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SPECTROPHOTOMETRIC DETERMINATION OF QUINIDINE SULFATE BY ION-PAIR FORMATION

Mamdouh M. F. Metwally
Analytical Chemistry Department, Faculty of Pharmacy,
Zagazig University, Zagazig- Egypt.

ABSTRACT

A simple method for the determination of quinidine sulfate in tablets is based on the formation of an ion-pair between quinidine sulfate and thymol blue (TB) at pH=5.5 in aqueous-methanol solution. The absorbance of the ion-pair formed is measured and the concentration of the drug is calculated. The molar ratio of the ion-pair is determined and found to be 2:1 and with general formula $[Q]^{+4}$ 2. $[T.B]^{-1}$ SO_4^{-2} HSO_4^{-1} as calculated by elemental analysis. Using the present method quinidine sulfate in tablets was assayed. The results were statistically compared with those obtained by the official method.

INTRODUCTION

Chemically, quinidine sulfate is α- (6-methoxy-4-quinolyl)-5-vinyl-2-quinuclidine methanol sulfate, (2:1) salt dihydrate, with empirical formula $C_{40}H_{54}N_4O_{10}S$ and chemical structure as shown in Fig. (1).

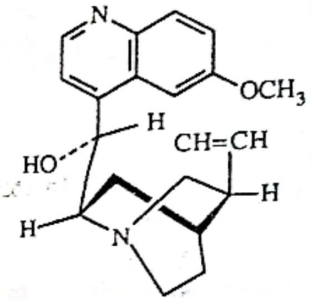

Fig (1) quinidine

Quinidine sulfate dihydrate have molecular weight 782.95 with elemental composition, C, 61.36%; H, 6.95%; N, 7.16%; O, 20.44%; S, 4.09% (dihydrate). It is used as a typical myocardial depressant and as a potent defibrillating agent.

Many analytical methods have been developed for the determination of quinidine sulfate, among these method, is the spectrophotometric methods which are based on the development of a colour formed between quinidine sulfate and chromogen as charge transfer complex formation e.g. the use of rose bengal (1).

Proton NMR relaxation times for conformational analysis of quinidine (2), and over pressure layer chromatographic method for separation and quantitative determination of quinine, quinidine(3), continuous flow chemiluminescent for assay of quinine and quinidine(4), gas chromatography and gas-mass spectrometry for determining quinidine and six butyrophenones (5) and Abbott TDX Analyzer for analysis of quinidine phenobarbital in post mortem samples (6).

In the meantime, thymol blue sodium salt reagent (Fig. 2) FW 488.58 have λ_{max} = 590 (378)nm with transition interval acid pH=1.2 (red) to pH=2.8 (yellow) and transition interval alkaline pH=8 (yellow) to

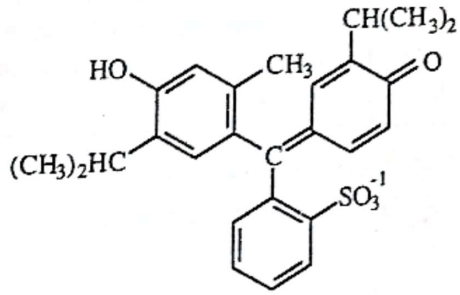

Fig. (2) Thymol blue

pH=9.2 (blue). When quinidie sulfate solution is added to thymol blue solution a red colour is formed on using small concentration of both the drug and the indicator while on using high concentration of both the ion pair precipitate is formed. This paper describes the colorimetric method for determining quinidine in pure and crude form and its application to the pharmaceutical dosage form.

MATERIALS AND METHODS

Materials: Quinidine-Pure Grade-Prolabo Chemical co. 90% Purity, remainder hydroquinidine. Quindine-Sulphate tablet USP XVII, The Nile co. for Pharmaceuticals and Chemical Industries, Cairo, (R.C.C., 115668), Egypt. Thymol blue indicator, analytical grade from Aldrich Chem. co. All Chemicals and solvents used were of analytical grade.

Apparatus: A Shimadzu 260 UV double beam computerized self-recording spectrophotometer.

All spectroscopic investigations including UV, NMR, IR and elemental analysis were carried out at the micro-analytical centre Cairo University-Faculty of Science. pH-meter for measuring pH of the solution with glass indicator electrode. Orion Research Co.

Procedures:

A- preparation of thymol blue indicator reagent:

$1x10^{-2}$M solution of thymol blue prepared by triturating the specified amount of thymol blue 0.489 in 0.1N NaOH quantity sufficient (20 ml) till a

homgeneous paste is obtained; then the slurry is transferred into a measuring flask and completed to the volune (100 ml by distilled water).

B- Preparation of quinidine sulphate sample:

$1x10^{-2}$M solution of quinidine sulphate is prepared by dissolving the specified amount of the drug 0.783 g. in distilled water with aid of 0.1 N H_2SO_4 acid quantity sufficient till the quinidine sulfate dissolve. The solution is completed to volume (100 ml) by distilled water.

Methods of Assay:

A sample of 0.01-10.15 ml of the quinidine solution ($1x10^{-2}$M) was measured using micro automatic pipette syringe and normal by pipette into a measuring flasks and the half volume of thymol blue reagent into the same measuring flasks. 10ml buffer solution with pH=5.5 was added and the volume completed to mark (25ml) with methanol as solvent. The solution was measured against blank solution of thymol blue reagent and buffer at λ_{max}=231.5nm, λ_{max}=254 nm and at λ_{max}=334nm. Caliberation cure was prepared at λ_{max} 231.5 nm

Examination and preparation of ion-pair associates :

The ion pair associate was prepared by the addition of the aqueous quinidine sulphate solution to the thymol blue reagent at pH=5.5 and the formed precipitate was filtered, washed then dried and subjected to elemental analysis, NMR, IR and UV spectroscopy (Tables 1 &2).

RESULTS AND DISCUSSION

Quinidine sulfate aqueous solution when mixed with thymol blue reagent gives ion-associate which has deep red colour in solid form and yellow orange in aqueous-methanolic solution at pH=1.4-5.5 this red precipitate dissolves in excess dilute H_2SO_4 acid, methanol, chloroform, ethanol and slighly soluble in water, therefore miscible solvent with water is preferable than immiscible solvent. The ion associate have blue colour in basic medium at pH=12.85 using buffer system pH=12.85 . The blue associate is soluble in chloroform, ethanol and methanol.

Quinidine sulphate (in buffer) against buffer pH=4 shows absorption curve (1) plotted in figure (3) with λ_{max}=226 nm. In the same figure the indicator thymol blue (in buffer) is measured against buffer shows absorption curve (II) differ from (I) and with λ_{max} =215 nm. In the same figure the indicator thymol blue and the drug quinidine (in buffer) aganist buffer shows absorption curve (III) that differ from (I) with λ_{max}=231.5 nm. The difference is in the peak shoulders and the broadening of the absorption curve. Therefore the ion-associate absorption curve offer an advantage than the drug absorption in the pure form.

The ion-associates of the quinidine-thymol blue formed shows different asorption curves in different pH as shown in figure (4) which indicate that pH is influencing parameter.

The isolateted solid ion -associate complex:

The dried solid ion associate is subjected to elemental analysis and spectroscopic study.

Elemental analysis of the quinidine-thymol blue complex: shows %N=4.39%, %C=65.3-65.4 and %H=5.6-58% and shows that the blue ion associate is formed by 2:1 ratio; Fig. (5).

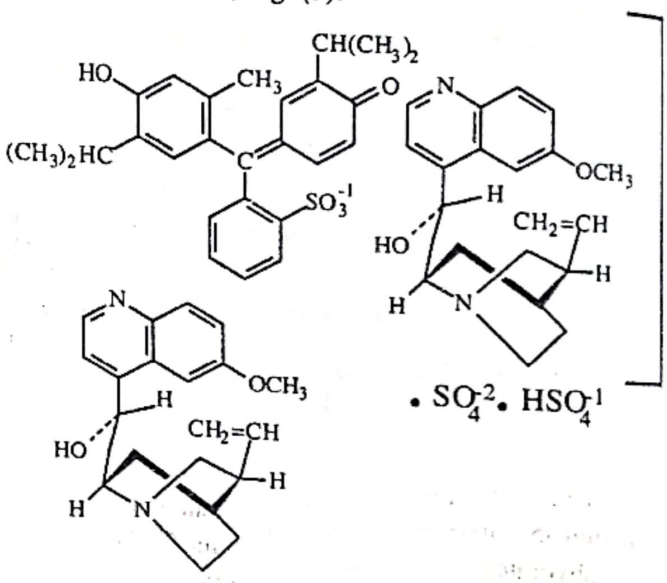

Fig (5) Structure of ion-associate of quinidine-thymol blue

I.R spectra was carried out using FT-IR 1650 (Perkin Elmer). Threshold 2.00% emission base, 18 peaks was found (Fig. 6,7) UV visible absorption bands of quinidine thymol blue ion associates shows absorption bands due to presence of) n=1 absorption and due to n = 2 max was found at 231.5 nm in methanol with = 15416. The UV-visible spectrum of quinidine-thymol blue complex were scanned in ethanol and methanol from 200 to 800 nm using DMSO-d_6 90 Varian spectrophotometer-double beam self recording scan speed 10 nm/min. Scan range (20 nm/cm) from 200-800 nm and using concentration 100mg/1ml and using Shimadzu 260 UV spectrophotometer double-beam-self recording, computerized. in ethanol λ_{max}=404 nm, λ_{max}=254nm. (ε_{404}=1688); [ε_{254}=4805]

Proton magnetic resonance spectra:

The pmr-proton magnetic resonance-spectra of quinidine-thymol blue complex ion associates in DMSO-d_6 was recorded on a Varian 60A-60 MHz NMR spectrometer using TMS as an internal reference Fig. (8).

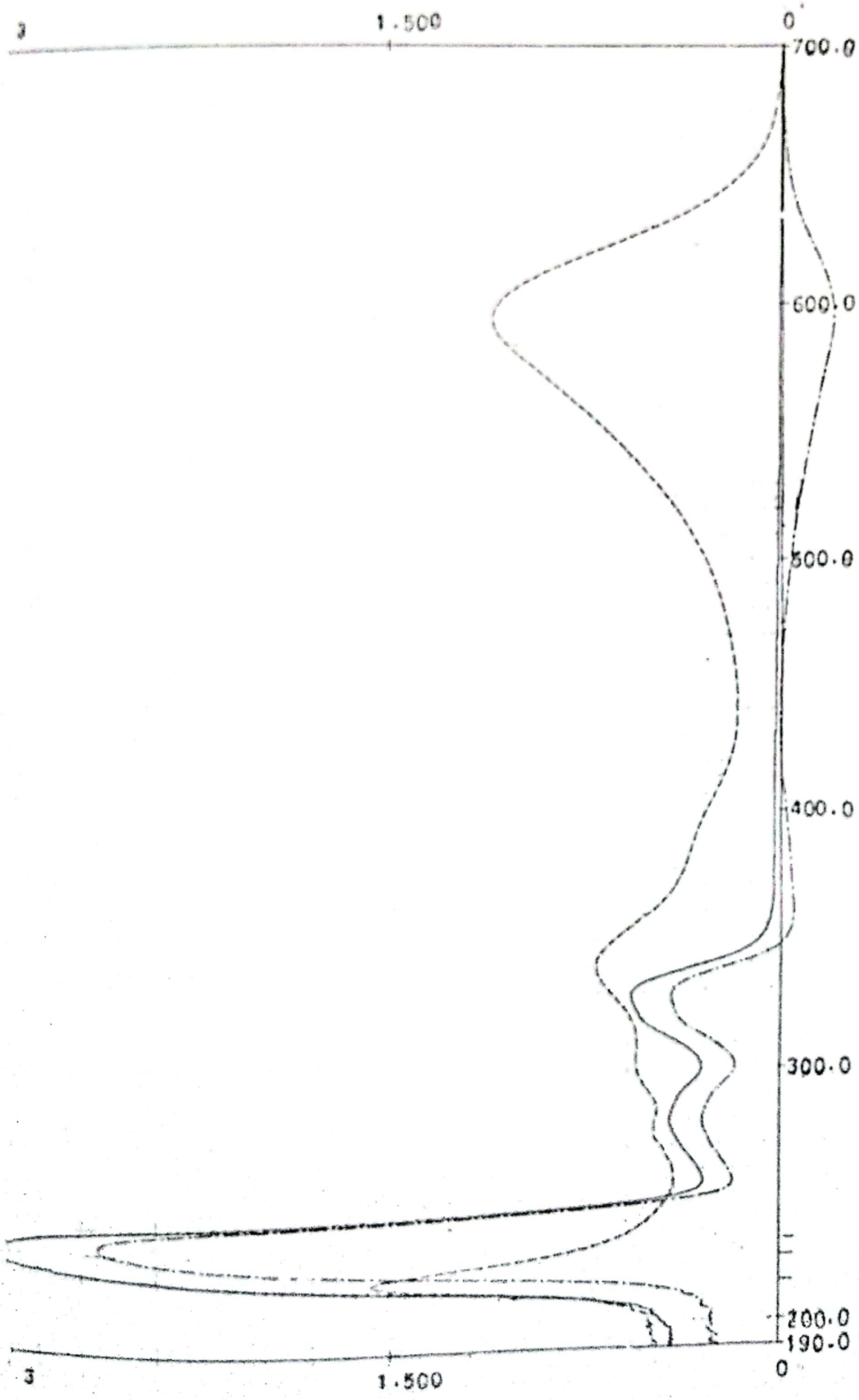

Fig (3) : I- The absorption curve of quinidine against buffer (—) at 226 nm.
II- The absorption curve of thymol blue against buffer(---) at 231.5 nm
III- The absorption curve of quinidine - thymol blue ion pair associates against buffer (·——·) at λ max =215 nm.

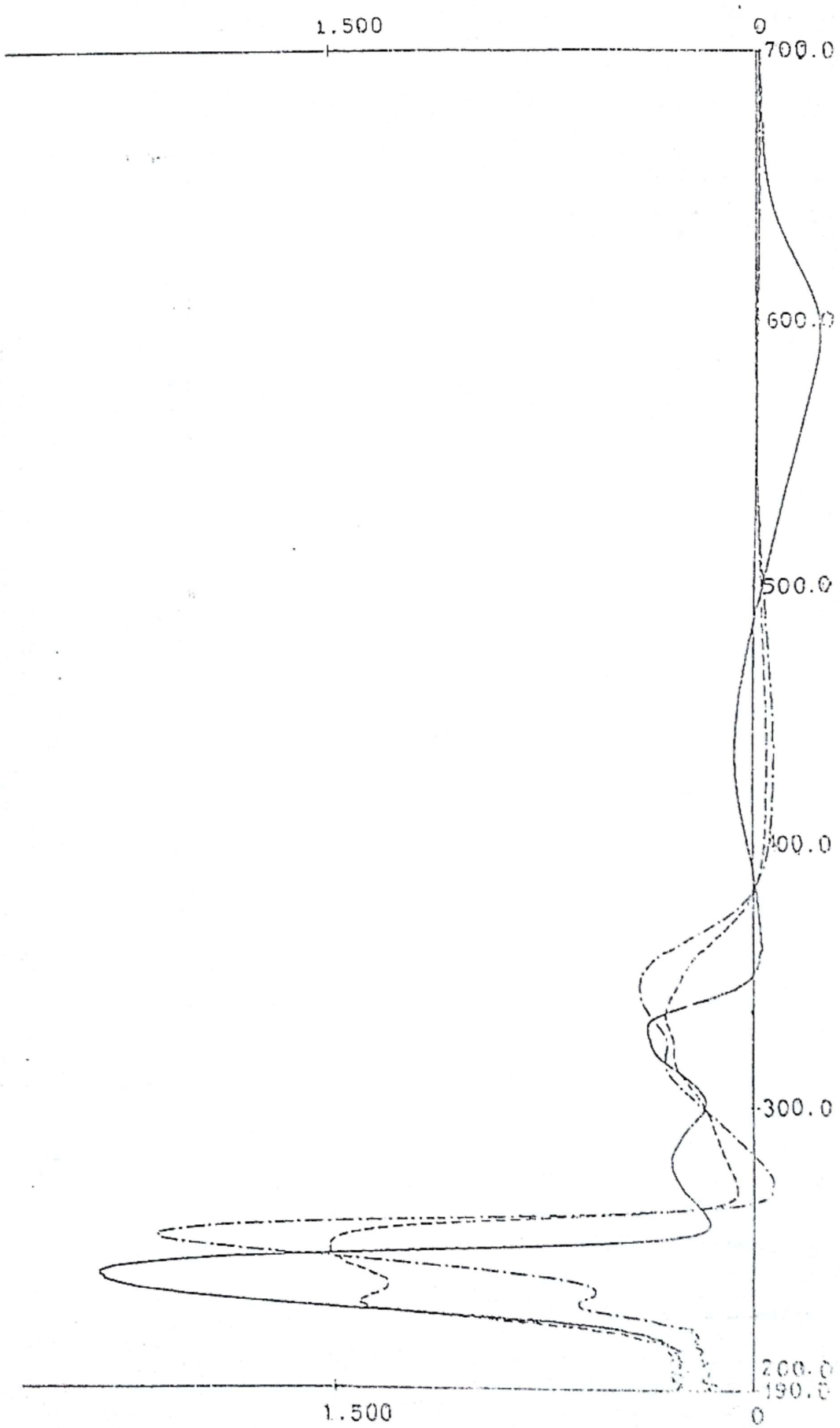

Fig (4) : The absorption curves, of quinidine-thymol blue ion-associates complex in different pH : at pH=8.5 (——), at λ max = 233 nm, at λ max=246 nm.

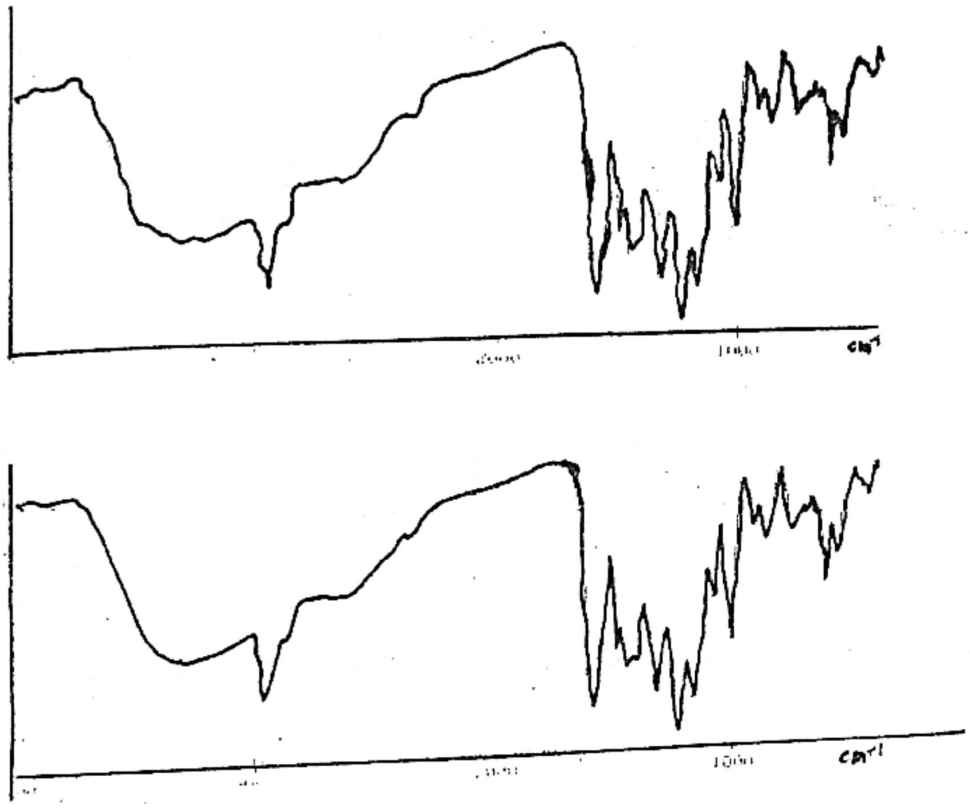

Fig (6) : The I.R. spectrum of quinidine sulfate- thymol blue ion associate.

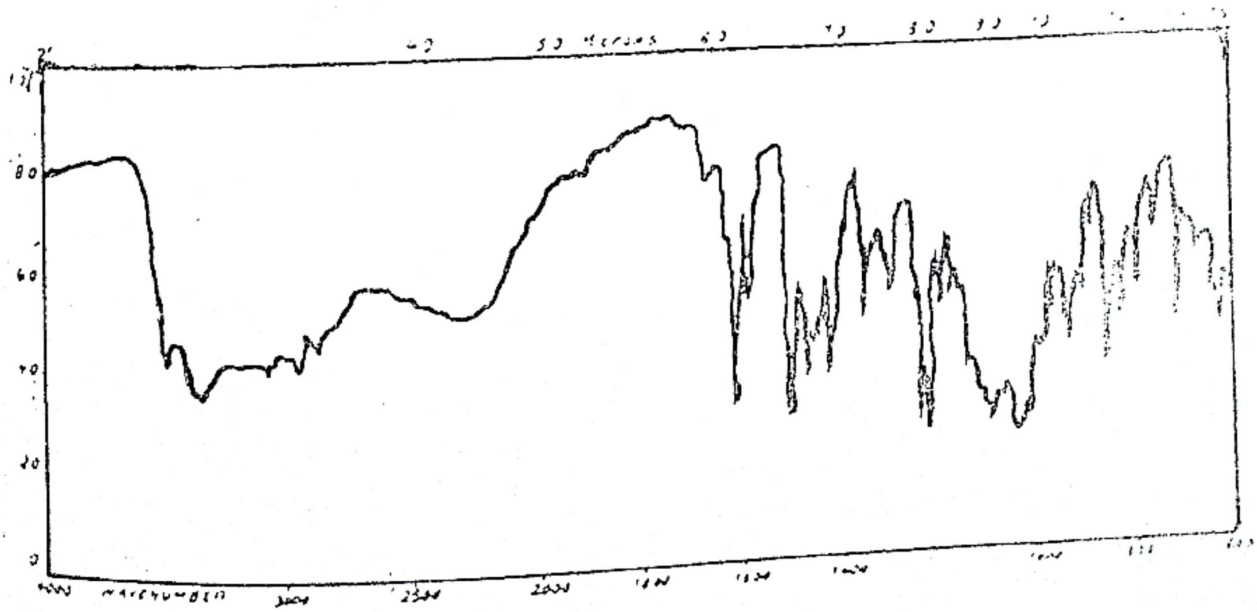

Fig (7) : The IR spectrum of quinidine sulfate as KBr Disc.

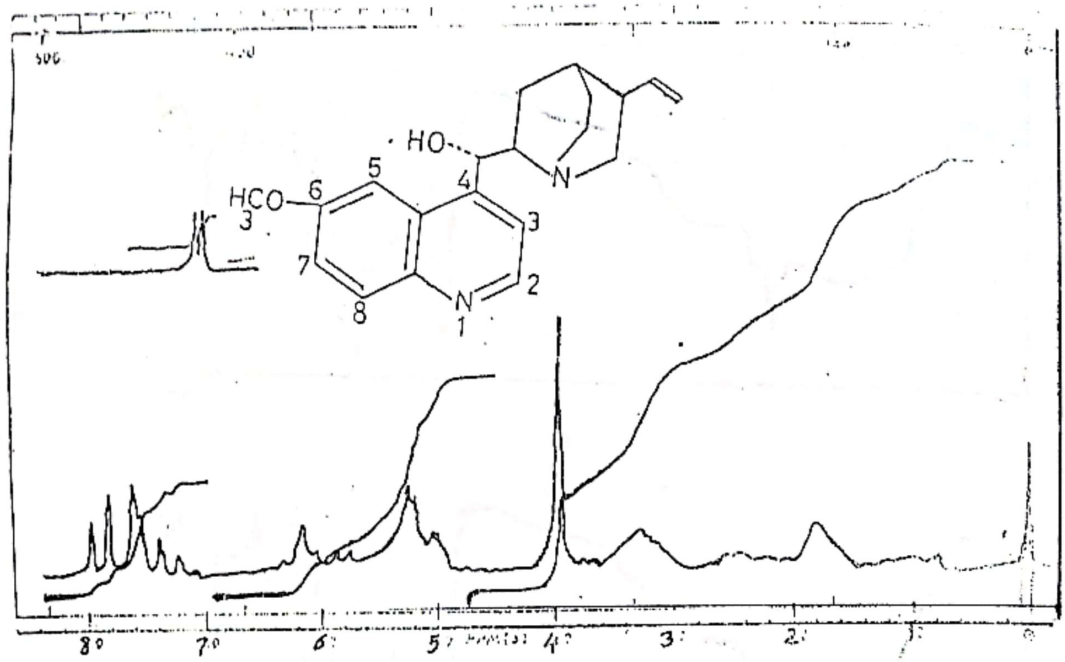

Fig (8) : PMR spectrum of quinidine sulfate- thymol blue ion associate.

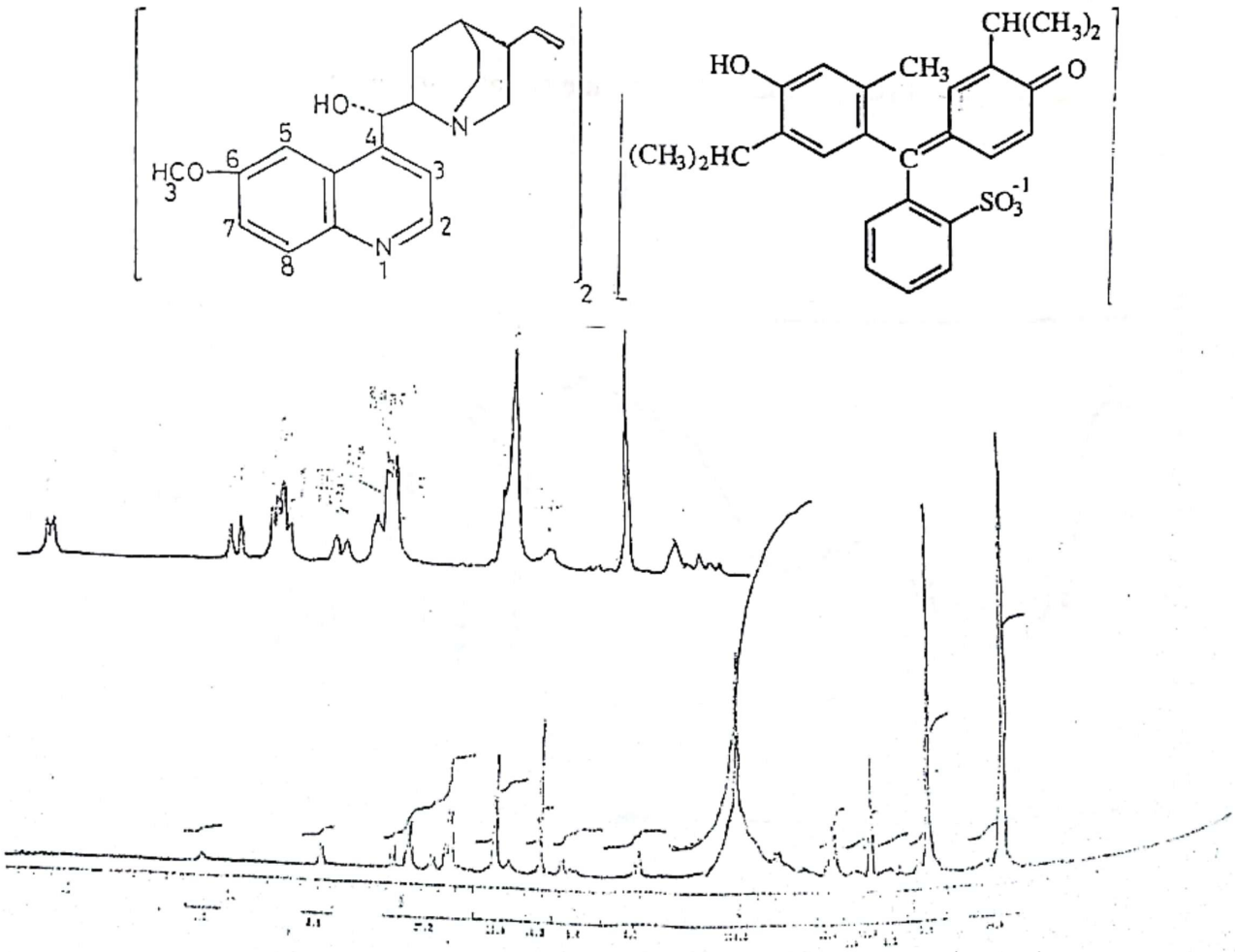

Fig (8) : PMR spectrum of quindine sulfate in DMSO-D_6

Zagazig J. Pharm. Sci., June 1997,
Vol. 6, No 1, pp 33-40

Table (1): IR Spectra of quindine-thymol blue complex ion associates.

Frequency (cm^{-1})	Peak Height percent	Group Assignment
3231.9	35.12	OH Stretch
2961.2	22.71	CH Stretch
1665.7	51.45	C=O Stretch
1595.9	14.28	aromatic
1501.3	36.29	$^{(+)}$NH group
1457.6	27.98	S=O Stretch
1088.7	51.48	S=O Stretch
1017.6	36.56	OH-CH, C-O Stretch
1337.1	18.98	
1175.8	16.87	$CH(CH_3)$, doublet
1242.3	4.32	C-O (H) St.
868.6	71.82	Asym. trisubstituted aromatic benzene.
919.0	76.44	alkenyl group ($CH-CH_2$)
731.1	78.21	0-di substituted aromatic benzene.
763.1	74.56	
6672	80.34	
614.5	56.36	C-S stretch
564.3	65.95	
432.9	86.73	

Table (2) : PMR spectrum of quindine-thymol blue complex ion associates .

Chemical Shift (δ) ppm	Splitting	Number of protons	Groups
8.96	(d)	1 H	quinoline ring
7.7	(d)	1 H	H_2 , H_3 , H_5
7.6	(bs)	3 H	H_7 , H_8
6.15-6.17	(m)	3 H	$-CH_2=CH$ Vinylic group
0.93	(d)	12 H	2 CH_3 of $CH(CH_3)_2$
1.9 1.8	(d)		
6.94-6.98	(d)	2 H	Aromatic 2, 3, 5, 6 tetrasubstituted benzene
4.0 7.90-7.89	(m) (d)	4 H	Aromatic 1, 2- disubstituted benzene ring
7.65-7.70	(d)	4 H	
2.8	(m)		methine H of $CH(CH_3)_2$
2.9	(m)		
10-40	(S)	1 H	OH-Phenolic
7.6-8	(m)	5 H	Aromatic quinoline

Calibration curve:

The quinidine-thymol blue ion pair associates in different concentration and at different pH were prepared. The following results were given and listed in table (4 & 5).

The ion-associates complex of quinidine- thymol blue, when dissolved in aqueous methanol gives the regression equatin :

$X = 0.03 + 1.25 \times 10^{-3} Y$ Y = absorption

$X = -0.0146 + 4.85 \times 10^{-3} Y$ X = concentration $\mu g\text{-}ml^{-1}$

The λ_{max} is 231.5 nm in a concentration range 40-200μgml^{-1}

The regression equation is calculated according to the analytical procedure mentioned in the methods of assay.

Table (3): Determination of the quinidine sulfate in tablet by using the proposed method.

µg/ml taken	µg/ml found	% recovery
1.691	1.670	98.83%
3.367	3.349	99.46%
4.635	4.619	99.66%
6.372	6.359	100.19%
8.612	8.603	99.9%

- The regression linear equation is
$Y = 0.0238 + 8.6838\ x$ for the ion associates in solution
- where Y = concentration µg/ml.
X = absorption r= 0.99999

Table (4) : The UV-Visible absorption spectrum of the quinidine thymol blue ion associates complex and quinidine sulfate.

Quinidine Sulfate		Quinidine-thymol blue ion assocciates complex	
λ max. at nm	ε epsilon	λ max. at nm	ε epsilon
226 nm	31320	404	1688
317.5 nm	5089.5	254	4805
331 nm	4581	231.5	15416

Table (5) : Beer's Law of the ion-associates at different pH and concentration.

Concentration (µg)	pH	λ_{max} at nm	ε epsilon
200-800 µg	2	335	6400
74-768 µg	3	250	8570
74-768 µg	4	220	
200-800 µg	5	316	1025
40-200 µg	5.5	231.5	15416

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تعيين كبريتات الكينيدين بالتحليل الطيفى من خلال تكوين زوج أيونى

ممدوح محمد فكرى متولى

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

فى هذا البحث تم استحداث طريقة بسيطة لتعيين كبريتات الكينيدين فى الأقراص تعتمد على تكوين زوج أيونى بين كبريتات الكينيدين والشيمول الأزرق عند معامل تركيز أيون الهيدروجين مقداره ٥ . ٥ فى محلول ميثانولى مائى.

كذلك تم تعيين درجة الامتصاص لزوج أيونى المتكون وتم قياس درجة تركيز الدواء وحسابها. ووجد أن المعدل الجزئى للأيون الزوجى ١:٢ مع تركيبه عامه هى [كينيدين]$^{+٤}_{٢}$. [الشيمول الأزرق]$^{-١}$ كب أ$^{-٢}_{٤}$ يد كب أ$^{-١}_{٤}$. بطريقة التحليل العنصرى.