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# SPECTROPHOTOMETRIC DETERMINATION OF SOME HALOGENATED 8-HYDROXYQUINOLINES WITH ZIRCONYL CHLORIDE

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## ABSTRACT

*A spectrophotometric method is described for the determination of 8-hydroxyquinoline (oxine) and three of its halogenated derivatives :5-chloro-7-iodo-8-hydroxyquinoline (clioquinol), 5,7-diiodo-8-hydroxyquinoline (iodoquinol) and 7-iodo-8-hydroxy-5-quinoline sulphonic acid (chiniofon). The method involves the use of zirconyl chloride in methanolic medium to give highly absorbing chelates with $\lambda_{max}$ at 364 nm (oxine), 367 nm (chiniofon), or 389 nm (clioquinol and iodoquinol). The molar ratio of the reaction was established and the characteristic features of the I.R. spectra of the chelates were discussed. The procedure described was applied successfully to the determination of the named compounds in dosage forms and the results obtained were comparable with official methods.*

## INTRODUCTION

Halogenated 8-hydroxyquinolines are widely used in many countries as antidiarrheal, antimycotic, antibacterial agents and in the treatment of inflamed skin conditions such as eczema, athletes foot and other fungal infections[1].

Several methods are availabe for their determination either in the pure form or in pharmaceutical dosage forms. These include : oxygen flask combustion (2), gravimetry (3,4) potentiometry (5), polarography (6), UV-spectrophotometry (2,3) colorimetery (7-17), IR-spectrophotometry (3), X-ray spectrometry (18), TLC (19,20), GLC (2,7,21, 22) and HPLC (23-25). Among the spectrophotometric metal ions have special importance in the determination of 8-hydroxyquinolines. Cupric (8), nickel (9), vanadium (10), ferric (11) and uranium (15) are generally used.

In the present report, the development of an analytical procedure based on the formulation of highly absorbing chelates with zirconyl chloride is reported. The method is simple, rapid, sensitive, reproducible and readily adaptable to unit dose analysis.

## EXPERIMENTAL

### Apparatus :

The spectrophotometric measurements were performed with Uvidec-320 spectrophotometer (JASCO, Tokyo, Japan) and Unicam SP 1025 Infrared spectrophotometer (England).

### Materials and Reagent :

Oxine (Merck), chiniofon (Riedel), clioquinol (Ciba) and iodoquinol (May and Baker) were used as working standards. Zirconyl chloride (BDH)

Zirconyl chloride solution-0.2% w/v in methanol. This solution is stable for 1 week at 4°C.

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Solvents used were of analytical grade (Prolabo, France). Pharmaceutical dosage forms analyzed were :

Enteroquin tablets (ADCO, Egypt) containing 250 mg of iodoquinol per tablet.

Furakin tablets (Misr Co. for Pharm. Ind., Egypt) containing 300 mg iodoquinol, 50 mg furazolidone and 80 mg chloroquine phosphate per tablet.

Entocid tablets (CID, Egypt) containing 200 mg iodoquinol, 200 mg phthalylsulphthiazole and 200 mg streptomycin sulphate per tablet.

Neo-carbotrina tablets (ADCO, Egypt) containing 125 mg iodoquinol , 125 mg phthalylsulphathiazole, 100 mg charcoal and 10 mg belladonna extract per tablet.

Percural-N suspension (The Nile Co, Egypt) containing 150 mg sulfaguanidine, 150 mg succinylsulphathiazole, 150 mg clioquinol, 10 mg dihydroperparine chloride and 0.1 mg homatropine methylbromide per 5 ml.

Enteroquin compound suspension (ADCO, Egypt) containing 125 mg iodoquinol, 150 mg phthalysulphathiazole and 150 mg sulphadimidine per 5 ml, in addition to bismuth carbonate, kaolin, homatropine methylbromide, vitamins $B_1$, $B_2$, $B_6$, nicotinamide and calcium pantothenate.

Viona lotion (The Nile Co, Egypt) 10 % iodoquinol.

Entocid compound powder (CID, Egypt) containing 72 mg diiodoquinol, 43.2 mg streptomycin sulphate, 282 mg sulphaguanidine, 72 mg sulphadiazine and 144 mg succinylsulphathiazole per packet 1.2 gm, in addition to pectin, kaolin, vitamins $B_1$, $B_2$, $B_6$, nicotinamide and methyl cellulose.

Locacorten-Vioform cream (Ciba, Switzerland) containing 3 % clioquinol + 0.02 % flumethazone pivalate.

Vioderm cream (Kahira, Egypt) 3% clioquinol.

Viopanthen cream (The Nile Co, Egypt) 3 % clioquinol + 5 % panthenol.

Preparation of Samples :

Powder forms : Dissolve about 20 mg, accurately weighed, of the working standard or sample in methanol and complete to 100 ml with the same solvent. Gentle heating is needed in cases of iodoquinol and clioquinol.

Tablets : Finely powder accurately weighed 20 tablets and weigh an amount of the powder equivalent to about 20 mg of the drug and dissolve in about 80 ml of methanol by heating on a water bath for 10 min . Cool the mixture, filter into a 100-ml volumetric flask, wash the residue 3 times each with 5 ml of methanol and complete to 100 ml with methanol.

Suspensions : Shake well and take a volume equivalent to about 20 mg of the drug in a conical flask. Add about 80 ml methanol, heat on a water bath for 10 min and then complete as directed under tablets.

Packets : Transfer an accurately weighed quantity of the compound powder, equivalent to about 20 mg of the drug into a conical flask . Extract by heating with about 80 ml methanol on a water bath for 10 min and then complete as directed under tablets.

Creams : Transfer an accurately weighed portion of the cream equivalent to about 20 mg of the drug. Extract with 50 ml of DMF-water mixture (4:1) by heating on a water bath for 10 min. Cool in ice for 10 min, allow to stand at room temperature, filter into a 100-ml volumetric flask, and complete to volume with methanol.

Analytical Procedure :

Pipette 5.0 ml of assay solution into a 25-ml volumetric flask. Add 5.0 ml of zirconyl chloride solution and mix thoroughly. Heat the mixture on a water bath at 60 $^{o}$C for 15 min and cool to room temperature. Complete with methanol to the mark, and measure the absorbance

of the solution at 364 nm (for oxine), 367 nm (for chiniofon) or 389 nm (for iodoquinol and clioquinol) against a blank similarly treated substituting zirconyl chloride solution with 5.0 ml of methanol. The concentration of the assay solution is found from a properly constructed calibration graph.

Construction of Calibration Graphs :

Dissolve 60 mg, accurately weighed, of the working standard in methanol and dilute to volume in a 100-ml volumetric flask. Dilute the solution quantitatively and stepwise to give a series of concentrations suitable for construction of the calibration graph in the linear range for each compound (Table 1), 5.0 ml of each solution being utilized for chelate formation with zirconyl chloride as directed under analytical procedure.

## RESULTS AND DISCUSSION

When zirconyl chloride is allowed to react in methanolic medium with 8-hydroxyquinoline and three of its halogenated derivatives, highly absorbing chelates are formed giving intense absorption in the vicinity of 364-389 nm . Absorption spectra of the four chelates are shown in Fig.1 and their spectral characteristics are summarized in Table 1.

Four factors were found to affect the absorption intensity of the resulting chelates : reagent concentration , reaction time, pH and diluting solvent. The optimum concentration of zirconyl chloride for mixmum absorption intensity was found to be 5 ml of 0.2 % solution per 25 ml of the assay solution (Fig. 2). Increasing reagent concentration did not affect the intensity.

Maximum absorption intensity could be achieved by heating the mixture of drug solution and zirconyl chloride on a water bath at 60°C for 15 min. Further heating did not affect the chelate formation. Effect of pH was also studied. In alkaline medium (above pH 7.5) precipitation of the reagent as hydroxide occured while in acid medium (below pH 6) decrease in absorption intensity occured.

The solvent used for dilution was found to affect the intensity of maximum absorption. The solvents studied were water, methanol ethanol, isopropanol, n-butanol, acetone , dioxane and pyridine. Table II shows that methanol gives the highest absorption intensity. The absorbance readings of the chelate solutions in all the solvents investigated were stable for at least 3 hr. When water was used as a diluting solvent, no precipitation occured either spontaneously or within 3 hours. Therefore, water can be used also for dilution.

Beer-Lambert law was obeyed by the four compounds tested in the concentration ranges given in Table 1. The molar absorptivities were calculated (Table 1) and ranged from $2.6 \times 10^3$ to $6.9 \times 10^3$. The quantitative parameters of the assay are presented in Table I.

To examine the precision of the procedure, 10 determinations were made on the same solution (Final concentration 40 mc/ml) of oxine and its halogenated derivatives. The following relative standard deviations were obtained : ± 0.88 % for oxine ± 0.45 % for clioquinol, ± 0.80 % for iodoquinol and 0.67 % for chiniofon.

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Investigation of the molar ratio of each of the four compounds and zirconyl chloride shows that the compound-metal ratio is 4:1 (Fig 3). Another strong evidence for chelate formation was given by the infrared spectrum of the reaction product of diiodoquinol with zirconyl chloride under the assay conditions. A strong peak at 9 μm appeared in the I.R spectrum of the chelate and not in the spectrum of the free compound. This peak is due to a bond in the 5,7-diiodo-8-quinolinate anion, whose vibration frequency is modified by chelation. This can serve as a characteristic peak for identification of the bond between the metal ion and the 8-quinolinate anion through oxygen[26].

A broad peak was also observed around 13.5 μm which was reported previously for cobalt, nickel, magnesium and bismuth chelates with 8-hydroxyquinoline[26,27].

Table III shows the results obtained for the determination of oxine, clioquinol, iodoquinol and chiniofon in pure and dosage forms, both by means of the proposed method and by the official methods. Tablet excipients such as starch talc, soluble saccharin and gelatin do not interfere in the assay. Also, substances that are likely to be present with halogenated 8-hydroxyquinolines in tablets, suspensions, ointments, creams and compound powders such as furazolidone, chloroquine phosphate; phthalylsulphath iazole, sulphaguanidine, sulphadimidine, streptomycin sulphate and homatropine methylbromide do not interfere in the determination. The proposed procedure is rapid, simple and suitable for routine quality control analysis. It has two advantages over methods utilizing other chelating metals. First, no interference from sulphadiazine, sulphathiazole, succinyl sulphathiazole or phthalylsulphathiazole, which form stable complexes with cupric ions. Second, stability of zirconium chelates towards water, traces of which decompose the ferric chelate.

Table I: Spectral characteristics and quantitative parameters for the chelates of 8-hydroxyquinolines with zirconyl chloride.

| Compound | Spectral characteristics | | | Quantitative parameters* | | |
|---|---|---|---|---|---|---|
| | $\lambda_{max}$ | $\varepsilon_{max} \times 10^{-3}$ | Linear range µg/ml | a | b | r |
| Oxine | 364 | 2.62 | 10-60 | -0.0086 | 0.0181 | 0.9948 |
| Chiniofon | 367 | 6.92 | 10-60 | 0.0101 | 0.0197 | 0.9997 |
| Clioquinol | 389 | 3.88 | 10-80 | 0.0095 | 0.0127 | 0.9996 |
| Iodoquinol | 389 | 4.13 | 10-80 | 0.0458 | 0.0104 | 0.9970 |

* a= intercept of regression line; b= slope of regression line and r= correlation coefficient.

Table II: Effect of solvent on the absorption intensity of zirconium chelate of clioquinol

| Solvent | Absorbance at 389 nm* | Solvent | Absorbance at 389 nm* |
|---|---|---|---|
| Water | 0.423 | n-butanol | 0.476 |
| Methanol | 0.518 | acetone | 0.476 |
| Ethanol | 0.486 | dioxan | 0.188 |
| Isopropanol | 0.490 | pyridine | 0.391 |

* Final concentration 40 µg/ml.

Table III: Analysis of 8-hydroxyquinolines in pure and dosage forms by the proposed and official methods

| Sample | Recovery% ± SD. | |
|---|---|---|
| | proposed method | Official method |
| Oxine | 99.70 ± 0.88 | |
| Clioquinol | 99.99 ± 0.45 | 99.79 ± 1.29* |
| Iodoquinol | 101.76 ± 0.80 | 101.79 ± 0.88** |
| Chiniofon | 100.35 ± 0.67 | 100.30 ± 1.42** |
| Enteroquin tablets | 102.88 ± 0.56 | 101.25 ± 1.51** |
| Furakin tablets | 98.99 ± 0.34 | |
| Entocid tablets | 100.77 ± 0.87 | |
| Neo-carbotrina tablets | 101.05 ± 0.91 | |
| Percural-N suspension | 101.65 ± 0.40 | |
| Enteroquin compound suspension | 98.00 ± 0.21 | |
| Viona lotion | 102.34 ± 1.87 | |
| Entocid compound powder | 100.33 ± 0.21 | |
| Locacorten vioform cream | 100.00 ± 1.00 | 101.18 ± 1.00* |
| Vioderm cream | 101.11 ± 0.44 | 101.83 ± 1.30** |
| Viopanthen cream | 99.44 ± 0.76 | |

* B.P. 1980 ** B.P. 1958.

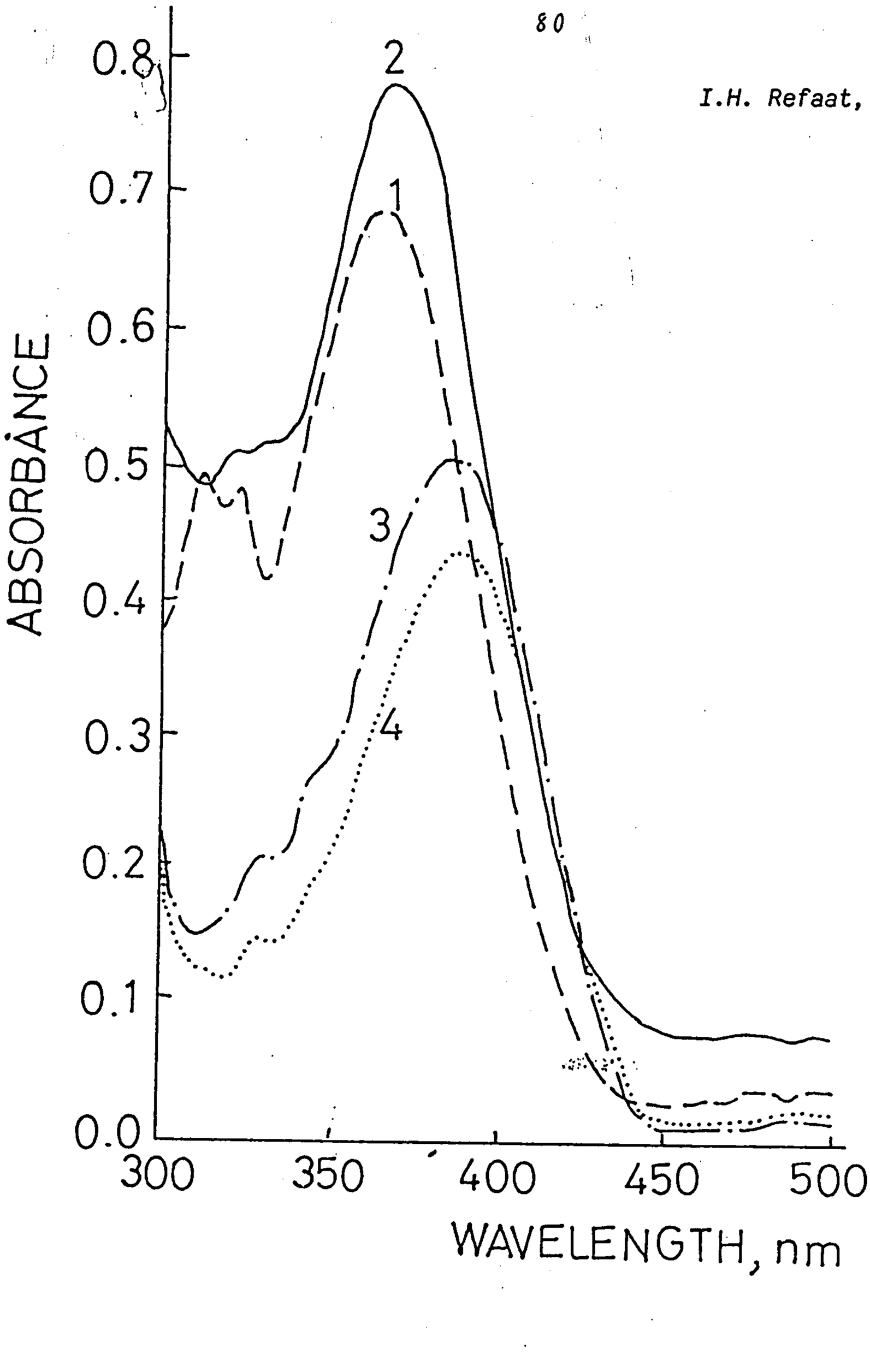


Fig. 1: Absorption spectra of the chelates of zirconyl chloride with (1)oxine,(2)chiniofon,(3)clioquinol and (4) iodoquinol. Final concentration 40μg/ml.

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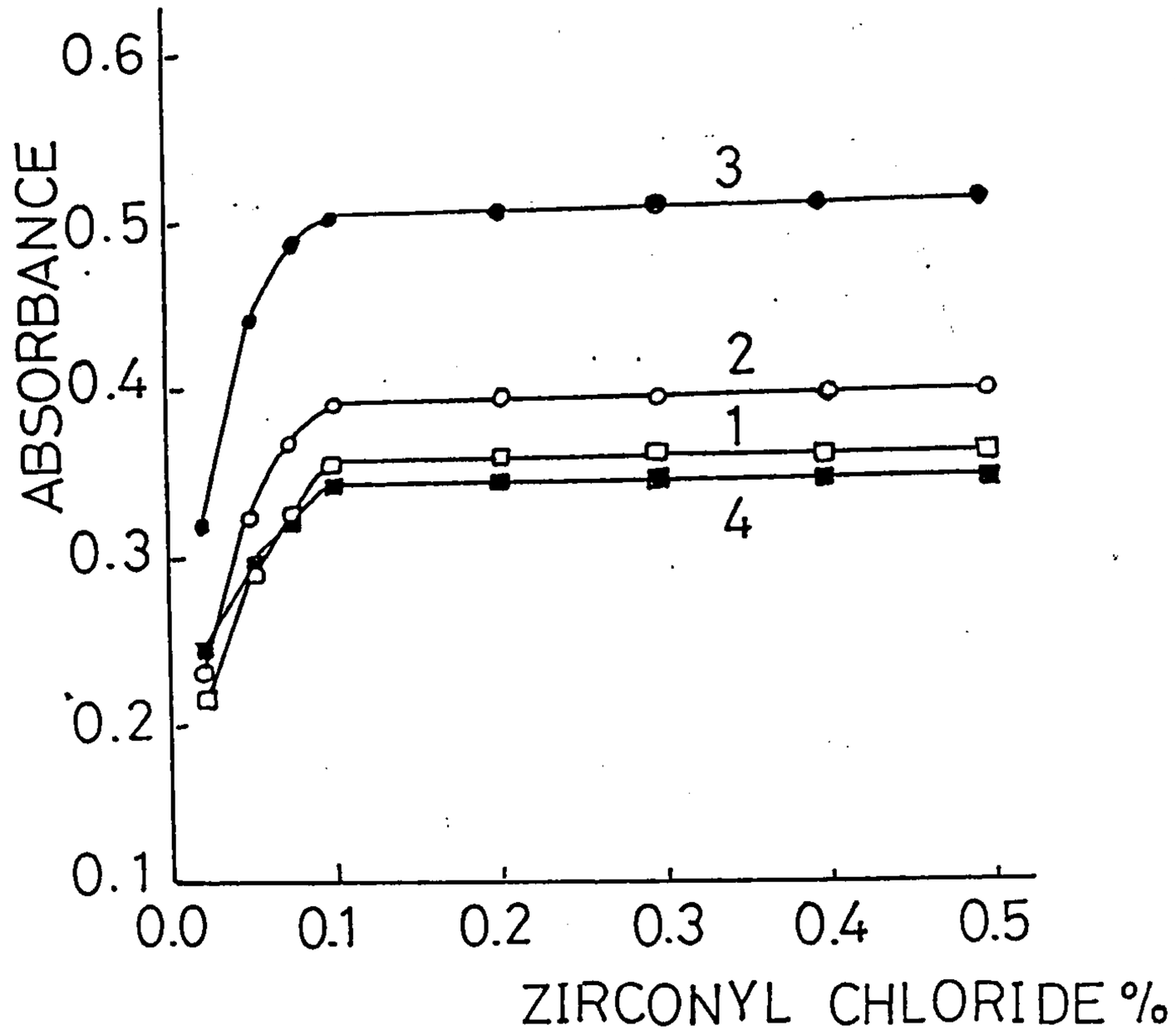


Fig. 2: Effect of reagent concentration on absorption intensity of the zirconium chelates of:(1)oxine, (2)chiniofon,(3)clioquinol and (4)iodoquinol.

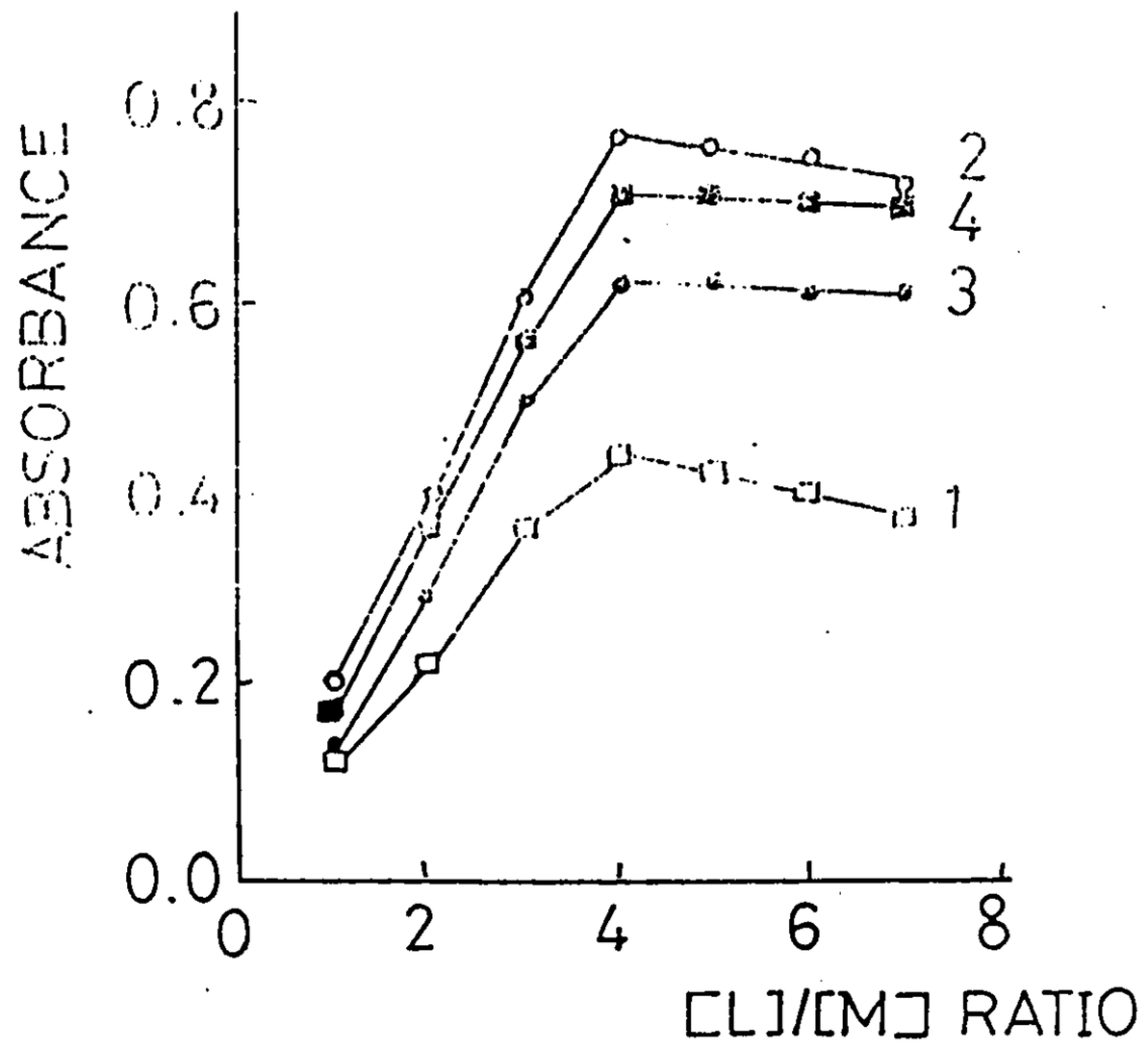


Fig. 3 : Molar ratio plots for the zirconium chelates of: (1) oxine, (2) chiniofon, (3) clioquinol and (4) iodoquinol.

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# التقدير الطيفى لبعض مشتقات
# ٨ ـ هيدروكسى كينولين الهالوجينية بواسطة كلوريد الزركونيل

ابراهيم حسن رفعت ـ ميشيل ايليا القمص ـ حسن حسن فرج ـ نوال على الرباط
قسم الكيمياء الصيدلية ـ كلية الصيدلة ـ جامعة أسيوط ـ أسيوط

فى هذا البحث تم استحداث طريقة طيفية للتقدير الكمى للمركبات الاتية :
٨ ـ هيدروكسى كينولين ( أوكسين ) ، ٥ ـ كلورو ـ ٧ ـ يودو ـ ٨ ـ هيدروكسى كينولين (كليوكوبينول ) ٥ر٧ ثنائى يودو ـ ٨ ـ هيدروكسى كينولين (يودوكوينول ) ، ٧ ـ يودو ـ ٨ ـ هيدروكسى ـ ٥ ـ كينولين حمض السلفونيك (شينيوفون ) . وتعتمد الطريقة على استعمال كلوريد الزركونيل فى وسط من الكحول الميثيلى لتكوين مركبات معقده ذات درجة امتصاص عاليه للضوء ويتم قياس درجة امتصاص الضوء عند أطوال الموجات الاتيه :
٣٦٤ ن م ( بالنسبة للاوكسين ) ٣٦٧ ن م ( بالنسبة للشينيوفون ) ، ٣٨٩ ن م ( بالنسبه للكليوكوينول واليودوكوينول ) .

وقد وجد أن درجة الامتصاص الجزيئية للمركبات المعقده الناتجة من التفاعل هى : ٢٦٠٠ ، ٦٩٠٠ ، ٣٩٠٠ ، ٤١٠٠ للاوكسين والشينيوفون والكليوكوينول واليودوكوينول على التوالى . وقد وجدت علاقه خطيه بين التركيز ودرجة امتصاص الضوء فى حدود التركيزات الاتية :
١٠ ـ ٦٠ مكجم / مل ( بالنسبة للاوكسين والشينيوفون ) ، ١٠ ـ ٨٠ مكجم / مل ( بالنسبه للكليوكوينول واليودوكوينول ) .

وقد تم فصل المركب المعقد الناتج من يودوكوينول كمثال . وتمت دراسه امتصاصه للاشعه تحت الحمراء بالمقارنه مع المركب الاصلى كما ثبت أن النسبة الجزيئية بين الزركونيوم ومشتق ٨ ـ هيدروكسى كينولين هى ١ : ٤ .

وقد تم تطبيق الطريقة بنجاح على الاقراص والاشربة والمراهم والمساحيق التى تحتوى على الكليوكينول واليودوكوينول وقد وجد أن النتائج مطابقة لنتائج طرق دساتير الادوية .

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