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SPECTROPHOTOMETRIC ESTIMATION OF SOME NITROGENOUS PHARMACEUTICAL COMPOUNDS BY CHARGE TRANSFER COMPLEXATION

Magda M. Ayad, Hawa M. Khalil, Magda El-Henawee and Mervate Hosny
Analytical Chemistry Dept., Faculty of Pharmacy, University of Zagazig, Zagazig-Egypt.

ABSTRACT

Three simple and sensitive colorimetric methods have been developed for the estimation of trazodone, timolol and piribedil through electron transfer complexation reaction. The methods involve the reaction of these drugs as p-donors with either n-electron acceptors [P-chloronilic acid (PCA) and tetracyano-quinodimethane (TCNQ)] and iodine as acceptor to give a stable and highly coloured radical anion. The coloured products were measured spectrophotometrically. The optimization of the different experimental conditions has been studied. The suggested methods were applied to assay the tested compounds in their pharmaceutical preparations. The results obtained agreed well with the reference methods.

INTRODUCTION

Several methods have been described for the quantitative estimation of the cited drugs including spectrophotometric[1-6], and chromatographic[7-14] methods. Other miscellaneous methods[15-19] have been also described as differential pulse voltammetry[20-22] and potentiometric method using monoalkyl phosphoric acids for determination of timolol[23].

P-chloronilic acid was used for estimation of different drugs as codeine, emetine and pilocarpine [24], chlorphenoxamine hydrochloride[25] and antihistaminic drugs [26]. TCNQ was applied for the quantitative analysis of pharmaceutical and related compounds [27-29] and iodine as acceptor was also applied for the estimation of alkaloids [30], metochlopramide [31] and cephalosporine [32].

EXPERIMENTAL

Apparatus :

Shimadzu U.V. and visible recording spectrophotometer (U.V. 260).

Reagents and Materials:

All reagents were of analytical grade and all solvents were of spectroscopic grade.

1) Piribedil (Servier):

Working solution was prepared to give 2.0 mg m^{-1} and 0.1 mg ml^{-1} in acetonitrile and 0.25 mg ml^{-1} in chloroform. 1 x 10^{-3} M (29.84 mg %) and 8 x 10^{-4} M (23.86 mg %) in acetonitrile 3x10^{-4} (8.95 mg %) in chloroform.

2) Timolol (E.P.I. CO):

The working solution was prepared to give 2.0 mg ml^{-1}, 0.1 mg ml^{-1} in acetonitrile and 0.5 mg ml^{-1} in chloroform. 1x10^{-3}M (31.64mg%) solution in acetonitrile. 3x10^{-4}M (9.49mg%) solution in chloroform.

3) Trazodone:

Working solution was prepared to contain 1.0 mg ml^{-1}, 0.2 mg ml^{-1} trazodone in acetonitrile and 0.5 mg ml^{-1} in chloroform. 1 x 10^{-1} M (37.19 mg %) solution in acetonitrile. 7 x 10^{-1} M (26.03 mg %) solution in chloroform.

Preparation of working solution of trazodone:

Weigh accurately the appropriate amount of the drug salt, transfer into 60 ml separating funnel, dissolve the powder in 10 ml water, then put 3 ml saturated solution of sodium hydroxide and extract with chloroform. Combine the chloroform extracts and dry with anhydrous sodium sulphate for 5 min., filter (through dry filter paper) in case of P.CA, TCNQ acceptors, evaporate the chloroformic extract equivalent to (50-325 μg ml^{-1} and (4-16 μg ml^{-1}) respectively, at 70°C, then dissolve the residue in acetonitrile.

4) P.CA:

0.04%, 0.06% and 0.08% w/v in 20 ml acetonitrile + 80 ml chloroform. 1 x 10^{-3} M (20.9 mg %) w/v in 20 ml acetonitrile + 80 ml chloroform.

5) TCNQ:

0.07%, 0.16% w/v in acetonitrile. 1 x 10^{-3} M (20.419 mg %) in acetonitrile. 8 x 10^{-4} M(16.335 mg%) in acetonitrile.

6) Iodine solution :

1 x 10^{-3} M (25.38 mg %) in chloroform. 7 x 10^{-4} M (17.76 mg %) in chloroform. 3 x 10^{-4} M (7.61 mg %) in chloroform.

7) Pharmaceutical preparations:

(A)Trittico (100) tablets, each tablet was labelled to contain 100 mg Trazodone HCl.

(B)Timolol eye drops (0.25%), each 1 ml was labelled to contain 2.5 mg timolol.

(C)Trivestal each tablet was labelled to contain 20 mg piribedil.

PROCEDURES:

I-Charge transfer complexation with P.CA.:

General procedures:

For bulk powder:

To accurately measured aliquots of working solution of the three drugs, the specified volume of P.CA was added in a 10 ml volumetric flask. The content of each flask was mixed and diluted to volume with chloroform, the absorbance of the resulting colour was measured at the specific λ max as shown in Table (1) against blank.

For Pharmaceutical preparations :

1) Trittico tablets (100 mg):

Weigh and finely powder 20 tablets, dissolve the quantity of tablets equivalent to 25 mg of trazodone in 20 ml water filter, add 3 ml of saturated sodium hydroxide solution, extract with chloroform, then dry with anhydrous sodium sulphate for 5 minutes, filter through dry filter paper, take volumes of chloroformic extract equivalent to 100 $\mu g\ m^{-1}$ then evaporate chloroform at 70°C, dissolve the residue in acetonitrile, then proceed as under general procedures.

2) Trivestal tablets:

Weigh and finely powder 20 tablets, dissolve a quantity equivalent to (200 mg of piribedil) in about 90 ml acetonitrile, filter, complete to 100 ml with the same solvent, take an aliquot of this solution equivalent to 40 $\mu g\ ml^{-1}$ and proceed as under general procedures.

3) Timolol eye drops (0.25%):

To separate timolol from its eye drops ; apply the following procedure of the USP method [10] . 5 ml timolol eye drops was diluted with water to 25 ml (solution A), then to 5 ml of solution A add 15 ml of buffer (pH 9.7) and 20 ml toluene, shake for 1 min, take aqueous layer again with 20 ml toluene and shake again for 1 minute. Combine the toluene extracts, add 10 ml buffer, shake for 1 minute. Discard the aqueous layer, take the toluene layer, wash the separating funnel with 2 ml toluene, collect the toluene layer and washings and add 0.1 N H_2SO_4 (2 x 20 ml). Complete to 100 ml with 0.1 N H_2SO_4 , render alkaline using saturated sodium hydroxide solution, extract with chloroform and complete to 100 ml with the same solvent. Take an aliquot equivalent to (120 $\mu g\ ml^{-1}$), evaporate the chloroform at 70°C, dissolve the risdue in acetonitrile and proceed as under general procedure.

Determination of stoichiometric ratio using continuous variation method (Job's Method) [33].

A series of standard equimolecular (1 x 10^{-3} M) solution of each drug (vd) and P.C.A. (va) in different complementary volumes totaling 10 ml (from 0 + 10 to 10+ 0 inclusive) were prepared in 10 ml calibrated flasks. The absorbance of the produced colour was measured at suitable λ max, (Table 1).

II-Charge transfer complexation with TCNQ:

General procedures :

For bulk powder:

To accurately measured volumes of working solution add convenient volume of TCNQ in 10 ml calibrated flasks, the content of each flask was mixed and allowed to stand for appropriate time for complete reaction at specific temperature, complete the volume with acetonitrile and measure the absorbance, at λ max, Table (1).

For Pharmaceutical preparations:

1) Trittico tablets (100 mg):

Prepare the tablets solution as under P.CA method, take an aliquot of chloroformic extract equivalent to 6 $\mu g\ ml^{-1}$ and proceed as under general procedures.

2) Trivestal tablets (20 mg):

Weigh and finely powder 20 tablets, dissolve a quantity of the powder equivalent to 5 ml drug in 40 ml acetonitrile filter, then complete to 50 ml with the same solvent. Take an aliquot of this solution equivalent to 3 $\mu g\ ml^{-1}$ and proceed as under general procedures.

3)Timolol eye drops (0.25%):

Prepare timolol solution as mentioned under (P.CA) method, then take volume of the solution equivalent to 4 $\mu g\ ml^{-1}$, evaporate the chloroform dissolve the residue in acetonitrile, proceed as under general procedures.

Determination of stoichiometric ratio using Job's Method [33] :

By using equimolecular solutions of (TCNQ), and each of the three drugs (1 x 10^{-3} M for timolol and trazodone, 8 x 10^{-4} M for piribedil) proceed as in **Job's** method described under P.CA.

III- Iodine Method:

General Procedures:

For Bulk Powder:

To accurately measured volumes of drug in 10 ml calibrated flasks, add appropriate volume of iodine solution, leave to stand for complete reaction and complete to volume with chloroform, measure the absorbance at specified λ max (Table 1).

Table (1) :Analytical parmeters for P.C.A. TCNQ and iodine methods for the determination of timolol, trazodone and piribedial.

Acceptor	Drug	Linear range of Beer's Law g ml-1	Conc. of acceptor gm% w/v	Temperature °C	Solvent	Time for complete reaction (minute)	γ max	Statistical data of the regression equations		
								K	B	R
P.C.A.	Timolol	80-320	4.0ml 0.08%	Ambient (25°C)	1	5	533.6	515.52	-1.6008	0.9999
	Trazodone	50-325	4.0ml 0.06%	Ambient (25°C)		5	530.4	438.73	-20323	0.9997
	Piribedil	40-240	5.0ml 0.04%	Ambient (25°C)		5	353.2	260.71	-0.3212	0.9999
TCNQ	Timolol	4-11	2.0ml 0.07%	70°C ±5		30	842	20.015	-1.0398	0.9997
	Trazodone	4-16	1.0ml 0.16%	70°C ±5	2	10	842	21.153	-1.6838	0.9999
	Piribedil	3-10	2.0ml 0.07%	70°C ±5		30	842	16.366	-1.5392	0.9999
Iodine	Timolol	10-60	1.5ml of $1x10^{-3}$M	Ambient (25°C)		5	299.8	50.148	1.8269	0.9999
	Trazodone	25-85	1.0 ml of $1 x 10^{-3}$ M	Ambient (25°C)	1	20	258.8	121.20	1.6543	0.9999
	Piribedil	5-30	1.5 ml of $1 x 10^{-3}$ M	Ambient (25°C)		20	151.0	41.735	0.3943	0.9999

Solvent : 1 Chloroform 2 Acetonitrile

For Pharmaceutical preparations:

1) Trittico tablets (100 mg):

Prepare tablets solution as under P.CA method, take volume of chloroformic extract equivalent to 25 μg ml^{-1} and proceed as in general procedures for bulk powder.

2) Trivestal tablets (20 mg):

Weigh and finely powder 20 tablets, take a quantity of the powder equivalent to (10 mg), dissolve in chloroform, filter, complete to 25 ml with the same solvent, take an aliquot of this chloroformic extract equivalent to 10 μg ml^{-1} complete as under general procedures for bulk powder.

3) Timolol eye drops (0.25%):

Separate timolol from its eye drops as under (P.CA) method. Take an aliquot of the chloroformic extract equivalent to 10 μg ml^{-1}, complete as under general procedures for bulk powder.

Molar ratio method (Yoe Method) [34] :

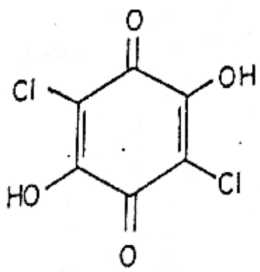
Aliquot volumes of 1 ml of $3 x 10^{-4}$ M solution of timolol, piribedil and $7 x 10^{-4}$ M solution of trazodone (vd) were treated with varying volumes (0.5, 1, 1.5, 2, 2.5 ml) of the same molarity iodine solution in chloroform (va), in 10 ml calibrated flasks. Each flask was then left for complete reaction and its absorbance was measured at appropriate λ max, against reagent blank. A graph was then plotted for absorbance versus va/vd for each flask.

RESULTS AND DISCUSSION

The selected drugs were considered as electron-donors when these drugs were reacted with selected acceptors (P.CA, TCNQ and I_2), they produce a new band at a suitable λmax, which was characteristic for each complex. These new bands were used for a quantitative determination of them.

I- Reaction with (P.CA):

The drugs studied react instantaneously with P.CA in chloroform to give a purple chromogen exhibiting maximum absorbance at lmax, 533.6, 530.4 and 535.2 for timolol, trazodone and piribedil respectively Fig. (1). An ion pair salt was formed by a proton transfer from P.CA to the basic centre (B) in the drug molecule [35,36] , the reaction can be written as follows:



$H_2A \rightarrow (H^+ + HA^-$ **(Purple)**

$B + H^+ \rightarrow BH^+$ **(colourless)**

P.C.A. (H_2A)

BH^+ formed an ion pair salt with HA- giving a purple colour which was responsible for the quantitative measurements. Optimum conditions as well as the molar-ratio for drug-chloranilic acid ion-pair was studied.

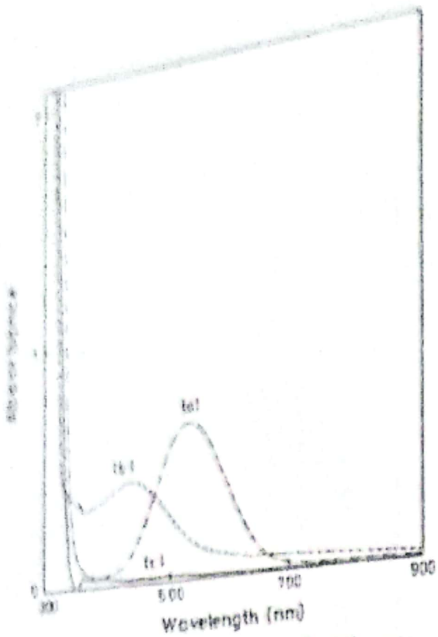
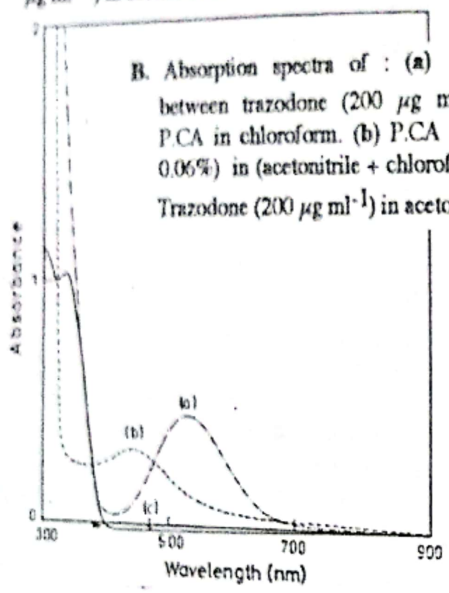
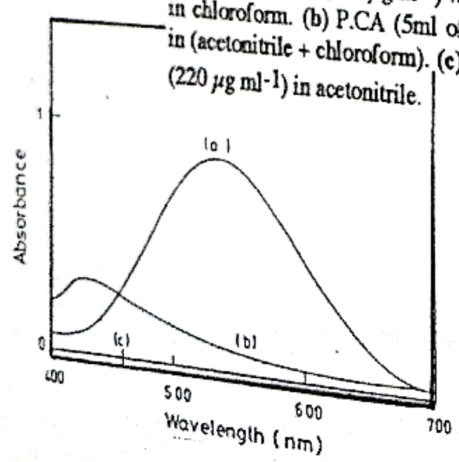


Fig. (1) A. Absorption spectra of : (a) reaction between timolol (320 $\mu g\ m^{-1}$) with P.CA in chloroform. (b) P.CA (4 ml of 0.08%) (acetonitrile+ chloroform). (c) Timolol (320 $\mu g\ ml^{-1}$) in acetonitrile.



B. Absorption spectra of : (a) reaction between trazodone (200 $\mu g\ m^{-1}$) with P.CA in chloroform. (b) P.CA (4 ml of 0.06%) in (acetonitrile + chloroform). (c) Trazodone (200 $\mu g\ ml^{-1}$) in acetonitrile.



C. Absorption spectra of : (a) reaction between piribedil (220 $\mu g\ m^{-1}$) with P.CA in chloroform. (b) P.CA (5ml of 0.04%) in (acetonitrile + chloroform). (c) Piribedil (220 μg ml-1) in acetonitrile.

Stoichiomtric relationship:

This was determined by Job's continious variation method[33] from the stoichiometric relationship, it was found that molar ratio between the reactants (D:A) is (1:1), where only one mole of P. chloranilic aci d was consumed in the reaction with the three drugs, to form radical anion, which was responsible for the produced violet colour.

Linearity of Beer's Law plot:

A linear relationship was obtained for the absorbance of P.CA with the three drugs in concentration range of (80-320 $\mu g\ ml^{-4}$), (50-325 $\mu g\ ml^{-4}$) and (40-240 $\mu g\ ml^{-4}$) for timolol, trazodone and piribedil, respectively.

The calibration graphs showed almost a zero intercept and were described by the equations:

Conc = Abs. K + B. Where K = constant, B = intercept.

(a) Timolol: 515.52 x Abs. -1.6908.
(b) Trazodone: 438.73 x Abs. -2.0323.
(c) Piribedil: 260.71 x Abs. -0.3212.

II- Reaction with TCNQ:

When the acetonitrile solutions of drugs (Lewis bases) were mixed with acetonitrile solution of TCNQ acceptor (Lewis acid), an intense bluish green colour was developed in the visible region showing minor bands at 680 and 664 and major bands at 842, 822, 762 and 743. Fig. (2). These bands may be attributed to the formation of TCNQ radical anion. $D + A \rightarrow D^+ + A^-$.

Stoichiometric relationship:

TCNQ acceptor posesses higher electron affinity due to the presence of four strong electron withdrawing cyano-groups in its molecule. This high electron affinity allows it to interact with even weak donors, and causes ease of dissociation of the original electron donor acceptor complex to the radical ion.

Determination of molar ratio of donors with TCNQ in the complex was studied by Foster[37] and others [38,39], the three cited drugs showed molar ratio of 1:4 (donor: acceptor).

Linearity of Beer's Law Plot:

A linear relationship was obtained for timolol, trazodone and piribedil in the range of (4-11 $\mu g\ ml^{-1}$, 4-16 $\mu g\ ml^{-4}$ and 3-10 $\mu g\ ml^{-1}$,), respectively, (Table 1).

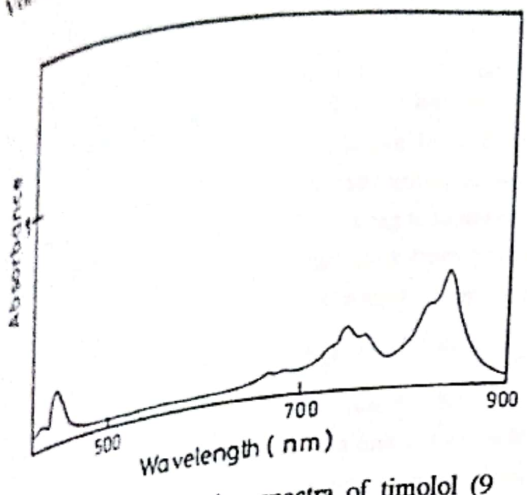
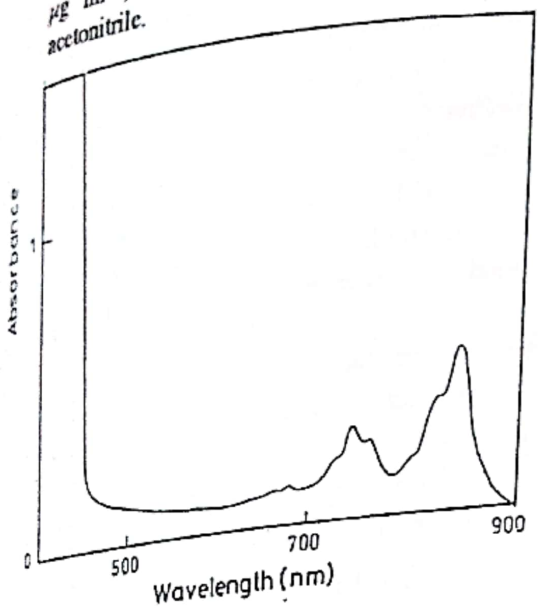
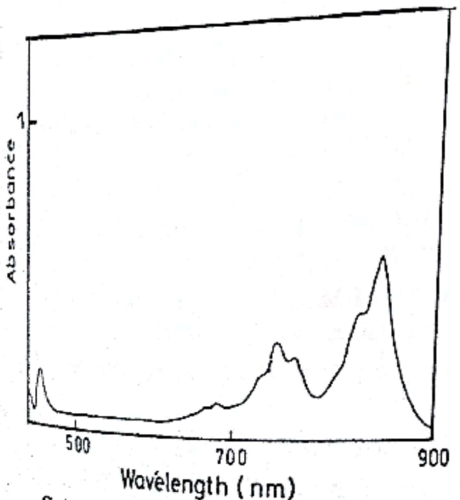


Fig. (2) A. Absorption spectra of timolol (9 μg ml^{-1}) and 2 ml 0.07% TCNQ in acetonitrile.



B. Absorption spectra of trazodone (12 μg ml-1) and 1 ml 0.16% TCNQ in acetonitrile.



C. Absorption spectra of piribedil (7 μg ml^{-1}) and 2 ml 0.07% TCNQ in acetonitrile.

Conc = K. Abs + B.

(a) Timolol: 20.015 x Abs. -1.0398.

(b) Trazodone: 21.153 xAbs. +1.6838.

(c) Piribedil: 16.366 x Abs. -1.5392.

III- Reaction with iodine:

A simple and accurate spectrophotometric method for the determination of timolol, trazodone and piribedil based on the charge-transfer complex formation between these drugs as electron-donors and iondine as an acceptor is described. The formed charge transfer complexes with iodine showed two maxima at (299.8, 240.6), (258.4, 301.8) and (251.0, 289.0) for timolol, trazodone and piribedil, respectively. (Fig. 3) .

The immediate change of the violet colour of iodine in chloroform to lemon yellow or yellowish purple upon reaction with the three drugs suggested charge-transfer complex formation.

The stoichiometry of the reaction was studied by the molar-ratio method. The molar-ratio was found to be 1 : 4 (Donor: acceptor).

In order to make use of this complex formation for the determination of these drugs, the concentration of iodine must be suitable for quantitative reaction, and should not be much higher than drug concentration in order to avoid the formation of termolecular complexes[40] with a consequent positive deviation from Beer's law. Absorbance must not be measured after long time in order to minimise changes in the absorbance with time owing to the conversion of the outer complex into the inner complex, the latter form being common for electron donor complexes with iodine [41].

Linearity of Beer's Law plot:

Beer's law was obeyed in the rangs of (10-60 μg ml^{-1}), (25-85 μg ml^{-1}) and (5-30 μg ml^{-1}) for timolol, trazodone and piribedil, respectively (Table 1):

Concentrations of drugs can be calculated from the following equations:

Conc = K. Abs + B.

(a) Timolol: 50.148 x Abs + 1.8269.

(b) Trazodone: 121.20 x Abs + 1.6543.

(c) Piribedil: 41.735 x Abs + 0.3943.

Investigation of the assay parameters:

Effect of Solvent:

For P.CA, many solvents were tried; dioxane gave low results; chloroform, acetonitrile and methylene chloride gave better results but chlororform was the most convenient solvent as it is cheaper.

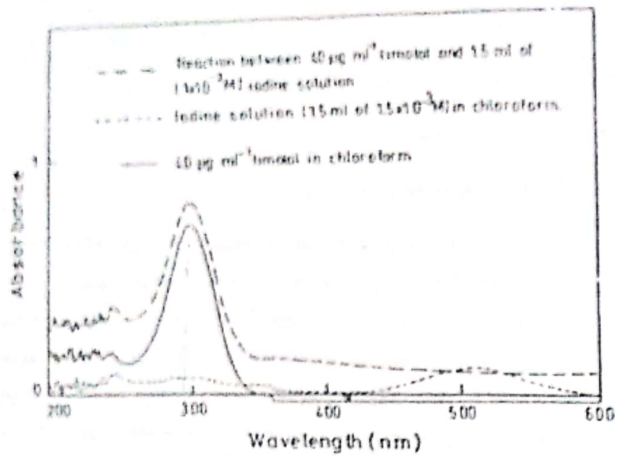
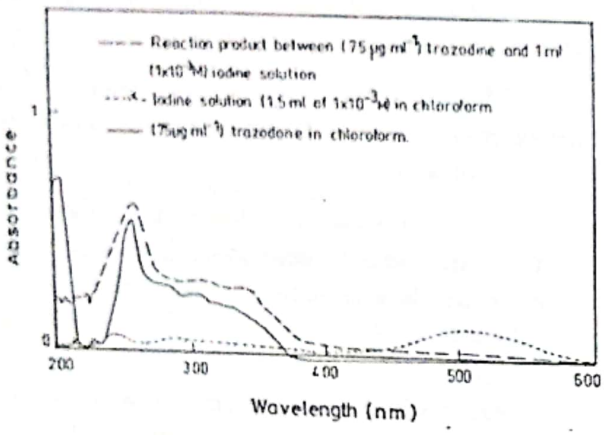
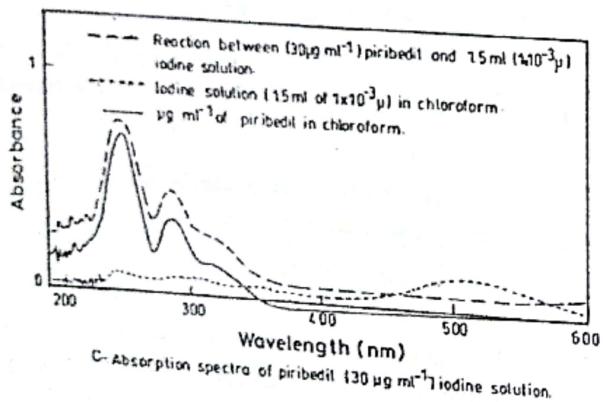


Fig. (3) : A. Absorption spectra of timolol (40 μg ml^{-1}) and 1.5 ml of (1 x 10^{-3}M) iodine solution.



B. Absorption spectra of trazodone (75 μg ml-1) and 1 ml of (1 x 10^{-3}M) iodine solution.



C- Absorption spectra of piribedil (30 µg ml⁻¹) iodine solution.

C. Absorption spectra of piribedil (30 μg ml^{-1}) iodine solution.

Acetonitrile was found to be the best solvent for TCNQ because it has a high relative permitivity which ensures the maximum yield of TCNQ but chloroform, carbon tetra chloride, benzene were unsuitable owing to the limited solubility of reagent in these solvents. In case of iodine, chloroform was found to be convenient solvent as it gave high and stable results. Beer's law was not obeyed with methylene chloride, while in case of methanol a high blank reading was obtained.

Quantification, accuracy and precision:

A linear correlation was found between absorbance and concentration at the specific λ max for each drug in the range given in Table (1), standard deviation, relative standard deviation, standard error, molar absorptivities and Sandel's sensitivity for the cited drugs were calculated.

The validity of the proposed methods was confirmed by its application for the analysis of different pharmaceutical formulation, by standard addition technique. The result, were compared with official and reference methods, Table (2-5), results obtained showed good agreement with those obtained by reference methods (t, F-tests). The calculated values did not exceed the theoretical ones, moreover, in case of piribedil the reference method need high concentrations in contrast to the proposed methods. The proposed procedures are easy to follow and require no complicated instrument.

IR (KBr) spectrum of timolol, P.CA reaction product was reported. Timolol gaves principal peaks at 1497, 1527, 1120, 1230, 1590, 1620 and 1750 cm^{-1}. Disappearance of peaks in region of 1600-1750cm^{-1} indicate the reaction due to the absence of NH group in the reaction product.

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Table (2) : Determination of timolol using P.C.A. and iodine methods compared with the USP method (1).

Items	USP method	P.CA method	TCNQ method	Iodine method
Mean (P=0.05)	100.8 ±0.91*	99.97 ±0.63*	99.89±0.68*	99.89±0.78*
N	5	6	6	6
V	0.83	0.39	0.46	0.59
S.D	0.91	0.63	0.68	0.77
R.S.D.	0.90	0.63	0.68	0.77
S.E.	0.41	0.26	0.28	0.31
t		1.79 (2.262)	1.71 (2.262)	1.80 (2.262)
F		2.13 (5.19)	1.89 (5.19)	1.41 (5.19)

* Mean ± S.D.

Table (3) : Determination of piribedil using P.CA. TCNQ and iodine methods compared with reference non aqueous method.

Items	USP method	P.CA method	TCNQ method	Iodine method
Mean (P=0.05)	100.8 ±0.50*	100.06 ±0.04**	99.89±0.41**	100.04±0.265**
N	5	6	7	7
V	0.25	0.16	0.17	0.07
S.D	0.50	0.40	0.41	0.265
R.S.D.	0.50	0.399	0.41	0.264
S.E.	0.22	0.16	0.15	0.10
t	--	0.97 (2.262)	0.69 (2.228)	1.09(2.228)
F	--	1.56 (5.19)	1.48 (4.53)	3.38 (4.53)

* Servier specifications ** Mean ± S.D.

Table (4) : Determination of piribedil using P.CA. TCNQ and iodine methods compared with USP method (1)

Items	USP method	P.CA method	TCNQ method	Iodine method
Mean (P=0.05)	99.8±0.75*	100.07 ±0.894*	9.09±0.94*	99.95±0.71*
N	5	5	6	5
V	0.26	0.80	0.89	0.50
S.D	0.75	0.894	0.94	0.71
R.S.D.	0.75	0.893	0.95	0.71
S.E.	0.33	0.40	0.38	0.32
t	--	1.87 (2.306)	0.096 (2.262)	1.76 (2.306)
F	--	1.43 (6.39)	1.59 (5.19)	1.12 (6.39)

* Mean ± S.D.

Table (5) : Determination of trittico (100) tablets using P.CA, TCNQ and iodine methods compared with reference spectrophotometric method*

Items	USP method	P.CA method	TCNQ method	Iodine method
Mean (P=0.05)	99.62±0.67**	00.61 ±0.608**	98.98±0.624**	99.64±0.707**
N	5	5	5	5
V	0.46	0.37	0.39	0.50
S.D	0.68	0.608	0.624	0.707
R.S.D.	0.68	0.610	0.630	0.709
S.E.	0.30	0.27	0.28	0.32
t	--	Zero (2.306)	1.53 (2.306)	1.7 (2.306)
F	--	1.24 (6.39)	1.18 (6.39)	1.09 (6.39)

* Mean ± S.D. * E. B. I. Co. Specifications

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الملخص العربى

التقدير الطيفى لبعض المركبات النيتروجينية الصيدلية بتكوين معقد بنقل الشحنات

ماجدة عياد، حواء خليل ، ماجدة الحناوى ، مرفت حسنى
قسم الكيمياء التحليلية- كلية الصيدلة- جامعة الزقازيق - الزقازيق - مصر

يصف هذا البحث استخدام طرق نقل الشحنات بإستخدام حامض الباراكلورانيلك ورباعى سيانوكيتودای ميثان واليود كطريقة طبيعية لتحليل التمولول والترازودون والبيريبديل تقديرا كميا دقيقا عن طريق تكون معقد له درجة امتصاص قوى . ويتعرض هذا البحث إلى تحليل المركبات المذكورة فى المستحضرات الصيدلية وقد قورنت النتائج التى تم التوصل اليها بطريقة التحليل فى دستورى الأدوية البريطانى والأمريكى وطريقة تحليل الشركة المنتجة . فتميزت الطريقة المقترحة بالدقة والاتقان والبساطة بالاضافة إلى حساسيتها الفائقة.