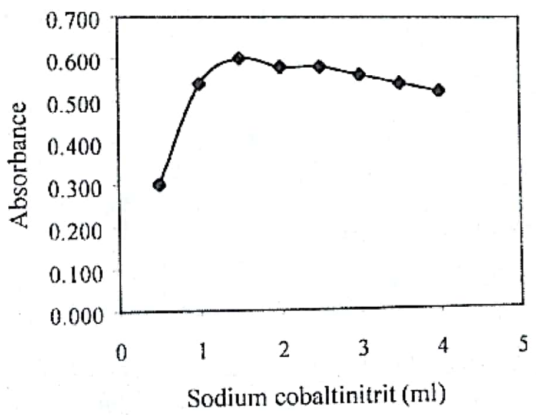


Fig. (2): Effect of volume of sodium cobaltinitrite on the reaction of terbutaline sulphate

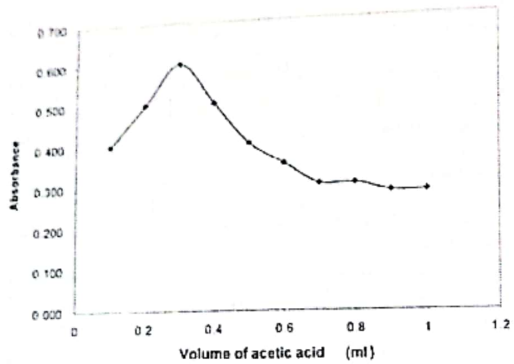


Fig. (3):Volume of 6% acetic acid solution on the reaction of terbutaline sulphate and sodium cobaltinitrite

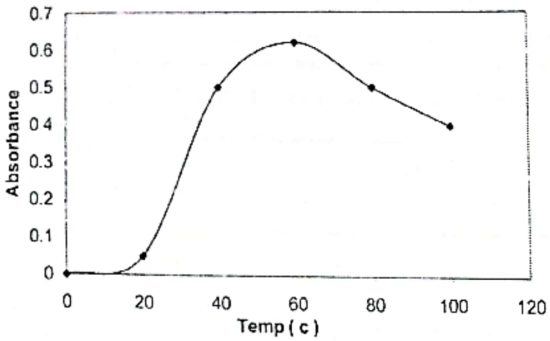


Fig. (4): Effect of temperature on the reaction of terbutaline sulphate and sodium cobaltinitrite

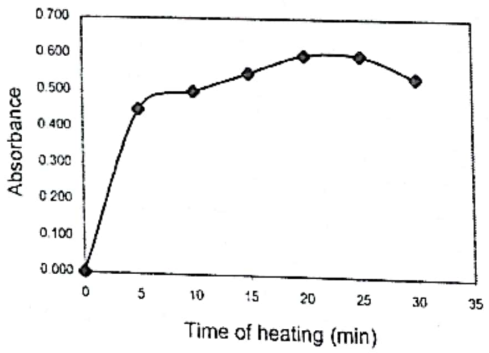


Fig. (5): Heating time on the reaction of terbutaline sulphate and sodium cobaltinitrite

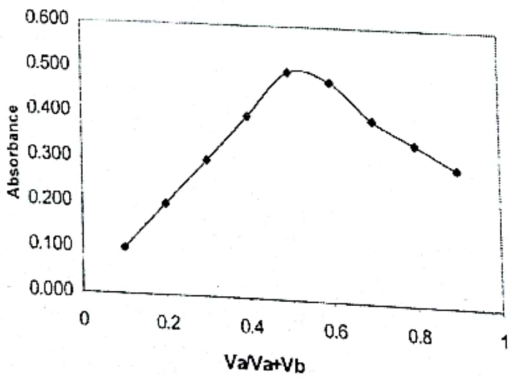


Fig. (6): Determination of the stoichiometry on the reaction between (3×10^{-3} M) terbutaline sulphate and (3×10^{-3} M) sodium cobaltinitrite by continuous variation method

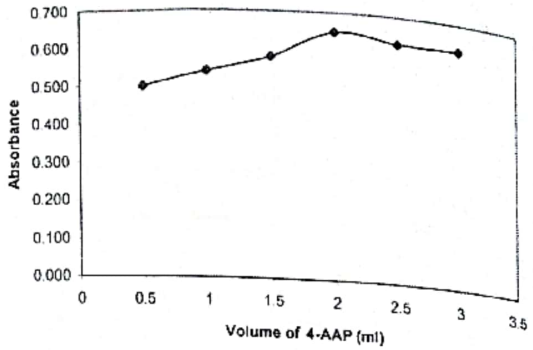


Fig. (7): Effect of volume of 4-AAP on the reaction of terbutaline sulphate

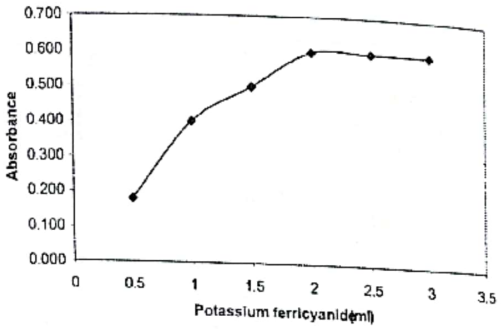


Fig. (8): Volume of potassium ferricyanide on the reaction between terbutaline sulphate and 4-AAP

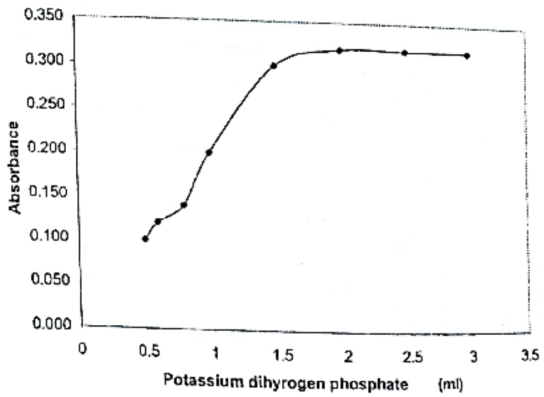


Fig. (9): Volume of potassium dihyrogen phosphate on the reaction between terbutaline sulphate and 4-AAP

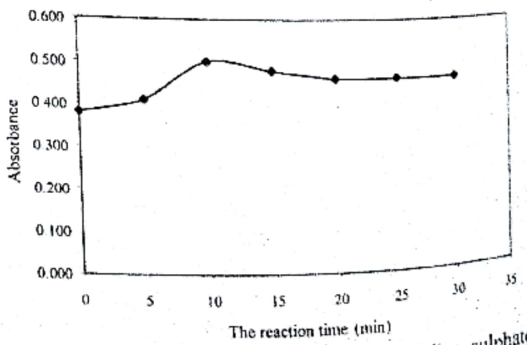


Fig. (10): The reaction time between terbutaline sulphate and 4-AAP

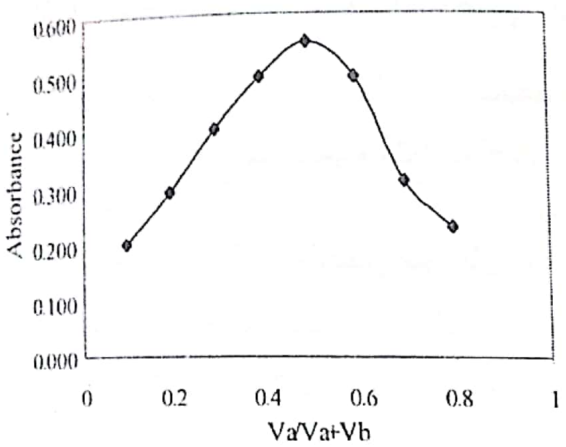


Fig. (11): Determination of the stoichiometry on the reaction between (3×10^{-3} M) terbutaline sulphate and (3×10^{-3} M) 4-AAP by continuous variation method

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طرق طيفية جديدة لتحليل المركب الصيدلي التيربيوتالين وذلك في صورته النقية أو في صورة مركباته الصيدلية

محمد نجيب محمد البلقيني

قسم الكيمياء التحليلية – كلية الصيدلة– جامعة الزقازيق– الزقازيق – مصر

تـــم استحداث طريقتين طيفيتين سريعتين وذلك لتعيين مركب التيربيوتالين الطريقة الاولى تعتمد على تعين المركب المعقـــد الـــناتج من إضافة صوديوم كوبلتينيتريت وذلك بقياس درجة امتصاص الطيفي عند ٤٤٢ ثم والطريقة الثانية تعتمد علـــى تفاعـــل المـــركب الصـــيدلي مع مادة ٤ امينو انتي بيرين. (4-AAP) وذلك في وجود كل من محلول وسطي من البوتسيوم ثنائي هايدروجين الفوسفات وبوتاسيوم فيراسيند وقياس الطيف الناتج عند درجة ٤٩٠نم

وقـــد تـــم اختـــبار الطريقتين وتم مقارنتهما بالطرق الدستورية الأخرى (كدستور الأدوية الإنجليزى) ووجدت النتائج المتحصلة كانت طيبة.