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A simple kinetic spectrophotometric method for the determination of oxamniquine in formulations and spiked biological fluids

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Abstract

A simple and sensitive kinetic method for the determination of oxamniquine in pharmaceutical preparations and biological fluids was developed. The procedure is based upon a kinetic investigation of the oxidation reaction of the drug with alkaline potassium permanganate at room temperature for a fixed time of 20 min. The absorbance of the colored manganate ions was measured at 610 nm. Alternatively, the decrease in the absorbance of potassium permanganate after addition of the drug was measured at 525 nm. The absorbance concentration plots in both procedures were rectilinear over the range 0.5–4 μg ml^{-1}. The concentration of oxamniquine is calculated using the corresponding calibration equation for the fixed-time method. The determination of oxamniquine by fixed-concentration and rate-constant methods was feasible with the calibration equations obtained but the fixed time method had been found to be more applicable. Both procedures were applied to the determination of oxamniquine in formulations. The results obtained were in good agreement with those obtained using the official method. The fixed time method of 20 min was further applied to spiked human urine and plasma, the recoveries (%) were 100.94 ± 0.57 and 98.07 ± 0.88 for urine and plasma, respectively, at 610 nm, and 97.51 ± 1.27 and 95.69 ± 1.23 for urine and plasma, respectively, at 525 nm. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Kinetic determination; Oxamniquine; Potassium permanganate; Pharmaceutical analysis; Urine; Plasma

1. Introduction

Oxamniquine, 1,2,3,4-tetrahydro-2 [(isopropylamino) methyl]-7-nitro-6-quinoline methanol is an antischistosomal agent that is indicated for the treatment of schistosoma mansoni (intestinal schistosomiasis) infection. It has been shown to inhibit DNA, RNA and protein synthesis in schistosomes. The oral bioavailability of oxamniquine is good and effective plasma levels are achieved in 1–1.5 h [1].

Oxamniquine is the subject of a monograph in the USP (XXIII) [2] whereby a spectrophotometric method is recommended for its determination, whether in its pure form or in capsules. Other

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methods reported include spectrophotometry [3,4], non-aqueous titration [5,6], gas chromatography [7], high-performance liquid chromatography [8–12], capillary electrophoresis[10], polarography[13], flow injection analysis [14], cyclic voltammetry [15] and fluorimetry [16].

The literatures are still poor in analytical procedures based on kinetics especially for pharmaceutical or biological fluids.

Furthermore, some specific advantages in the application of kinetic methods can be expected [17]:

1. selectivity due to the measurement of the evolution of the absorbance with the time of reaction instead of the measure of a concrete absorbance value;
2. possibility of no interference of the colored and/or turbidity background of the samples, and …
3. possibility of no interference of other active compounds present in the commercial product if they are resisting the chemical reaction conditions established for the proposed kinetic method.

The aim of the present work was to study the reaction between oxamniquine and potassium permanganate kinetically in an attempt to evaluate the drug in dosage forms, spiked human urine or plasma. The results obtained were promising. The proposed method was simple and did not need sophisticated instrument or special skill.

2. Experimental

2.1. Apparatus

UV-1601, Shimadzu recording spectrophotometer (P/N 206-67001) equipped with kinetic accessory provided with temperature controlled cell (TCC-240A) thermoelectrical temperature. Recording range, 0–0.5; wavelength, 610 nm; factor, 1; number of cell, 1; reaction time, 20 min; cycle time, 0.1 min.

2.2. Reagents and materials

The following reagents were used, potassium permanganate (Merck, Germany), 5×10^{-3} M aqueous solution; sodium hydroxide (BDH, UK), 1 and 0.5 M aqueous solution; acetonitrile (Aldrich, Germany); and ether (Aldrich). Oxamniquine was kindly supplied by Pfizer (Sandwich, UK). Stock solution containing 10 mg of oxamniquine in 50 ml of acetonitrile is prepared and it is stable for several days when kept in refrigerator. Capsules containing oxamniquine were obtained from commercial sources. Urine was obtained from healthy volunteers. Plasma was obtained from Mansoura University Hospital, Mansoura, Egypt.

Two different methods were adopted for the determination of oxamniquine in pharmaceutical preparations and biological fluids.

The first one is based upon measuring the absorbance of the reaction product at 610 nm; while, the second one is based upon measuring the decrease in the absorbance of potassium permanganate after reaction with the drug at 525 nm.

2.3. General procedure

2.3.1. First method

A stock solution containing 10.0 mg of oxamniquine in 50.0 ml of acetonitrile was prepared. This solution was diluted with water to give final solution containing 20 μg ml^{-1}. Accurately measured aliquots of this solution were transferred into separate 10 ml volumetric flasks; after that 1 ml of 0.5 M NaOH was added followed by 2 ml of 5×10^{-3} M potassium permanganate, the mixture was shaken well, and then the evolution of the absorbance at 610 nm with time was scanned during 20 min at ambient temperature (25°C). The oxamniquine concentration was determined by measuring the rate of the reaction as the tangent to kinetic curve during the first 20 min of reaction and using the appropriate graphs. Log reaction rate versus log concentration of oxamniquine was plotted to get order of the reaction after 20 min. To get the standard calibration graph, the above procedure was carried out and the reaction mixture was allowed to stand for 20 min. Volume with water was added. Measure the absorbance of the resulting solution prepared at 610 nm against a blank solution prepared simultaneously. Plot the values of the absorbance against

the final concentration in μg ml^{-1}. Alternatively, the regression equation was derived.

2.3.2. The second method

A stock solution containing 10.0 mg of oxamniquine in 50 ml of acetonitrile was prepared. It was diluted with water to give 20 μg ml^{-1} oxamniquine working standard solution. Accurately measured aliquots of this solution were transferred into 10-ml volumetric flasks. Then 1 ml of 0.5 M NaOH was added followed by 0.6 ml of 7.6×10^{-3} M $KMnO_4$ and then the mixture was shaken. It was let to stand for 20 min, and then made up to volume with water. The absorbance of the solution was measured at 525 nm. The values of the absorbance versus the final content of the drug were plotted. Log reaction rate ($\log \Delta A/\Delta t$) against log concentration of the drug was plotted to get the order of the reaction.

2.4. Procedure for capsules

The contents of ten capsules were emptied out as completely as possible. An accurately weighed amount of the powder equivalent to 20.0 mg of the drug was transferred into a small conical flask and extracted with 3×30 ml of acetonitrile. The contents were transferred into a 100-ml standard flask and diluted to the mark with acetonitrile. Aliquots of this solution were transferred into a 10-ml standard flask. We should proceed as mentioned under general procedures. The absorbance intensity of the resulted solution was measured at 610 or at 525 nm as mentioned above. The nominal content of the capsules was calculated either from a previously plotted calibration graph or using the regression equation.

2.5. Procedure for spiked biological fluids

A standard calibration curve was prepared by spiking plasma or urine with varying amounts of oxamniquine. A stock solution containing 20.0 μg ml^{-1} of oxamniquine was also prepared. Spike control samples of plasma or urine with different quantities of oxamniquine to give a final drug concentration were cited in Table 6. Into 1.0 ml of spiked plasma or urine, 0.8 ml of 1 M NaOH was added with gentle shaking and 5 ml of diethyl ether. Vortex the solution for 2 min before being centrifuged at 2500 rpm for 5 min. The resulting supernatant was transferred into a small conical flask, and then extracted with 2×5 ml of diethyl ether. The combined extracts were evaporated to dryness under a stream of nitrogen at ambient temperature. The dry residue in 2.0 ml of acetonitrile was dissolved, and the above general procedure was then followed. A blank experiment was carried out simultaneously adopting the above procedure.

3. Results and disscussion

3.1. Kinetic and optimization of the reaction conditions

The reaction between oxamniquine and $KMnO_4$ in alkaline medium yields a green color due to the production of manganate ion, which absorbs at 610 nm (Fig. 1). The absorbance of the oxidation product remains stable for at least 50 min. As the intensity of the color increases with time, this was used as a useful method for the determination of oxamniquine in pharmaceuticals and biological fluids. The reaction was studied under various conditions of reagent concentration and alkalinity, also the effect of solvents was equally studied.

Acetonitrile was used to dissolve the drug, since $KMnO_4$ oxidize other solvents with the production of green MnO_4^{2-} ion.

At room temperature, the reaction rate increased substantially as the color development increased. Therefore, room temperature was selected as the optimum temperature. Heating the solution was found to increase the rate of the reaction but MnO_2 was precipitated.

The reaction rate and maximum absorbance increased with time, and with increasing $KMnO_4$ concentration. It was found that 2.5 ± 0.2 ml of 5×10^{-3} M $KMnO_4$ was adequate for the maximum absorbance (Fig. 2).

The influence of NaOH concentration on the reaction rate was also studied using 0.1–3 ml of 0.5 M NaOH. It was found that increasing the volume of 0.5 M NaOH would increase the absorbance of the reaction product up to 1 ml, after which further increase in the volume of 0.5 M NaOH resulted in no change in the absorbance of the reaction product, thus, 1 ml of 0.5 M NaOH was found to be the most suitable concentration for maximum absorbance (Fig. 3).

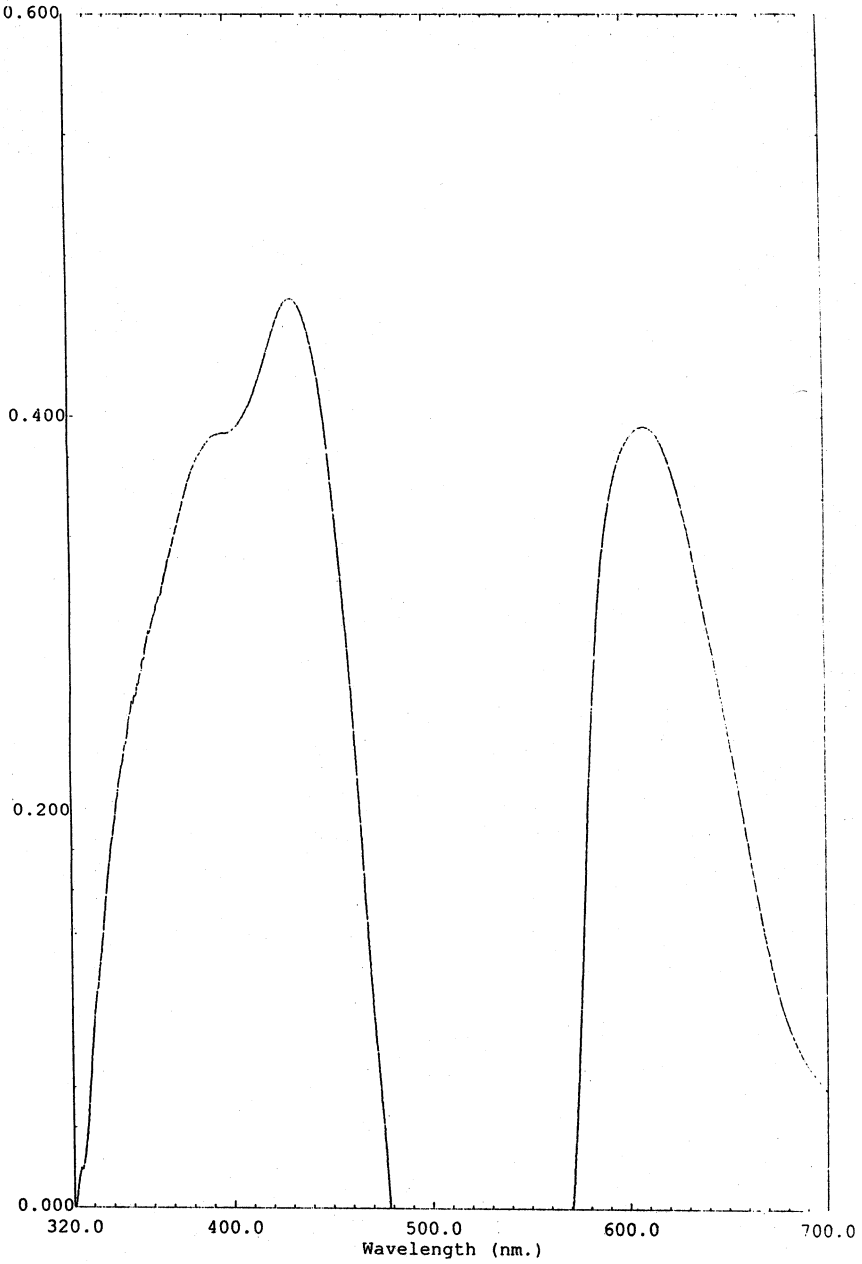

Fig. 1. Absorption spectrum of oxamniquine (4 μg ml^{-1}) after reaction with $KMnO_4$ (a) oxidation product; (b) manganate ions.

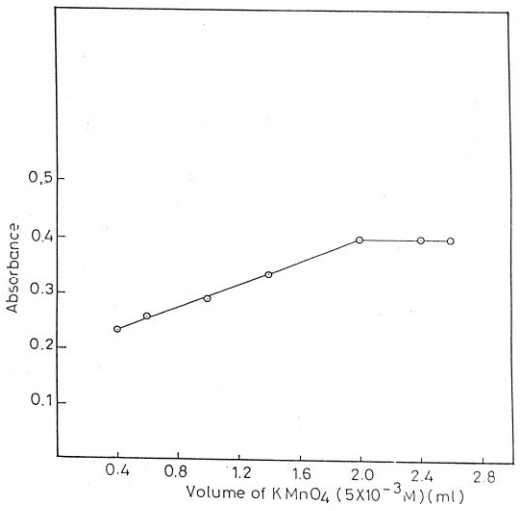

Fig. 2. Effect of volume of (5×10^{-3} M) $KMnO_4$ on the absorbance intensity of oxaminquine (4 μg ml^{-1}) at 610 nm.

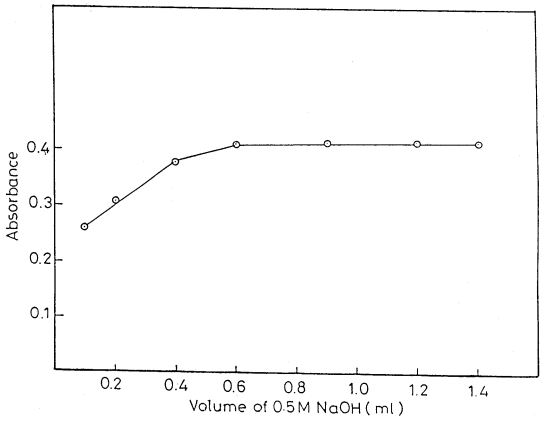

Fig. 3. Effect of volume of NaOH (0.5 M) on the absorbance intensity of oxamniquine (4 μg ml^{-1}) at 610 nm.

Oxidation of oxamniquine with $KMnO_4$ was carried out in the presence of NaOH. Trials were made to determine oxamniquine through oxidation with $KMnO_4$ in neutral and acidic media, but no oxidation of oxamniquine had been observed.

Different oxidants have been used to determine oxamniquine, such as 10% H_2O_2 in alkaline medium, potassium persulphate in alkaline medium and potassium periodate in strong acid medium. In case of H_2O_2, complete decomposition of the drug was observed. In case of persulfate, complete decomposition of the drug was also observed, as revealed by the absence of any chromophoric groups in the absorption spectrum of the reaction product. In case of periodate, oxidation of the drug resulted in hypsochromic shift and hypochromic effect, λ_{max} of the reaction product was at 236 nm, and this was in agreement with the reported results of the oxidation of amino–alcohol compounds [18].

The rate of reaction was also found to be concentration-dependent. The rate of reaction was followed at room temperature with various concentrations of the drug in the range of 0.5–4 μg ml^{-1}, keeping $KMnO_4$ and NaOH concentrations constant (Fig. 4).

An alternative spectrophotometric method for the determination of oxamniquine based upon measuring the decrease in the absorbance of $KMnO_4$ at 525 nm (Fig. 5) was also developed. The difference in the absorbance was plotted against the concentration of the drug, furthermore, logarithmic analysis of the reaction rate (R) was plotted against log concentration of the drug.

The rate of reaction was also found to be dependent on oxamniquine concentrations. The rates were followed at room temperature with various concentrations of oxamniquine in the range of 0.5–4 μg ml^{-1} keeping $KMnO_4$ and NaOH concentrations constant. The reaction rate was found to obey the following equation:

$$\text{Rate} = K^{-}[\text{oxamniquine}]^{n} \quad (1)$$

where K^{-} is the pseudo-order rate constant and n is the order of the reaction.

The rate of the reaction may be estimated by the variable-time method measurement [19] as $\Delta A/\Delta t$, where A is the absorbance and t is the time in seconds. Taking logarithms of rates and concentrations (Table 1), Eq. (1) is transformed into:

$$\log(\text{rate}) = \log\frac{\Delta A}{\Delta t} = \log k^{-} + n \log[\text{oxamniquine}] \quad (2)$$

Regression of log (rate) versus log (oxamniquine) gave the regression equation:

$$\log \text{ rate} = -1.25 + 0.997 \log C \quad (r = 0.9997)$$

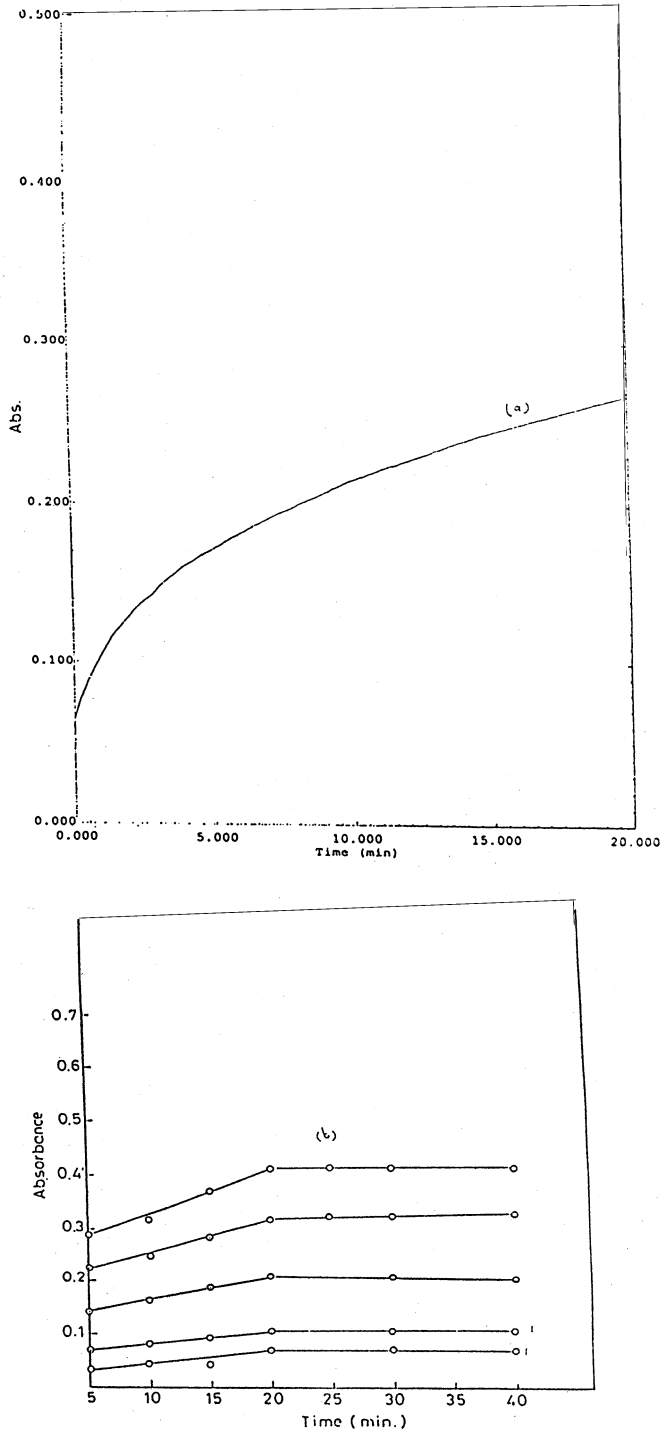

Fig. 4. Absorbance versus time graphs for the reaction between oxamniquine and potassium permanganate showing the dependence of the reaction on oxamniquine concentration. Concentrations of oxamniquine are, (a) 8.95×10^{-6} M; and (b) (1) 1.79×10^{-6}, (2) 3.58×10^{-6}, (3) 7.16×10^{-6}, (4) 1.074×10^{-5}, and (5) 1.432×10^{-5} M, respectively.

Hence $K^{-} = 5.623 \times 10^{-2}\ s^{-1}$ and the reaction is first order ($n = 0.99$) with respect to oxamniquine.

$$\log \text{ rate} = 1.47 + 1.018 \log C$$

Hence $K^{-} = 29.5\ s^{-1}$ and the reaction is first order ($n = 1.018$).

4. Evaluation of the kinetic methods

The quantitation of oxamniquine under the optimized experimental conditions outlined above would result in a pseudo-first order with respect to their concentrations where $KMnO_4$ concentration was at least 40 times of the concentration of

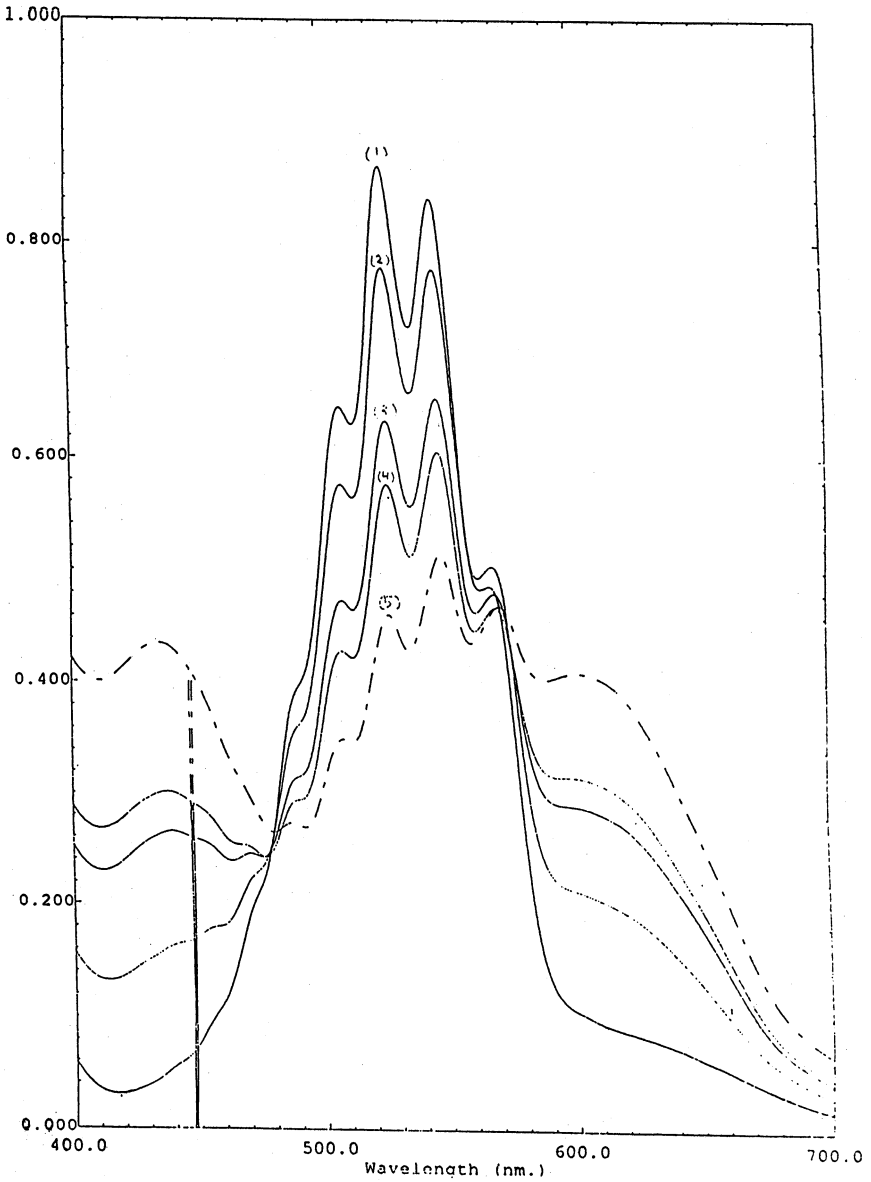

Fig. 5. Absorption spectrum of oxamniquine after reaction with $KMnO_4$ at different concentrations (μg ml^{-1}). (1) $KMnO_4$, (2) 1 (3) 2 (4) 3 and (5) 4 μg ml^{-1}.

Table 1
Logarithms of rates for different concentrations at room temperature

log $\Delta A/\Delta t$	log [oxamniquine] (M)
(a) At 610 nm	
−4.4798	−5.747
−4.1788	−5.446
−3.8833	−5.145
−3.6972	−4.969
−3.5829	−4.844
(b) At 525 nm	
−4.0793	−5.446
−3.7632	−5.145
−3.6007	−4.969
−3.4612	−4.844

Table 2
Values of K^- calculated from slopes of log A vs. t graphs at 610 nm

K^- (s^{-1})	[Oxamniquine] (M)
-5.27×10^{-4}	1.790×10^{-6}
-4.90×10^{-4}	3.580×10^{-6}
-4.50×10^{-4}	7.160×10^{-6}
-4.03×10^{-4}	1.074×10^{-5}
-3.60×10^{-4}	1.432×10^{-5}

Table 3
Values of reciprocal of time taken at fixed absorbance for different rates of variable concentrations of oxamniquine at constant concentrations of NaOH and $KMnO_4$ at room temperature

$1/t$ (s^{-1})	[Oxamniquine] (M)
1.11×10^{-3}	1.61×10^{-5}
1.67×10^{-3}	1.79×10^{-5}
3.33×10^{-3}	2.15×10^{-5}

oxamniquine and NaOH concentration was at least 500 times the initial concentration of oxamniquine.

However, the rate will be directly proportional to oxamniquine concentration in a pseudo-first order rate equation as follows:

$$\text{Rate} = K^-(\text{oxamniquine}) \quad (3)$$

where K^- is the pseudo-first order constant. Several experiments were then carried out to obtain oxamniquine concentration from the rate data according to Eq. (3). Initial rate, rate constant, fixed-concentration and fixed time methods [20,21] were tried and the most suitable analytical method was selected taking into account the applicability, the sensitivity, the intercept and the correlation coefficient (r).

5. Rate-constant method

Graphs of log absorance versus time for oxamniquine concentration in the range of 1.790×10^{-6}–1.432×10^{-5} M were plotted and all appeared to be rectilinear. Pseudo-first order rate constants (K^-) corresponding to different oxamniquine concentrations (C) were calculated from the slopes multiplied by −2.303 and are presented in Table 2. Regression of (C) versus K^- gave the equation:

$$K^- = -5.42\times10^{-4} + 12.46C \quad (r = 0.9953)$$

6. Fixed-concentration method

Reaction rates were recorded for different oxamniquine concentrations in the range of 1.61×10^{-5}–2.10×10^{-5} M. A preselected value of the absorbance (0.3) was fixed and the time was measured in seconds. The reciprocal of time ($1/t$) versus the initial concentration of oxamniquine (Table 3) was plotted and the following equation of the calibration graph was obtained:

$$1/t = -5.70\times10^{-3} + 418C \quad (r = 0.9961)$$

7. Fixed-time method

Reaction rates were determined for different concentrations of oxamniquine. At a preselected fixed-time, which was accurately determined, the absorbance was measured. Calibration graphs of absorbance versus initial concentration of oxamniquine were established at fixed times of 5, 10, 15, 20 min with the regression equations assembled in Table 4.

Table 4
Regression equation for oxamniquine at different fixed time over the range 1.790×10^{-6}–1.432×10^{-5} M at room temperature at 610 nm

Time (min)	Regression equation	Correlation coefficient (r)
5	$A = -0.0006 + 0.073C$	0.9999
10	$A = 0.0015 + 0.079C$	0.9999
15	$A = -0.0007 + 0.093C$	0.9995
20	$A = 0.0002 + 0.105C$	0.9998

It is clear that the slope increases with time and the most acceptable values of the correlation coefficient (r) and the intercept were obtained for a fixed time of 20 min, which was therefore chosen as the most suitable time interval for measurement.

After optimizing the reaction conditions, the fixed time method was applied to the determination of oxamniquine in pure form over the concentration range 0.5–4 μg ml^{-1}. Analysis of the data gave the following regression equations:

$$A = 0.0002 + 0.105C \quad (r = 0.9998)$$

where A is the absorbance at 610 nm.

$$A = -0.0040 + 0.104C \quad (r = 0.9994)$$

where A is the absorbance at 525 nm and C is the concentration in μg ml^{-1}.

The LOD was found to be 9.78×10^{-3} μg ml^{-1} and LOQ was found to be 0.5 μg ml^{-1}.

Statistical analysis [22] of the results obtained by the proposed and official methods, using Student's t-test and variance ratio F-test revealed no significant difference between the performance of the two methods regarding the accuracy and precision.

The validity of the method was evaluated by statistical analysis of the regression data. Standard deviation of the residual (Sy/x) was 2.78×10^{-3}, S.D. of the intercept (S_a) was 4.89×10^{-3}, S.D. of the slope (S_b) was 9.72×10^{-4} and Er% was 0.33.

The precision of the method was evaluated by analyzing standard solutions of oxamniquine. The results for pure sample were in accordance with those obtained by the official method [2]. The method was also applied to capsules containing oxamniquine (Table 5). The results in Table 6 agreed with those obtained by the official method [2].

The within-day precision was evaluated through replicate analysis of plasma sample spiked with oxamniquine at different concentration levels. The percentage recoveries based on the

Table 5
Spectrophotometric determination of oxamniquine capsules[a] at different wavelengths

Wavelength (nm)	Taken (μg)	Found (μg)	Recovery (%)	
			Proposed method	Official method [2]
610	1.0	1.0052	100.52	
	2.0	1.9890	99.45	
	3.0	3.0204	100.68	
	4.0	4.0116	100.29	
Mean ± S.D.			100.24 ± 0.47	100.56 ± 0.77
525	1.0	1.0163	101.63	
	2.0	2.0010	100.05	
	3.0	3.0102	100.34	
	4.0	3.9672	99.18	
Mean ± S.D.			100.30 ± 0.87	100.56 ± 0.77

[a] Vansil capsules (containing 250 mg of oxamniquine).

Table 6
Spectrophotometric determination of oxamniquine in spiked urine and plasma

Sample	Wavelength (nm)	Taken (μg)	Found (μg)	Recovery (%)
Urine	610	2.0	2.0348	101.74
		3.0	3.0144	100.48
		4.0	4.0244	100.61
	Mean ± S.D.			100.94 ± 0.57
Urine	525	2.0	1.958	97.09
		3.0	2.8737	95.79
		4.0	3.9536	98.84
	Mean ± S.D.			97.51 ± 1.27
Plasma	610	2.0	1.956	97.8
		3.0	2.9142	97.14
		4.0	3.9704	99.26
	Mean ± S.D.			98.07 ± 0.88
Plasma	525	2.0	1.9076	95.38
		3.0	2.8305	94.35
		4.0	3.8932	97.33
	Mean ± S.D.			95.69 ± 1.23

average of three separate determinations at 610 nm were 98.07 + 0.88, thus indicating the high precision of the method.

The inter-day precision was evaluated through replicate analysis of urine sample spiked with 3 μg ml^{-1}. The percentage recoveries based on the average of three separate determinations at 610 nm are 97.14 ± 1.06, thus indicating the high accuracy of the method.

Excipients such as talc, starch, gelatin, magnesium stearate and lactose did not interfere with the assay.

The high sensitivity of the proposed method allowed the determination of oxamniquine in biological fluids. The proposed method was further applied to the determination of oxamniquine in spiked biological fluids. Oxamniquine is readily absorbed following oral ingestion, and a peak concentration in plasma occurs within about 3 h. The presence of food significantly delays absorption and limits the concentration achieved in plasma during the first several hours after administration. Urinary excretion is the major route of elimination in man [23]. Oxamniquine is given orally in a dose of 250 mg three times daily; this leads to a final blood level concentration of about 5 μg ml^{-1} i.e. higher than the upper limit of the working range of the proposed method. Thus the high sensitivity of the proposed method allowed the determination of oxamniquine in biological fluids. The results are shown in Table 6.

The extraction procedure described by Woolhouse and Wood [7] was adopted here. The results are satisfactorily accurate and precise.

The metabolic products of oxamniquine were the 2 and 6 carboxylates [23] which did not interfere with the determination of the drug by the proposed method. Hence the proposed kinetic method could be used for the determination of oxamniquine in the presence of its metabolites. A highly sensitive and accurate method was developed for the determination of oxamniquine in urine and plasma.

8. Mechanism of the reaction

The stoichiometry of the reaction was studied adopting Bent and French method [24]. The slopes of the curves for oxamniquine and potassium permanganate were 1.692 and 3.75, respectively. Hence the molar ratio of the reaction is 3.75/1.692 pointing out to a ratio of 2:1 $KMnO_4$:oxamniquine.

Based on the obtained molar reactivity, the reaction pathway is proposed to proceed as follows:

$$R\text{–}CH_2OH + 2MnO_4^- + 2OH^- \rightarrow R\text{–}CHO + 2MnO_4^{2-} + 2H_2O$$

9. Conclusion

Different methods were established to determine oxamniquine concentration kinetically, the reaction rate method, rate constant and fixed time methods were applied over the concentration range 1.79×10^{-6}–1.432×10^{-5} M. The fixed concentration method was applied over the range 1.61×10^{-5}–2.15×10^{-5} M. Applying fixed time method, it was clear that the slope increased with time and the most acceptable values of correlation coefficient (r) and intercept were obtained for a fixed time of 20 min which was therefore chosen as the most suitable time interval for measurements.

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