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Research Article

Kinetic spectrophotometric method for determination of ciprofloxacin and lomefloxacin in their pharmaceutical dosage forms

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Abstract

A simple and sensitive kinetic spectrophotometric method has been developed and validated for the determination of ciprofloxacin (CIP) and lomefloxacin (LOM) in their pharmaceutical dosage forms. The method was based on the oxidation of CIP and LOM with alkaline potassium permanganate to give a green colored reaction product. The reaction was monitored spectrophotometrically by measuring the absorbance of the reaction product at 610 nm. The factors affecting the reaction was studied and optimized. The stoichiometries of the reaction were determined and the reaction pathway was postulated. The activation energy of the reaction was calculated and found to be 4.48 and 4.17 KJ mole^{-1} for CIP and LOM, respectively. The initial rate and fixed time (at 5 min) methods were utilized for constructing the calibration graphs. The analytical performance of both methods was fully validated, and the results were satisfactory. The proposed methods were successfully applied to the determination of both CIP and LOM in their commercial pharmaceutical dosage forms. The label claim percentages were 99.4 – 100.2 $\pm$ 1.15 – 1.81%. Statistical comparison of the results with those obtained by a reference method showed excellent agreement between the accuracy and precision of the two methods. The proposed method has a great value in its application to the analysis of CIP and LOM in quality control laboratories.

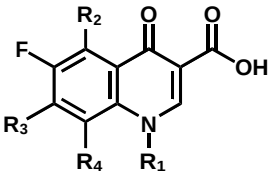
Keywords: Ciprofloxacin; Lomefloxacin; Kinetic spectrophotometry; Initial rate method; Fixed time method; Pharmaceutical analysis.

1. Introduction

Ciprofloxacin (CIP; 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic) and lomefloxacin (LOM; 1-ethyl-6,8-difluoro-1,4-dihydro-7-[3-methylpiperazin-1-yl]-4-oxoquinoline-3-carboxylic acid (Table 1) are synthetic fluoroquinolones (FQs) (John, 1995). CIP and LOM are relatively new, second-generation FQs antibiotics with an expanded spectrum of activity against Gram-positive and Gram-negative bacteria. They exert their effect by inhibition of DNA gyrase (topoisomerase II) and topoisomerase IV, the bacterial enzymes which are responsible for the bacterial chromosome replication. CIP and LOM have a broader spectrum of activity and more potent than the non-fluorinated quinoline antibacterials (e.g. nalidexic acid) (Korolkovas, 1998). They contain a piperazine group at position 7 of the 4-quinolone nucleus, which results in anti-pseudomonal activity (Crumplin, 1990). They are used in wide range of infections such as uncomplicated and complicated urinary tract, respiratory and gastrointestinal tract, as well as in skin structure and ocular infections (Delgado & Remers, 1988).

Because of the therapeutic importance of CIP and LOM, there is much interest in their determination for the purpose of pharmaceutical quality control. The analytical methods that have been reported for this purpose were the subject of many reviews (Al-Omar, 2004; Belal, 1999; Marzouq, 2007). Based on the number of reports cited in these reviews, spectrophotometry is considered the most widely used technique. This

Table 1. Structural formulae of the investigated fluoroquinolone compounds



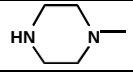
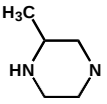
Compound	R1	R2	R3	R4
Ciprofloxacin		H		H
Lomefloxacin		H		F

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Table 2. Analytical parameters for the initial rate method of the spectrophotometric method for determination of CIP and LOM

Drug	Linear range [M]	Least square equation (Log K = log *K`* + *n* log *C*)[a]		Correlation coefficient (r)	LOD (μg ml^{-1})	LOQ (μg ml^{-1})
		Intercept (log *K*)	Slope (n)			
CIP	0.065×10^{-4}-2.07×10^{-4} (10-100) [b]	1.4804	0.8861	0.9992	0.46	1.39
LOM	0.13×10^{-4}-1.55×10^{-4} (5-60)	2.3100	0.8902	0.9995	0.66	2.01

[a] K is the reaction rate, *K`* is the conditional rate constant, *n* is the order of reaction, and C is the molar concentration of FQs.

[b] Figures in parenthesis are the linear range in μg ml^{-1}.

is attributed to its inherent simplicity, low cost and wide availability in most quality control laboratories.

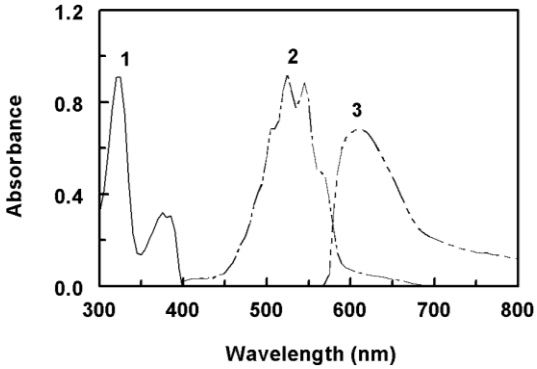


Figure 1. Absorption spectra of CIP (1; 35 μg ml^{-1}), KMnO4 (2; 1.2×10^{-3} M) and their reaction product (3) in presence of NaOH (0.4 M). The reaction of $KMnO_4$ with CIP was carried out at temperature (25±5°C) for 20 min.

Kinetic spectrophotometric methods are becoming of great interest in the pharmaceutical analysis (Chamjangali, 2006; Darwish, 2005; Rahman, 2006). The application of these methods offers some specific advantages such as improved selectivity, avoiding the interference of the colored and/or turbidity background of the samples, possibility of avoiding the interference of the other active ingredients present in the commercial products, and reduction of the analysis time when the analytical reaction requires long for completion.

No attempt has been made for the kinetic spectrophotometric determination of CIP and LOM. Therefore, the development of a kinetic spectrophotometric method for determination of CIP and LOM was necessary. The present study describes, for the first time, the development of a simple and sensitive kinetic spectrophotometric method for the determination of CIP and LOM. The method involved the oxidation of the drugs with alkaline potassium permanganate at room temperature and monitoring the reaction by measuring the absorbance at 610 nm. The initial rate and fixed rate methods, after their full validation, were adopted for the determination of both drugs in their commercial pharmaceutical dosage forms.

2. EXPERIMENTAL

2.1. Apparatus

Double beam V-530 (JASCO Co. Ltd., Kyoto, Japan) ultraviolet-visible spectrophotometer with matched 1-cm quartz cells was used for all the spectrophotometric measurements.

2.2. Chemicals and dosage forms

Ciprofloxacin HCl (Miles Inc. Pharmaceutical Division, West Haven, Germany). Lomifloxacin HCl (Searle, Illinois, USA). Potassium permanganate (Merck, Schuchardt, Munich, Germany) was 1.2×10^{-2} M aqueous solution. Sodium hydroxide (Aldrich Co Ltd., Gillingham-Dorst, Germany) was 4 M aqueous solution. All solvents and other chemicals used throughout this study were of analytical grade. Cipromax® tablets (Spimaco Al-Qassim Pharmaceutical, Saudi Arabia) are labeled to contain 500 mg CIP (as hydrochloride monohydrate) per tablet. Cipromid® tablets (Midpharma; Middle East Pharmaceutical Co., Jordon) are labeled to 400 mg LOM (as hydrochloride monohydrate) per tablet. Ciprolon® tablets (Hikma Pharmaceuticals, Amman, Jordon) are labeled to 750 CIP (as hydrochloride) per tablet. Lomax® tablets (Julphar; Gulf Pharmaceutical Industries, Ras Al-khaimah, United Arab Emirates) are

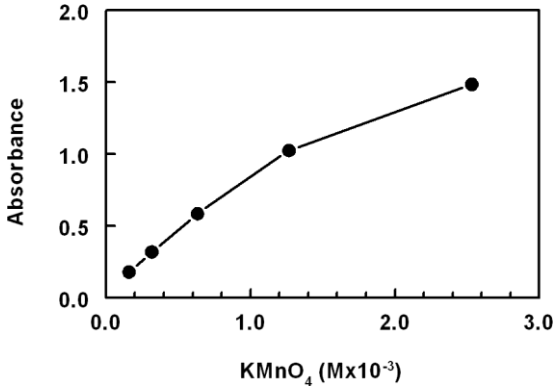


Figure. 2. Absorbance-concentration curve for $KMnO_4$ solution containing NaOH (0.4 M). The absorbances were measured at 525 nm.

labeled to contain 400 mg LOM (as hydrochloride) per tablet.

Table 3. Analytical parameters for the proposed fixed time spectrophotometric method for determination of CIP and LOM

Reaction time (min)	Linear range (μg ml^{-1})	Intercept	Standard deviation of intercept	Slope	Standard deviation of slope	Correlation coefficient	LOD (μg ml^{-1})	LOQ (μg ml^{-1})
CIP								
2	40-480	0.0039	0.0082	0.0021	0.000156	0.9992	12.9	39.0
5	8-180	0.0092	0.0045	0.0049	0.000192	0.9995	3.0	9.2
10	5-100	0.0151	0.0035	0.0083	0.000143	0.9995	1.4	4.2
15	4-80	0.0170	0.0031	0.0099	0.000174	0.9990	1.0	3.1
20	4-70	0.0026	0.0111	0.0111	0.000182	0.9991	0.8	2.3
LOM								
2	10-100	0.0078	0.0087	0.0102	0.00094	0.9985	2.8	8.5
5	5-75	0.0291	0.0052	0.0133	0.00213	0.9990	1.3	3.9
10	4-55	0.0414	0.0049	0.0171	0.00176	0.9992	0.9	2.9
15	2-50	0.0365	0.0034	0.0194	0.00287	0.9995	0.6	1.8
20	2-45	0.0377	0.0026	0.0220	0.00674	0.9992	0.4	1.2
25	1-40	0.0419	0.0021	0.0221	0.00345	0.9991	0.3	1.0
30	1-40	0.0655	0.0019	0.0228	0.00523	0.9982	0.3	0.8

2.3. Preparation of standard and sample solutions

2.3.1. Preparation of stock standard solution

Into a 50-ml calibrated flask, an accurately weighed amount (100 mg) of the standard drug (CIP and LOM) and was dissolved in 40 ml water. The resulting solution was completed to volume with water. This stock solution (2 mg ml^{-1}) was diluted with water to obtain working concentrations in the range of 80–1800 and 50–750 μg ml^{-1} for CIP and LOM, respectively.

2.3.2. Preparation of dosage forms sample solution

Twenty tablets were weighed and finely powdered. A quantity of the mixed powder equivalent to 100 mg of CIP and LOM was transferred into a 50-ml calibrated flask, dissolved in 25 ml water, swirled and sonicated for 5 min, completed to volume with water, shaken well for 10 min, and filtered. The first portion of the filtrate was rejected, and 25 ml of the filtrate was diluted with water to obtain working concentrations in the range of 80–1800 and 50–750 μg ml^{-1} for CIP and LOM, respectively.

2.4. General recommended procedures and data treatment

One milliliter of the standard (80–1800 and 50–750 μg ml^{-1} for CIP and LOM, respectively) or sample solution was transferred into 10-ml calibrated flasks. One milliliter of $KMnO_4$ solution (1.2×10^{-2} M) and 1 ml of NaOH (4 M) were added. The reaction mixture was mixed and completed to volume with water. After dilution and mixing, the reaction mixture was immediately transferred to a spectrophotometric cell and the absorbance was recorded (at 610 nm) as a function of time against reagent blank treated similarly.

The kinetic data that has been recorded were transformed to the Slide Write Plus software, version 5.011 (Advanced Graphics Software, Inc., CA, USA) for curve fitting, regression analysis, and statistical calculations. The initial rate (K) of the reaction at different concentrations was obtained from the slope of the tangent to the absorbance-time curve. The calibration curve was constructed by plotting the logarithm of the initial rate (log K) of reaction versus logarithm of the concentration (log C) of the drug (CIP and LOM). Alternatively, the calibration curve was constructed by plotting the absorbance measured after a fixed time of 5 min versus the concentration of the drug.

2.5. Determination of molar ratio of the reactions

The Job's method of continuous variation (Job, 1936) was employed. Master equimolar solutions (1.3×10^{-4} M) of CIP, LOM, and $KMnO_4$ were prepared. Series of 10-ml portions of the master solutions of the drugs (CIP and LOM) and the analytical reagent ($KMnO_4$) were made up comprising different complementary ratios [0:10, 1:9, 9:1, 10:0, inclusive] in 10-ml calibrated flasks. One milliliter of NaOH (4 M) was added, and the volumes were completed. The solutions were further manipulated as described under the general recommended procedures and data treatment.

3. RESULTS AND DISCUSSION

3.1. Involved reaction and absorption spectra

Oxidation-reduction reactions have been used as the basis for the development of simple and sensitive spectrophotometric methods for the determination of many pharmaceutical compounds (Darwish, 2008). $KMnO_4$ is a strong oxidant, and its oxidation for the organic compounds is a pH dependent. During the course of the reaction, the valance of manganese changes and the intermediate ions have been sug-

Table 4. Precision for the initial rate and fixed-time spectrophotometric methods for determination of CIP and LOM

Concentration (μg ml^{-1})	Recovery (± RSD) [a]			
	Initial rate method		Fixed time method	
	Intra-assay	Inter-assay	Intra-assay	Inter-assay
CIP				
10	101.2 ± 1.82	100.6 ± 1.85	100.5 ± 1.42	99.8 ± 0.77
40	98.2 ± 1.45	99.7 ± 1.67	99.7 ± 1.57	100.0 ± 1.09
70	102.5 ± 1.05	101.6 ± 1.02	100.3 ± 0.39	100.3 ± 0.07
LOM				
5	100.8 ± 1.94	98.4 ± 1.78	99.9 ± 1.69	98.8 ± 0.97
20	99.4 ± 1.52	101.2 ± 1.42	101.3 ± 1.69	100.5 ± 0.53
50	97.5 ± 0.85	100.6 ± 0.82	100.1 ± 0.62	100.1 ± 0.05

[a] Values are mean of three determinations.

gested as participating oxidants. The species that are considered as potential oxidants depend on the nature of the substrate and the pH of the medium (Askal, 1997; Rahman, 2004). $KMnO_4$ not been previously used for the spectrophotmetric determination of CIP and LOM. In the present study, the reaction of alkaline $KMnO_4$ with CIP and LOM was investigated, and it was found that both drugs are vulnerable by $KMnO_4$. This

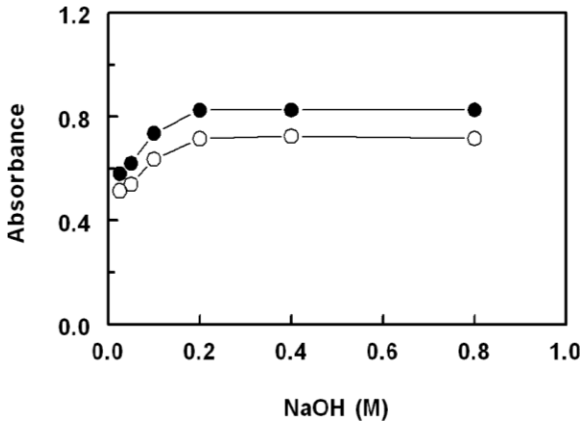


Figure. 3 Effect of NaOH concentrations on the reaction of $KMnO_4$ (1.2×10^{-3} M) with CIP (○; 60 μg ml^{-1}) and LOM (●; 60 μg ml^{-1}) in presence of NaOH (0.4 M). The reactions were carried out at temperature (25±5°C) for 20 min.

was evident from the decrease of its violet color (λ_{max} at 525 nm) and by the appearance of a green reaction product (λ_{max} at 610 nm). The formation of this colored product was monitored spectrophotometrically. The absorption spectrum for $KMnO_4$, CIP (as an example), and their reaction product is given in Fig. 1.

The following sections describe the optimization of different factors affecting the reaction, kinetics, and the use of the optimized conditions in the development of the assay procedures.

3.2. Optimization of reaction conditions

The factors affecting reaction conditions (concentrations of $KMnO_4$, alkalinity, temperature, and the diluting solvent) were studied by altering each variable in turn while keeping the others constant. The intensity of the developed color was recorded as a function of the concentrations of $KMnO_4$. It was found that the color intensity was dependent on the concentration of $KMnO_4$ (Fig. 2). Based on the above mentioned reaction, $KMnO_4$ solution should be added in excess to react with the investigated FQs. Accordingly, the blank experiment (zero concentration of FQs) should contain the highest $KMnO_4$ concentration that gives the highest absorption value within the practical sensitivity range of absorption values that is devoid from stary light effect (i.e. absorbance value of ≤ 1.5) (Görög, 2001). This concentration was found to be 1.2×10^{-3} M in the final reaction solution (1 ml of 1.2×10^{-2} M of the working $KMnO_4$ solution), and this condition was employed in all the subsequent experiments.

Different inorganic bases (borax, sodium hydroxide, disodium hydrogen phosphate, sodium carbonate and sodium bicarbonate, all used as 0.4 M in the final reaction solutions) were tested for alkalinization. Best results were obtained when NaOH was used. In separate experiments, the effect of NaOH concentration was investigated by carrying out the reaction in different concentrations of NaOH. As shown in Fig. 3, the color intensity increased as the concentration of NaOH increased and the maximum color intensity was obtained when the concentration of NaOH in the final reaction solution was 0.2-0.8 M. The subsequent experiments were carried out using 0.4 M NaOH in the final reaction solution (1 ml of 4 M working NaOH solution).

The reaction was carried out at room temperature (25±5 ℃) and at elevated temperatures (40-100 °C) using a thermostatically controlled water bath (Memmert GmbH, Co. Schwa bach, Germany). It was found that the color intensity slightly increases with temperature (Fig. 4). Nevertheless, the subsequent experiments were carried out at room temperature to simplify the analytical procedure (i.e. avoid using extra equipment; water bath) on the expense of lower limit of detection. This decision was based on the ICH guidelines for validation of analytical procedures ICH, 1995),

Table 5. Determination of CIP and LOM in their pharmaceutical dosage forms by the reference and the proposed initial rate and fixed time spectrophotometric methods [a]

Pharmaceutical dosage form	Reference method [a] (%± RSD)	Initial rate method			Fixed time method		
		Label claim (% ± RSD) [a]	t-value [b]	F-value [b]	Label claim (% ± RSD) [a]	t-value	F-value
Cipromax® tablets	100.1 ± 1.25	99.8 ± 1.58	1.32	1. 60	100.1 ± 1.32	0.19	1.12
Cipromid® tablets	99.8 ± 0.98	100.2 ± 1.15	2.34	1. 38	99.4 ± 1.54	1.49	2.47
Ciprolon® tablets	99.7 ± 1.43	99.6 ± 1.81	0.38	1. 60	100.1 ± 1.61	1.64	1.27
Lomax® tablets	100.2 ± 0.85	99.8 ± 1.64	1.91	3.72	99.8 ± 1.24	2.35	2.13

[a] References: British Pharmacopoeia 2005 & Darwish, 2006 for CIP and LOM, respectively. Values are mean ± RSD of five determinations.

[b] The tabulated values of t and F at 95% confidence limit are 2.78 and 6.39, respectively.

which do not include the detection limit as a part of the validation.

In order to select the most appropriate solvent for dilution, different solvents were tested: water, methanol, ethanol, propan-2-ol, acetonitrile, acetone, and dimethylformamide. The highest color intensity was attained when water was used as a diluting solvent, therefore it was selected for the further investigations.

3.3. Stoichiometry, mechanism, and kinetics of the reaction

The stoichiometry of the reaction of $KMnO_4$ with each of CIP and LOM was investigated by Job`s method (Job,

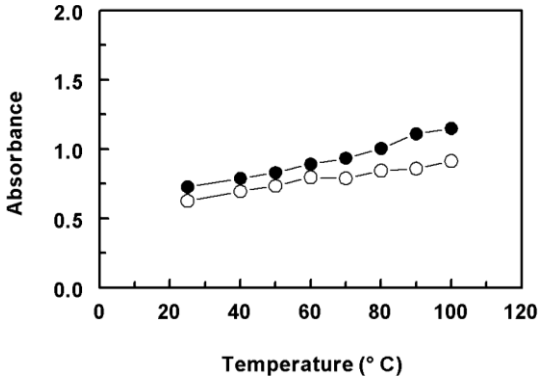


Figure. 4 Effect of temperature on the reaction of $KMnO_4$ (1.2×10^{-3} M) with CIP (○; 60 µg ml^{-1}) and LOM (●; 60 µg ml^{-1}) in presence of NaOH (0.4 M). The reactions were carried out for 20 min.

1936). The results indicated that the ratio of drug: $KMnO_4$ was 1:3. Based on this ratio, the reaction pathway was postulated to proceed as shown in Fig. 5. These findings were coincident with the reported results for oxidation of gatifloxacin with alkaline $KMnO_4$ (Marzouq, 2007).

Under the optimum conditions, the absorbance-time curves for the reaction of varying concentrations of CIP (0.06×10^{-4} – 2.59×10^{-4} M) and LOM (0.13×10^{-4} – 1.55×10^{-4} M) with a fixed concentration of $KMnO_4$ (1.2×10^{-3} M) in presence of NaOH (0.4 M) were generated (Fig. 6). The initial reaction rates (K) were determined from the slopes of these curves. The logarithms of the reaction rate (Log K) were plotted as a function of logarithms of GAT concentrations (log C). The regression analysis for the values was performed by fitting the data to the following equation:

$$\text{Log K} = \log k' + n \log C$$

where K is reaction rate, k' is the rate constant, C is the molar concentration of the analyte (CIP and LOM), and n (slope of the regression line) is the order of the reaction. Straight lines with slope values of 0.8861 and 0.8902 were obtained for CIP and LOM, respectively (Table 2). These values of the slopes (≈ 1) confirmed that the reactions were first order. However under the optimized reaction conditions, the concentrations of $KMnO_4$ and NaOH were in much more excess than that of CIP and LOM in the reaction solution. Therefore, the reactions were regarded as pseudo-first order reactions.

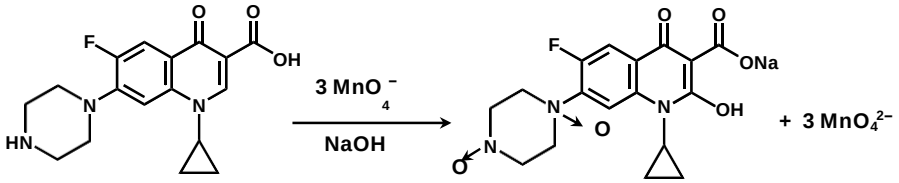
3.4. The apparent rate constant and activation energy

The absorbance-time curves at different temperatures (25-100 ° C) were generated using fixed concentration of CIP and LOM (0.52×10^{-4} M) and $KMnO_4$ (1.2×10^{-3} M). From these curves the apparent rate constants were calculated. The activation energy, defined as the minimum kinetic energy that a molecule possess in order to undergo a reaction, was determined using Arrhenius equation (Martin, 2004):

$$\text{Log k} = \log A - \text{Ea} / 2.303\ RT$$

where k is the apparent rate constant, A is the frequency factor, Ea is the activation energy, T is the ab-

solute temperature (°C + 273), and R is the gas constant (1.987 calories degree^{-1} mole^{-1}). The values of log k were plotted as a function of 1/T. Straight lines with slope (= – Ea/2.303 R) values of – 234.42 and – 218.03 for CIP and LOM, respectively were obtained (Fig. 7). From these data, the activation energy was calculated



Ciprofloxacin Oxidized ciprofloxacin

Figure. 5 Scheme for the reaction pathway of CIP with $KMnO_4$ in presence of NaOH

and found to be 4.48 and 4.17 k joule mole^{-1} for CIP and LOM, respectively. These low activation energies explained that $KMnO_4$ could be used as a useful reagent in the development of a sensitive spectrophotometric method for the determination of both CIP and LOM.

3.5. Quantitation methods

3.5.1. Initial rate method

Regression analysis was performed for the data, and it was found the relations between the logarithm of the reaction rate and the logarithm of the drug concentration were linear in the range of 10–100 and 5–60 g ml^{-1} for CIP and LOM, respectively. The limits of detection (LOD) were 0.46 and 0.66 μg ml^{-1} for CIP and LOM, respectively. These low values of LOD confirmed the high sensitivity of the method and consequently its capability to determine low amounts of the investigated drugs.

3.5.2. Fixed time method

In this method, the absorbance of the reaction solutions containing varying amounts of CIP and LOM were measured at a pre-selected fixed time. Calibration plots of absorbances versus the concentrations of CIP and LOM were established at fixed periods of time for the reactions. The regression equations, coefficients of correlation, and limits of detection are given in Table 3. Obviously, the LOD values decreased as the measuring fixed time increased. The widest linear ranges were obtained at 2 and 5 min in both CIP and LOM, however poor linearity and/or imprecise results were obtained at 2 min. According to the ICH guidelines for validation of analytical procedures (ICH, 1995), the LOD is not required to be part of the validation. Therefore, on the basis of wider concentration range and less time of analysis, the fixed time of 5 min was recommended for analytical procedures for both CIP and LOM.

3.6. Validation of the proposed methods

3.6.1. Precision

The precisions (intra- and inter-assay) of the proposed kinetic spectrophotometric methods were determined at three concentration levels (Table 4). The intra-assay precision was assessed by analyzing 5 replicates of each sample as a batch in a single assay run, and the inter-assay precision was assessed by analyzing the same sample, as triplicate, in a separate assay run on three consecutive days. The samples were analyzed by both the initial rate and fixed time methods. The relative standard deviations (RSD) for the results did not exceed 2 % (Table 4), proving the high reproducibility of the results and the precision of the method. This good level of precision was suitable for quality control analysis of both CIP and LOM in their pharmaceutical dosage forms.

3.6.2. Analytical recovery studies and selectivity

The analytical recovery of the proposed methods was also checked. The obtained mean recoveries and relative standard deviations were in the range 97.5 ±102.5

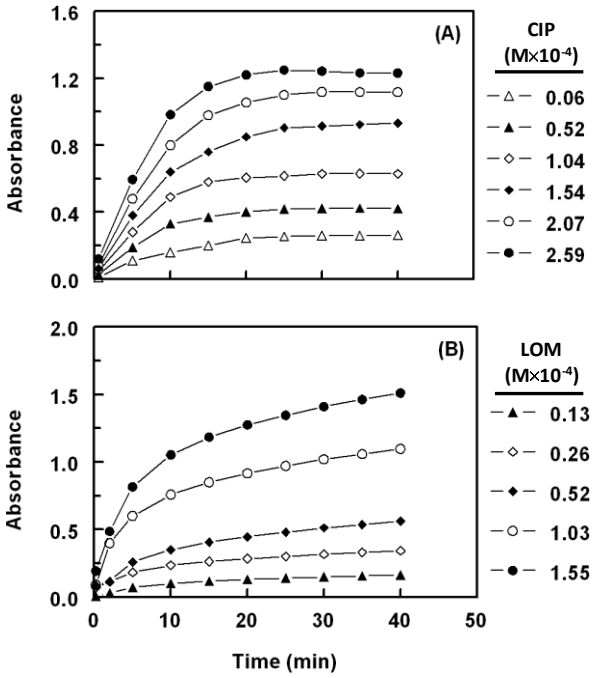


Figure. 6 Absorbance-time curves for the reaction of varying concentrations of CIP (A) and LOM (B) with $KMnO_4$ (1.2×10^{-3} M) in presence of NaOH (0.4 M). The reactions were carried out at temperature (25±5°C).

± 0.05 – 1.94% (Table 4). These results prove the accuracy of the proposed methods. It is worth noting that all the proposed kinetic spectrophotometric methods were performed in the visible region away from the UV-absorption region of the UV-absorbing interfering excipient materials that might be co-extracted from the dosage forms.

3.7. Application of the proposed methods

It is evidenced from the aforementioned results that the proposed spectrophotometric method gave satisfactory results for determination of CIP and LOM in bulk drugs. The proposed initial rate and fixed time

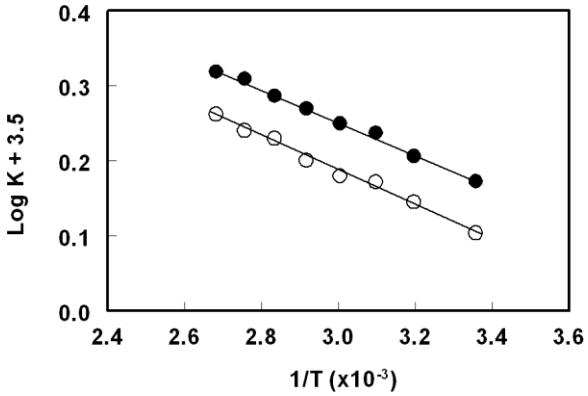


Figure 7. Arrhenius plot for the reaction of $KMnO_4$ (1.2×10^{-3} M) with CIP (○) and LOM (●) in presence of NaOH (0.4 M). T and K are the absolute temperature and the apparent rate constant, respectively. The concentrations of CIP and LOM were 1.30×10^{-4} and 1.03×10^{-4} M, respectively. 3.5 was added to each value of Log K (on the vertical axis) to eliminate the negative signs along the axis.

methods have been applied in the analysis of the commercial pharmaceutical dosage forms. The concentrations of CIP and LOM were computed from their corresponding regression equations. The results of the proposed methods (initial rate or fixed time) were statistically compared with those of the reference methods (British Pharmacopoeia, 2004; Darwish, 2006), with respect to the accuracy and precision. The obtained mean recovery values of the labeled amounts were 99.4 – 100.2 ± 1.15 – 1.81% (Table 5). In the *t*- and F-tests, no significant differences were found between the calculated and theoretical values of both the proposed and the reported methods at 95% confidence level. This indicated the similarities between the precision and accuracy of the proposed and the reference method for the determination of both CIP and LOM in their dosage forms.

3.7. Advantages of the proposed method over the reported spectrophotometric methods

The reported spectrophotometric methods for determination of CIP and LOM were based on the measurement of the ultraviolet absorption by the drugs (Zhang, 1997), formation of charge-transfer complexes (Mostafa, 2002), formation of extractive ion-pair associates (Gowda, 2003; Tan, 2001), formation of water-insoluble reineckate salts (Avadhanulu, 1999), and oxidation with cerium(IV) (Saleh, 1997; Rao, 1990).

The proposed method, because it involved measurements in the visible region, is more selective than the reported UV-based methods The proposed method is superior to the reported visible spectrophotometric methods that involved the formation of charge-transfer complexes and extractive ion-pair associates in terms of health and environmental safety, cost, and procedure simplicity. In the proposed method, safe and cheap water was used as a solvent, however the reported methods used costive organic solvents which impose health and environmental hazards, and they require special care for their sanitary disposal. The proposed method did not require tedious liquid-liquid extraction for the drug base (after its freeing for the acid salt in the charge-transfer based methods), or extraction of the chromophores (in the ion-pair based methods). As well, the proposed procedure is simpler than that of the methods based on the formation of water-insoluble reineckate salts, in which tedious procedures were involved in the quantitative separation of the colored reineckate precipitates before their dissolving with organic solvent and measuring their color intensities.

Although the oxidation reaction (the same basis of the proposed method) was involved in previous spectrophotometric methods, however the procedure of the proposed method is simpler and more time-saving. In the proposed method, one-step reaction was involved, however in the reported methods, two-step reactions were involved; the first step was the oxidation of the drugs with an excess cerium(IV) and the second step was the addition of a color developing reagent such as p-dimethylaminobenzaldehyde (Saleh, 1997) or 3-methylbenzothiazolin-2-one- hydrazone (Rao, 1990). Furthermore, the proposed procedure was carried out at room temperature, however the reported oxidation-based procedures were carried out at elevated temperature (in a water bath) for a longer time.

The high sensitivity and wide linear dynamic range that has been achieved in the proposed method confers the ease in preparation of the samples for analysis. From the economical point of view, all the analytical reagents are inexpensive, have excellent shelf life, and are available in any analytical laboratory.

These advantages encourage the application of the proposed method in routine analysis of CIP and LOM in quality control laboratories, as alternatives for the existing methods.

4. CONCLUSION

The present study described, for the first time, a simple and sensitive kinetic spectrophotometric method for

the determination of both CIP and LOM in their dosage forms. The proposed initial rate and fixed time methods can be easily applied as they do not require elaborate treatment of the samples and/or tedious procedures for the analysis. As well, both methods are sensitive enough for analysis of lower amounts of the drugs. Furthermore, the proposed methods do not require expensive instruments and/or critical analytical reagents. These advantages give the proposed methods a great value and encourage its application to the analysis of CIP and LOM in quality control laboratories.

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