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Derivative UV Spectrophotometric Analysis of Some Pharmaceutically Important Halogenated 8-Hdroxyquinoline Derivatives via Their Pd (II)-Complexes

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Abstract

A derivative UV-spectrophotometric method was developed for the analysis of two halogenated 8-hydroxyquinoline derivatives; iodochlorohyroxyquin (I) (Clioquinol) and di-iodohydroxyquin (II) (iodoquinol). The proposed method depends on the formation of Pd II-ligand complexes in methanol-acetonitrile mixture, which exhibits an UV-spectra with an appreciable value of ε. Zero order (^{0}D), first order (^{1}D) and fourth order (^{4}D) derivative measurements were applied for the quantitative analysis of the drugs. A linear correlation was established between absorbance and concentration for the ^{0}D mode in the range 2-14μg ml^{-1} and 2-18 μ g ml^{-1} for (I) and (II) with average % recoveries of 99.83 ± 1.04 and 99.91±0.64 respectively. Also a linear correlation was obtained between the trough of the peak and concentration for ^{1}D mode in the range of 0.16-0.8 μgml^{-1} for both drugs with average % recoveries of 100.23 ± 1.04 and 100.18 ± 1.14 for (I) and (II) respectively. Besides, the ^{1}D mode was successfully applied for the analysis of binary mixture containing both (II) and metronidazole (III) in tablet formulations. The average % recoveries were 99.42± 0.358 and 98.81 ± 0.973 for (II) and (III) respectively. In the ^{4}D mode, a linear correlation was attained between the amplitude of the peak and concentration in the range 0.1-0.8 μg ml^{-1} for (I) and (II), with average % recoveries of 99.6 ± 0.84 and 100.06 ± 0.98. The limit of detection (LOD) was 2.1ng ml^{-1} and 2.3ng ml^{-1} for (I) and (II) respectively. The suggested method was successfully applied for accurate, sensitive and selective analysis of the studied drugs in bulk and single or combined dosage forms with average % recoveries of 99.74 ± 0.480–99.84 ± 0.515 and 99.44 ± 0.71–100.58 ± 1.06 for (^{1}D) and (^{4}D) respectively. The results obtained were favorably compared to those given by a reference method.

Keywords: Derivative spectrophotometry, halogenated 8-hydroxyquinolines, Pd (II)-complexes, clioquinol, iodoquinol, dosage forms.

1. Introduction

Halogenated derivatives of 8-hydroxyquinoline have been widely used in treatment of various intestinal and vaginal infections. Greatest success was achieved with iodinated 8-hydroxyquinolines. Among the commonly used drugs are cliquinol (I) and iodoquinol (II). Acomprehensive study was reviewed earlier [1].

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Various techniques have been utilized for the analysis of the studied compounds, either *per se* or in dosage forms. These techniques include; spectrophotometry [2-4], polarography [5,6], TLC. [7,8] and HPLC in pharmaceutical preparations [9, 10] or in biological fluids [11,12].

8-Hydroxyquinoline derivatives have a great tendency to chelate with various metal cations. The complexation of (I) and (II) with Nb (V) [13], VO^{+2} [14], Co (II) [15], Cu (II) [16] and Sn (IV) [17] was investigated using different spectrophotometric techniques. Recently, Pd (II) was reported to form binary and ternary complexes with many drugs [18-26]. Hitherto, there are no reports on the use of Pd (II) for the analysis of the studied compounds via Zero order derivative spectroscopy. This led us to study the reaction of these halogenated 8-hydroxyquinolines with Pd (II) in an attempt to develop a simple, sensitive and selective method for their evaluation in bulk and in single or combined dosage forms.

2. Experimental

2.1. Apparatus

A Shimadzu UV-1601 PC, UV-visible, double beam spectrophotometer with matched 10mm path-length quartz cells, was used. The derivative conditions were: Delta lambda of 8nm, scaling factor of 30 and 3000 for ^1D and ^4D measurements respectively. The pH-Meter from Orion Research, model SA 210, with its combined electrode, was utilized.

2.2. Materials and Reagents

- Clioquinol (I) iodoquinol (II) and metronidazole (III) were kindly provided by Memphis Chemical Co. (Cairo, Egypt) and were used as received.
- Tablets containing these drugs were kindly provided by Chemical Industries Development (CID), (Giza, Egypt) and South Egypt Drugs Industries Company (SEDICO). Other pharmaceutical preparations were obtained from commercial sources.
- Palladium chloride (Merck): 0.1% aqueous solution was prepared by dissolving an accurately weighed 0.1 g in 5 ml de-ionized distilled H_2O containing 0.5 ml of concentrated HCl, warming the mixture in water-bath. The solution was cooled and diluted with water in a 100-ml measuring flask. 2×10^{-4} M solution was prepared by the same method:
- Methanol and acetonitrile: AR grade (BDH).

2.3. Stock Solution of (I) and (II): 0.2 mg ml^{-1} and 2×10^{-4} M solutions were prepared in methanol.

2.4. Standard Solution of (I) and (II): 100 μg ml^{-1} and 10 μg ml^{-1} solutions were prepared by serial dilution of the stock solution with methanol.

2.5. Procedure for calibration curves

Calibration curves were constructed using standard solutions containing 100 μg ml^{-1} for ^{0} D and 10 μg ml^{-1} for ^1D and ^4D modes. Aliquot volumes containing suitable

concentrations from each drug for ^0D, ^1D and ^4D modes were transferred into a 10ml measuring flask. 1 ml of Pd (II) 0.1% was added and further diluted to the mark with methanol/acetonitrile mixture. The solution was mixed well and the absorbance was measured for ^0D at 282 nm, and 285 nm, the trough of the peak for ^1D at 292nm and 295 nm and the amplitude of the peak for ^4D at 284 nm and 287 nm against a reagent blank prepared simultaneously for (I) and (II) respectively.

2.6. Procedure for dosage forms

2.6.1. Tablet Formulations

Twenty tablets were weighed and pulverised. An accurately weighed amount of the powder equivalent to 10.0 mg of each drug was extracted with 3 × 25 ml of methanol by sonnication for 5 minutes. The extracted solution was filtered into a 100-ml measuring flask, completed to the mark with the same solvent and mixed well. A suitable dilution was made to prepare a working solution of 10 μg ml^{-1}. The procedure under 2.5. was followed.

2.6.2. Ear drops

1 ml of ear drops (10 mg ml^{-1}) was transferred into a 100 ml measuring flask and completed to the mark with methanol. The solution was mixed well and a suitable dilution was made to prepare a working solution of 10 μg ml^{-1}. The procedure under 2.5. was followed.

2.6.3. Cream

The contents of five containers were mixed and a sample equivalent to 10.0 mg of the drug was accurately weighted into a 50-ml beaker. The sample was heated on water – bath for 5 minutes and extracted by sonication with 3x25ml of methanol, the solution was cooled in ice and filtered into a 100-ml measuring flask. The filtrate and washings were completed to the mark with the same solvent and mixed well. A solution containing 10μg ml^{-1} was prepared by dilution and the procedure under 2.5. was followed.

The concentration of (I) or (II) was calculated either from ^0D, ^1D or ^4D calibration curves or the corresponding regression equations.

2.7 Statistical analysis

The use of exact probability of getting a value as extreme or more extremes than the observed if null hypothesis is true, is more exact than using an observed statistics of testing its significance. In this instance the computed value of the test statistic is given along with the computed value of p. Results are expressed as mean values ± SD. Statistical differences were evaluated by variance analysis (32). The threshold of significance was $p<0.05$. The results are shown in table (1) indicate that there is no significant difference between the performance of the proposed and the reference methods, regarding accuracy and precision.

3. Results and discussion

3.1. Spectral characteristics of Pd (II) - complexes of the studied compounds.

Fig. 1 (A, B) for Zero order-absorption spectra shows absorption maxima at λ 252 nm for I and 254 nm for (II) which was shifted to 282 nm and 285 nm upon addition of Pd (II).

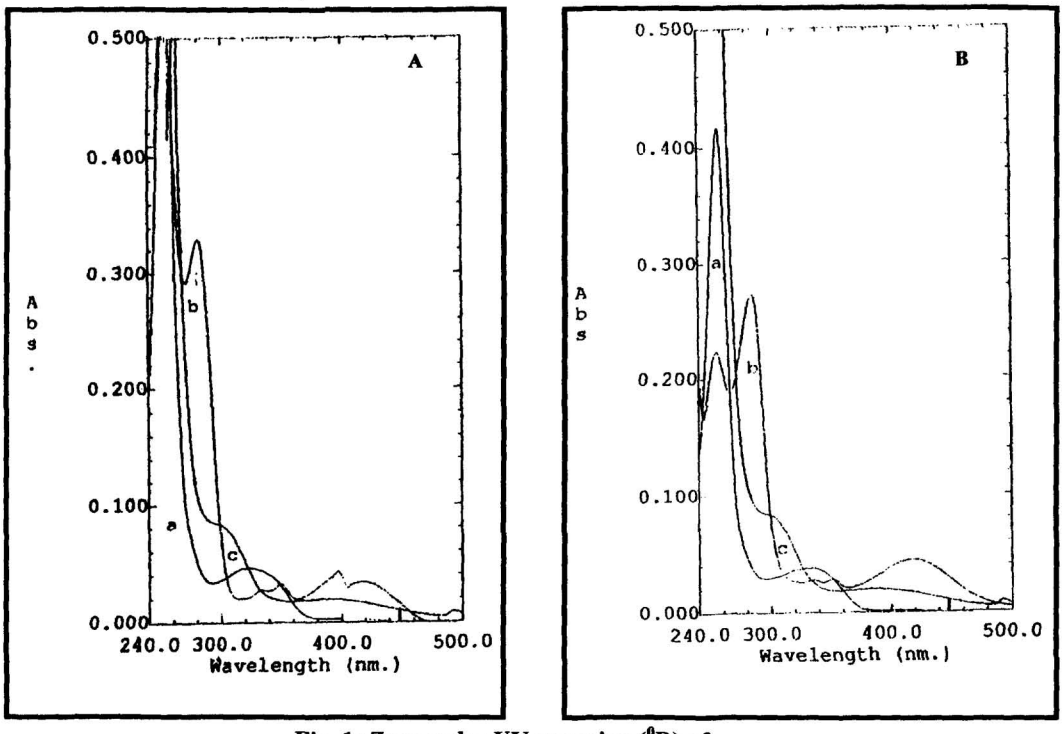

Fig. 1: Zero-order UV-scanning (^{0}D) of

A. Clioquinol
a- Clioquinol (5 μg ml^{-1})
b-Pd (II)– clioquinol complex
5 μgml^{-1} clioquinol, 0.1 mg ml^{-1} Pd (II).
c- Pd (II) (0.1 mg ml^{-1}).

B. Iodoquinol
a- Iodoquinol (5 μg ml^{-1})
b-Pd (II)– iodoquinol complex
5 μg ml^{-1} iodoquinol 0.1 mg ml^{-1} Pd (II).
c- Pd (II) (0.1 mg ml^{-1}).

A large number of preliminary tests were conducted to select the most convenient order of the derivatives and working range. Standardization of derivative spectrophotometry [27] required the establishment of optimum instrumental conditions such as derivative order, ordinate, differential wavelength, scan speed, noise attenuation and scaling factor. The optimum parameters were selected according to the best profile, and sensitivity of the spectral absorption permitted a better interpretation of substance behavior. First mode (^{1}D) and fourth mode (^{4}D) derivatives proved to be maximal. The ordinate axis was + 0.1-0.11 absorbance nm^{-1} (or nm^{-4}) and the differential wavelength employed was 8 nm with scaling factors 30 and 3000 for (^{1}D) and (^{4}D) respectively.

Fig.2 (A-D), shows (^{1}D), (^{2}D), (^{3}D) and (^{4}D) modes for (II) -as a model example- with a scaling factors of 30,100, 200, and 3000 respectively. It is evident that (^{1}D) and (^{4}D) modes have the best resolution of (^{1}D) and (^{4}D) absorption peaks between complex, drug and reagent.

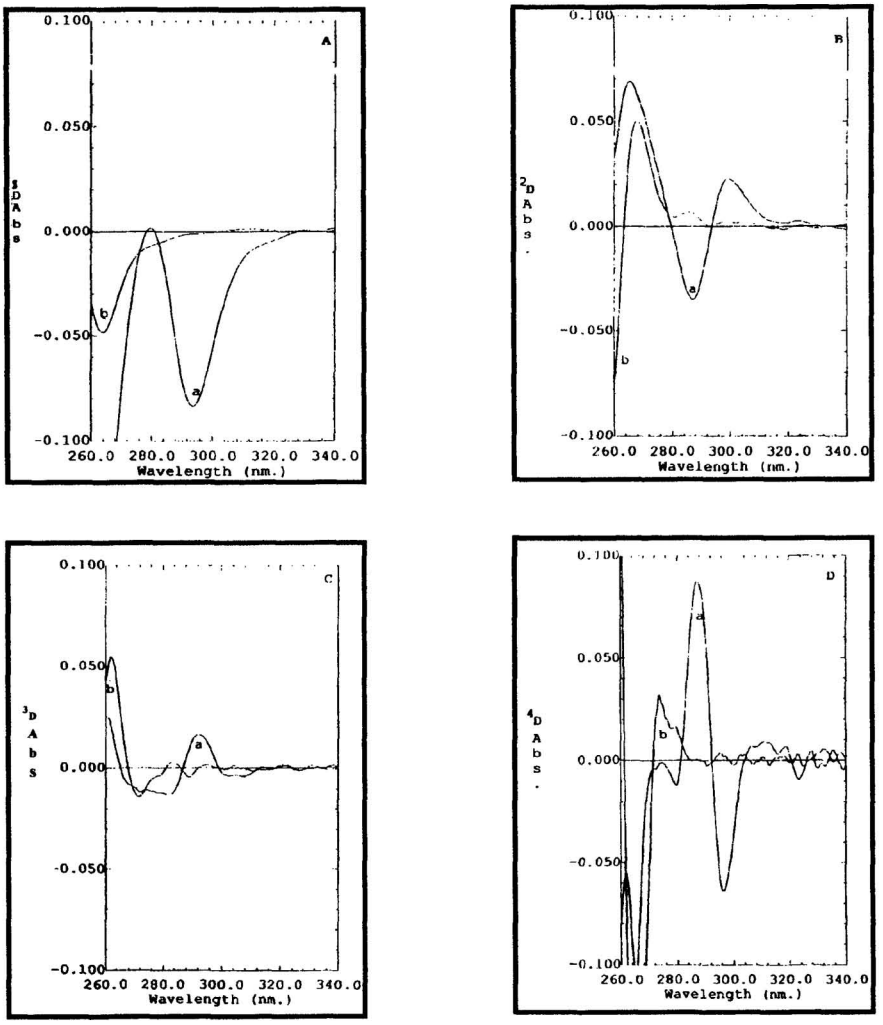

Fig. 2: Derivative UV spectra of Pd (II) – iodoquinol complex

A. First order (^{1}D). B. Second order (^{2}D).

C. Third order (^{3}D). D. Fourth order (^{4}D).

a. Pd (II) – clioquinol complex; 0.96 μg ml^{-1} clioquinol, 0.1 mg ml^{-1} Pd (II).

b. Iodoquinol (0.96 μg ml^{-1})

3.2. Optimization of the reaction conditions

3.2.1. Effect of solvent

The effect of solvent on the formation of the complexes between Pd (II) and (I) or (II) was studied by absorbance measurements. The results obtained show that the complexes have limited solubility in the aqueous medium, and then precipitated. In trials to select a suitable solvent for the complexes; $CHCl_3$, $CH2Cl_2$, CH_3OH, CH_3CN and in mixtures of different ratios were used. It was found that, the appropriate solvent for complex formation was a mixture of CH_3OH: CH_3CN (9:1).

3.2.2. Effect of palladium chloride concentration

The effect of different concentration of Pd (II)-chloride on the development of the formed complexes was studied; 1 ml of 0.1% solution was optimum for complete formation of the complex.

3.2.3. Effect of Time

The effect of time on the absorbance of Pd (II) -drug complex was investigated by measuring the absorbance of the complex solution at 5 minute intervals. The results revealed that maximum absorbance was obtained after 5 minutes and remained unchanged for at least one hour.

3.3. Stochiometry of the reaction

The composition of Pd II-drug complexes was determined by applying Job's method of continuous variation [28], Mole ratio method [29] and limiting logarithm method [30]. A molar ratio of 1:2.12, 1:2 and 1:2.17 for Pd II-drug was obtained by the three methods respectively. So, a structural formula of Pd $(L)_2$ complex can be proposed.

3.4. Quantification and linearity of Pd (II) - complexes.

3.4.1. Zero-order [^{0}D] analysis

^{0}D Investigations were made to choose the suitable concentration range for analysis. It was found that, the absorbance - concentration relationships for I and II at 282 nm and 285 nm were rectilinear over the range 2-14 μg ml^{-1} and 2-18 μg ml^{-1} with average % recoveries of 99.83 ± 1.036 and 99.91 ± 0.637 for (I) and (II), respectively.

The regression equations were:

$^0DA = 0.009 + 0.0697\ C_I$ (r = 0.99981)

With $A^{1\%}_{1cm}$, 697 and ε, 2.1×10^4 L mol^{-1} cm^{-1}.

$^0DA = 0.00503 + 0.0545\ C_{II}$ (r = 0.99999)

With $A^{1\%}_{1cm}$, 545 and ε, 2.2×10^4 L mol^{-1} cm^{-1}.

Where ^{0}DA is the absorbance and C is the concentration in μg ml^{-1}.

Statistical analysis of ^{0}D data for (I) and (II) gave standard deviation of residual ($S_{y/x}$): 7.2×10^{-3} and 2.4×10^{-3}, standard deviation of slope (S_b): 6.6×10^{-4} and 1.5×10^{-4} and standard

deviation of intercept (S_a): 5.7×10^{-3} and 1.6×10^{-3}, the Er % was 0.39.3% and 0.213% for the two drugs, respectively.

3.4.2: First order [^{1}D] analysis

For the analysis of either drugs, (^{1}D) is useful in providing measurements through trough of peaks as they correspond to shoulders or inflections previously seen in the (^{0}D) spectra. In this work, Fig. 3 (A, B), the (^{1}D) peak of the complexes formed with Pd (II) at 292 nm and 295 nm for (I) and (II) respectively was utilized for their analysis in pure form. The linear range of concentration for the analysis was 0.16-0.8 μg ml^{-1} with average % recoveries 100.23 ± 1.04 and 100.18 ± 1.14 for (I) and (II), respectively.

The regression equations were:

$^1DA = -0.0023 + 0.1336\ C_I$ (r = 0.99992)

With $^1D\ A^{1\%}_{1cm}$, 1346 and $^1D\ \varepsilon$, 4.1×10^4 L mol^{-1} cm^{-1}.

$^1DA = -0.00263 + 0.1011\ C_{II}$ (r = 0.99971)

With $^1D\ A^{1\%}_{1cm}$, 1011 and $^1D\ \varepsilon$, 4.0×10^4 L mol^{-1} cm^{-1}.

Where ^{1}DA is the trough of the peak and C is the concentration in μg ml^{-1}.

Statistical analysis of ^{1}D data for (I) and (II) gave values of standard deviation of residual ($S_{y/x}$): 5.4×10^{-4} and 6.1×10^{-4}, standard deviation of slope (S_b): 1.07×10^{-3} and 1.20×10^{-3} and standard deviation of intercept (S_a): 1.8×10^{-3} and 2.1×10^{-3}, the Er % was 0.465 and 0.510 for the two drugs, respectively.

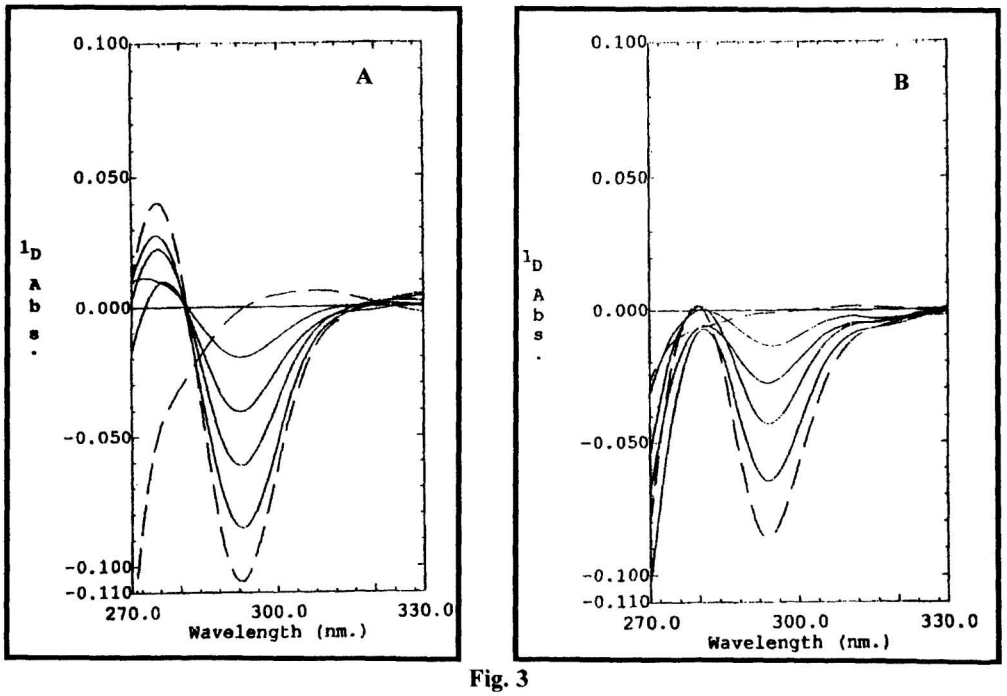

Fig. 3

A. ^{1}DA-concentration plots of Pd (II)-clioquinol complex; 0.16-0.18 μg ml^{-1} clioquinol, 0.1 mg ml^{-1} Pd (II).
B. ^{1}DA-concentration plots of Pd (II)-iodoquinol complex; 0.16-0.18 μg ml^{-1} iodoquinol, 0.1 mg ml^{-1} Pd (II).

3.4.3. Fourth order [^{4}D] analysis

The linearity of the amplitude of the peak ^{4}D A to the concentration of (I) and (II) at 284 nm and 287 nm respectively, was shown in Fig. 4 (A, B). It was rectilinear over the range 0.1-0.8 μg ml^{-1} with average % recoveries of 99.65 ± 1.15 and 100.06 ± 0.98.

The regression equations were:

$^4DA = 0.00125 + 0.09756\ C_I$ (r = 0.99977)

With $^4D\ A^{1\%}_{1cm}$, 975.6 and $^4D\ \varepsilon$, 2.98×10^4 L mol^{-1} cm^{-1}.

$^4DA = -0.00082 + 0.09125\ C_{II}$ (r = 0.99990)

With $^4D\ A^{1\%}_{1cm}$, 912.5 and $^4D\ \varepsilon$, 3.6×10^4 L mol^{-1} cm^{-1}.

Where ^{4}D A is the amplitude of the peak C is the concentration in μg ml^{-1}

Statistical analysis of ^{4}D data for (I) and (II) gave small values of standard deviation of residual ($S_{y/x}$): 5.3 $\times 10^{-4}$ and 3.7×10^{-4}, standard deviation of slope (S_b): 1.0×10^{-3} and 7.3×10^{-4} and standard deviation of intercept (S_a): 1.8×10^{-3} and 1.2×10^{-3}, the Er % was 0.376 and 0.438 respectively.

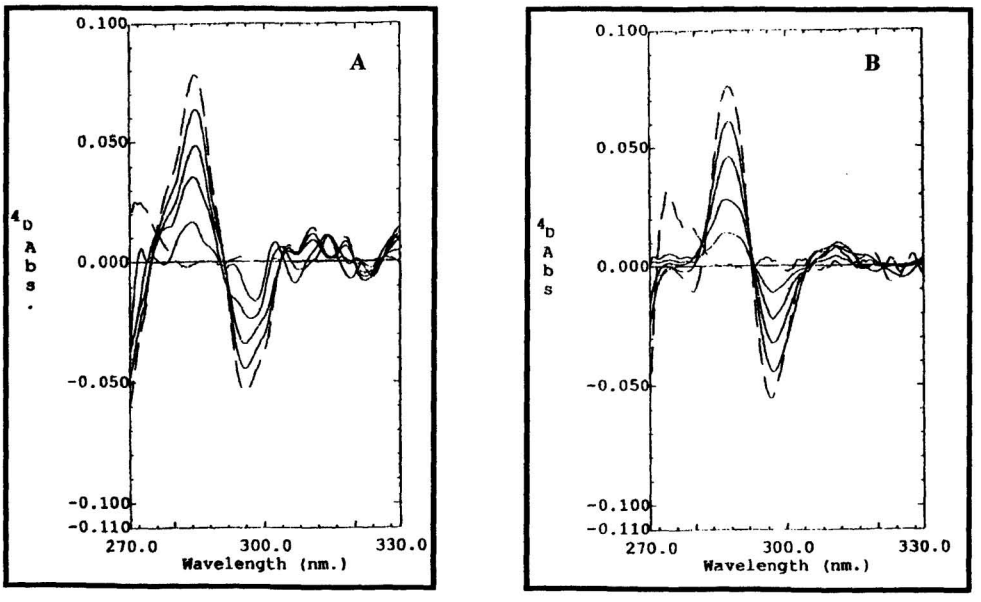

Fig. 4

A.^{4}DA-concentration plots of Pd (II)-clioquinol complex; 0.16-0.18 μg ml^{-1} clioquinol, 0.1 mg ml^{-1} Pd (II).

B.^{4}DA-concentration plots of Pd (II) -iodoquinol complex; 0.16-0.18 μg ml^{-1} iodoquinol, 0.1 mg ml^{-1} Pd (II).

3.5. Dosage forms analysis:

^1D and ^4D modes were successfully applied to the assay of (I) and (II) in different pharmaceutical preparations including; tablets, ear drops and creams. The average % recoveries of different concentrations attempted were based on the average of five replicate determinations. The results shown in table (1) in agreement with those obtained with the reference method [31]. The complexation ability of Pd (II) was applied for the analysis of the studied compounds as co-formulated with other drugs such as metronidazole (III), (Paramibe compound tablets). As shown in Fig. 5 (A) the presence of (III) interfered in the analysis of (II) by ^0D mode, while it did not interfere in the analysis by the ^4D mode, Fig. 5 (C), Table (1). The ^1D mode was used for determination of both (II) and (III) by Zero crossing measurements of their complexes at 296 nm and 328 nm for each drug, respectively Fig.5(B).

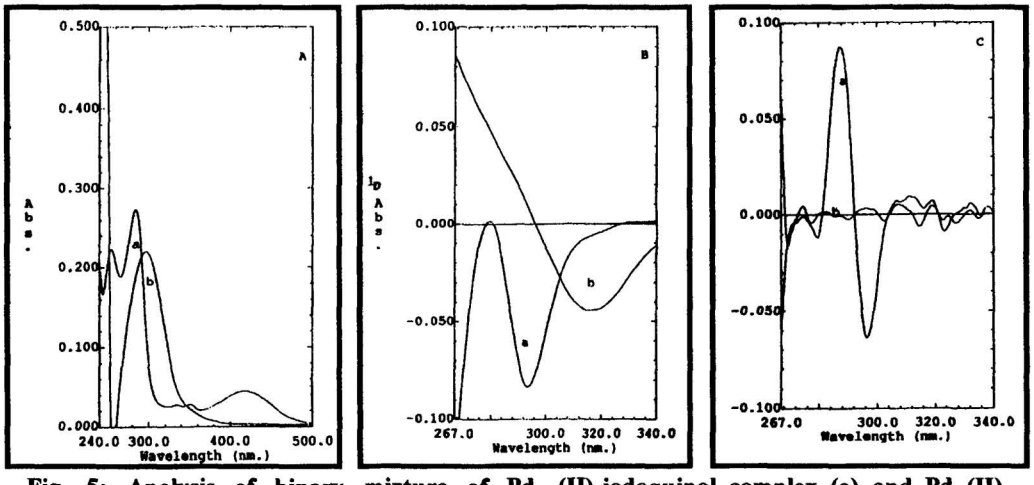

Fig. 5: Analysis of binary mixture of Pd (II)-iodoquinol complex (a) and Pd (II)-metronidazole complex (b)

A. ^0D (5 μg ml^{-1} each).

B. ^1D (0.8 μg ml^{-1} each), scaling factor 30.

C. ^4D (0.96 μg ml^{-1} each), scaling factor 3000.

using (0.1 mg ml^{-1}) Pd (II).

4. Conclusion:

The proposed procedure indicates reasonable sensitivity using ^1D and ^4D modes. The ^1D mode permits the successful analysis of binary mixtures of (II) and (III) with high accuracy without the need for prior separation. The ^4D mode could be used for determination of (II) without any interference from (III). The proposed method is simple, selective and sensitive as 100 ng ml^{-1} could be determined with high accuracy.

Table 1. Assay of clioquinol and iodoquinol in dosage forms using the proposed (^{1}D & ^{4}D) methods and reference method

Dosage forms / Parameters	Clioquinol						Iodoquinol						Iodoquinol Metronidazole		
	Locacorten vioform[1] ear drops 10 mg ml^{-1}			Vioderm hydrocortison[2] cream 3%			Paramibe tablet[3] 250 mg/tablet			Iodoquinol tablet[4] 250 mg/tablet			Paramibe compound[5] 250 mg/tablet		
	^{1}D	^{4}D	Ref	^{1}D	^{4}D	Ref	^{1}D	^{4}D	Ref	^{1}D	^{4}D	Ref	^{1}D	^{4}D	Ref
Percentage Recovery	99.75	98.44	99.69	99.94	101.56	101.04	98.29	99.69	100.12	99.75	100.31	101.01	99.45	98.75	101.20
	99.45	99.25	99.18	100.25	101.75	100.50	100.15	101.00	99.82	100.91	101.25	99.22	99.75	101.00	99.50
	100.15	99.79	98.15	100.15	100.21	98.80	100.25	101.07	100.72	98.92	99.79	100.12	99.51	100.00	100.87
	99.29	100.36	100.19	99.51	100.18	99.48	99.85	100.94	100.86	99.85	100.18	99.82	101.15	99.46	100.83
	100.55	99.38	99.94	99.12	99.22	101.55	99.95	99.88	100.01	99.35	100.21	100.86	99.87	100.78	99.50
Mean ($\bar{X}$)	99.84	99.44	99.43	99.79	100.58	100.21	99.70	100.52	100.31	99.76	100.35	100.21	99.95	100.00	100.58
Standard deviation (±) S.D.	0.515	0.71	0.81	0.472	1.06	1.25	0.803	0.67	0.457	0.742	0.54	0.74	0.695	0.93	1.05
p-value	0.368	0.984		0.502	0.627		0.142	0.562		0.365	0.741		0.263	0.570	

1. Product of Novartis Pharma, Cairo, Egypt.
2. Product of Cairo Pharmaceutical Co., Cairo, Egypt.
3. Product of Chemical Industries Development, Giza, Egypt.
4. Product of South Egypt Drug Industries Co., 6 October City, Egypt.
5. Product of Chemical Industries Development, Giza, Egypt.

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