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Interaction study of moxifloxacin with Cu(II) ion using square-wave voltammetry and its application in the determination in tablets

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Abstract: This work presents an electroanalytical method for the determination of moxifloxacin (MOXI) in tablets by its interaction with Cu(II) ion and subsequent electrochemical reduction at hanging mercury drop electrode (HMDE). A well-defined reduction peak at -0.21 V vs. Ag/AgCl in Phosphate buffer 0.04 mol L^{-1} pH 8.0 was observed for the complex reduction MOXI-Cu(II), using square-wave voltammetry (SWV). Using a 10 s of accumulation time at -0.40 V was found a limit detection of 3.60×10^{-8} mol l^{-1}. The obtained results have shown good agreement with those obtained by spectrophotometric method.

Keywords: moxifloxacin; electroanalysis; complexation of moxifloxacin.

Introduction

Moxifloxacin (MOXI) {1-cyclopropyl-7-[2, 8-diazobicyclo (4.3.0) nonane]-6-fluoro-8-methoxy-1, 4-dihydro-4-oxo-3-quinolone carboxylic acid} (Fig. 1) is a new 8-methoxyquinolone derivate of fluoroquinolones with enhanced activity *in vitro* against Gram-positives bacteria and maintenance of activity against Gram-negative bacteria [1-3]. The drug is rapidly absorbed, reaching maximum plasma concentrations between (1-4 h) after oral administration; its half-life of (11-15 h) allows a daily administration [3]. MOXI is administered to patients in 400 mg daily doses, being that the final concentrations in serum and urine for the treated patients are of 2-5 and 30-60 µg ml^{-1}, respectively [4].

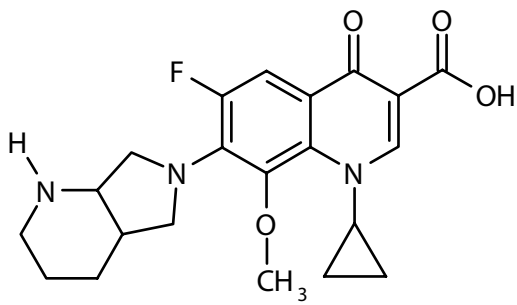

Figure 1. Structure of moxifloxacin.

Studies found in the literature [5-7] have shown that the absorption of quinolone drugs is lowered when they are consumed simultaneously with magnesium or aluminium antacids and others bivalent cations. The proposed mechanism of

the interaction between quinolone and metal cations was based on chelation between the metal and the carbonyl and carboxyl groups. Since these functional groups are required for antibacterial activity, it could be anticipated that all of the quinolones could be interacting with metal ions [8].

Complexation with metals has been utilized by several workers [9-15] for the development of electroanalytical and spectrophotometric methods for the determination of quinolones in pharmaceutical formulation [9]. The interaction of fluoroquinolones with metal ions has attracted considerable interest not only for the development of analytical methods, but also to provide information about the action mechanism of the pharmaceutical compound [10-12]. A differential-pulse polarographic (DPP) method was described for determination of ofloxacin in tablets based on complexation with Cu(II) ion [10] and norfloxacin, ciprofloxacin and sparfloxacin by complexation with Ni(II) ion [11]. The quinolones complexation with metal ions has also been used for characterization of the electrochemical behavior and development of analytical methods by cyclic and linear sweep voltammetric techniques [12-15].

Recently, electrochemical methods using square-wave voltammetry (SWV) and differential-pulse voltammetry (DPV) [16] and spectrofluorimetric [17] have been applied for determinations of MOXI in pure form in pharmaceutical formulation. In these studies, the linear ranges obtained were in the interval of concentration 4.40×10^{-7}–1.00×10^{-5} mol l^{-1} and 0.75×10^{-7}–7.50×10^{-7} mol l^{-1} with detection limits of 4.40×10^{-8} mol l^{-1} and 2.50×10^{-8} mol l^{-1}, respectively. However, no electroanalytical method has been reported in the literature for voltammetric determination of MOXI in pharmaceutical products by using its interaction with metal ions.

The present work presents a simple, fast and sensitive enough electroanalytical methodology for determination of MOXI in pharmaceutical formulation by using its interaction with Cu(II) ion by square-wave voltammetry at hanging mercury drop electrode (HMDE). The data were compared with those obtained by spectrophotometric method and by spectrofluorimetric reported methods [16], both chosen as reference for validation of the proposed method.

Experimental

Instrumentation

Electrochemical Analysis were performed using an μAutolab TYPE II (Eco Chemie BV) interfaced with a microcomputer supplied with a General Purpose Electrochemical System (GPES) software (Eco Chemie BV) for data acquisition. A three-electrode stand system (Metrohm 663 V) composed by one hanging mercury dropping electrode (HMDE) (area: 0.52 mm^2), Ag/AgCl reference electrode and a glassy carbon auxiliary electrode were used.

The spectrophotometric measurements were carried out using a Hitachi spectrophotometer (model U-3000) with 1.0 cm path length quartz cells. The solutions were scanned from 200-450 nm (with slit = 2.0 nm). All measurements were performed at room temperature.

All pH measurements were made using a combined glass electrode (type BlueLine; Shott) connected to the digital pH-meter (model alpha, Shott). The de-ionized water was purified with a Milli-Q plus system (Millipore). An ultra-son Unique (ultrasonic model) was used for dissolution of the Avelox® tablets and all reagents. A micropipette (Oxford®) was used to transfer the reactant solution to the cell throughout the experimental work.

Reagents

Solutions of MOXI (BAYER) and copper (II) (MERCK) (1.00×10^{-3} mol l^{-1}), all of analytical grade quality, were prepared by dissolving the solid products in methanol and de-ionized water, respectively. Working solutions were prepared daily by appropriate dilutions with de-ionized water. The working solutions have shown enough stability during all time of storage.

The solutions used as supporting electrolyte were prepared in the usual way: Britton–Robinson buffer 0.04 mol l^{-1} in a mixture of 0.04 mol l^{-1} acetic acid (Merck), 0.04 mol l^{-1} boric acid (Merck) and 0.04 mol l^{-1} in orthophosphoric acid (Merck), with the appropriated

amount of 0.20 mol l^{-1} sodium hydroxide (Merck) solution. The Phosphate buffer 0.04 mol l^{-1} also used a supporting electrolyte was prepared using di-sodium hydrogen Phosphate dihydrated (Merck) and sodium hydrogen Phosphate monohydrated (Merck).

Procedures

Procedure for making calibration graphs

An aliquot of 10 ml of the supporting electrolyte solution was introduced into the electrochemical cell and then de-aerated with pure nitrogen for 10 min. A selected accumulation potential was then applied to the hanging mercury drop, for a selected time period, while the solution was stirred at 1500 rpm. The stirring was then stopped, and after a 15 s rest period, a square-wave voltammogram was recorded from +0.10 to -1.60 V. After the background voltammogram had been recorded, the aliquot of the reactant MOXI and Cu(II) solution was introduced into the cell and the voltammogram was then recorded at a new mercury drop.

Procedure for Avelox® tablets

Avelox® tablets labeled containing 436.80 mg of moxifloxacin hydrochloride, equivalent to 400 mg of moxifloxacin drug and some inactive excipients were analyzed. Five Avelox® tablets were weighed and powdered. The average mass per tablet was determined. A quantity of the powder, equivalent to 400 mg of MOXI, was transferred accurately into a 1000 ml calibrated dark flask and dissolved in approximately 500 ml of water in ultra sonic bath for 20 min followed by dilution with de-ionized water. The solution was then filtered through a filter millex (0.22 μm pore size, Millipore) to isolate the insoluble excipients. The desired concentration for the drug was obtained by accurate dilution with de-ionized water. An aliquot of the clear supernatant liquor was then transferred to a voltammetric cell containing 20 ml (10 ml Phosphate buffer solution pH 8.0 and 10 ml water). The square-wave voltammograms were then recorded after 10 s of pre-concentration at -0.40 V and the drug content of each tablet was determined by standard addition method.

Procedure for calibration graph and analysis of MOXI in pharmaceutical formulations for UV-Vis spectrophotometry.

A stock solution of ($1.00x10^{-3}$ mol l^{-1}) moxifloxacin was prepared in methanol and stored in the dark inside in freezer. Accurate aliquots containing between (100–1500 μl) of MOXI were transferred to 25 ml calibrated flask and solution mixed with methanol up to a final volume of 25 ml. The absorbance was measured at λ_{max} 297 nm using methanol as the blank reagent.

The quantification was performed by standard addition method by dilution of an aliquot of the Avelox® drug solution prepared previously in to 10 ml calibrated flask with methanol and adopting the same procedure described above.

Results and discussion

Electrochemical behavior of MOXI-Cu(II) interaction

Typical square-wave voltammetry (SWV) behavior of MOXI in the absence and presence of Cu(II) ion are shown in Fig. 2. The reduction of MOXI presented a well-defined main reduction peak apparently irreversible at -1.38 V (Fig. 2a). It can also be observed in Fig. 2b that, Cu(II) solutions presented only one reduction peak at -0.05 V (Fig. 2b). However, Fig. 2c exhibits a new well-defined reduction peak at -0.21 V when Cu(II) is mixed with MOXI (Fig. 2c), indicating the occurrence of the complex MOXI-Cu(II) formation.

Effect of pH

The influence of the pH on the voltammetric behavior was tested for: Britton-Robinson (pH 2.0-11.0) and Phosphate (pH 5.0-9.0) buffer solution analyzing the yielding peak current after 10 s of pre-concentration ($t_{acc.}$) at -0.30 V ($E_{acc.}$). The best results with respect to shape, sensibility and reproducibility of the peak current were obtained in 0.04 mol l^{-1} Phosphate buffer solution pH 8.0.

Square-wave voltammograms recorded for $5.00x10^{-6}$ mol l^{-1} of MOXI in the presence of $5.00x10^{-6}$ mol l^{-1} Cu(II) ion in Phosphate buffer ($t_{acc.}$ = 10 s) exhibits a well-defined peak at -0.21 V in the whole pH range investigated (pH 5.0-

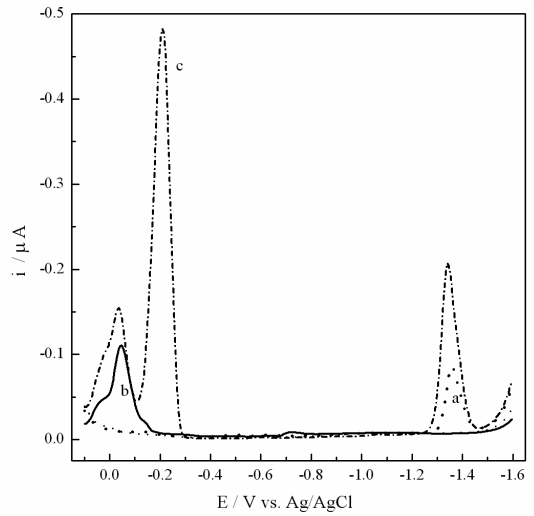

Figure 2. Square-wave voltammograms for MOXI in the presence of Cu(II); (a) 1.07x10^{-6} mol l^{-1} of MOXI; (b) 2.50x10^{-6} mol l^{-1} of Cu(II) and (c) 3.00x10^{-6} mol l^{-1} of MOXI mixing with 2.50x10^{-6} mol l^{-1} of Cu(II) in 0.04 mol l^{-1} Phosphate buffer pH 8.0. Other parameters: Accumulation time ($t_{acc.}$): 10 s; accumulation potential ($E_{acc.}$): -0.30 V; frequency (f) = 60 Hz, scan increment (ΔE_S) = 6 mV, pulse amplitude (E_{sw}) = 25 mV.

9.0). The effect of pH on peak current (i_p) and peak potential (E_p) of the MOXI-Cu(II) complex are shown in Fig. 3 (a and b), respectively. As can be seen, the i_p of the formed complex increases on going from pH 5.0 to 8.0, where the maximum value is obtained at pH 8.0. In larger pH values than 8.0 the i_p decreases abruptly. From the i_p vs. pH relationship it is seen that different ionic species are formed, whose present different diffusion coefficients in the solution.

From E_p vs. pH (Fig. 3b), it is observed that the reduction potential of MOXI-Cu(II) complex shifted to more negative values with pH increase, indicating the presence of a chemical reaction with participation of protons [18]. Two linear ranges were also observed. Firstly a linear relationship is obtained from 5.0 to 7.5 the pH increase, following the equation: {E_p(V) = -0.044 - 0.042 pH} and from 7.5 to 9.0 the pH increase, following the equation: {E_p(V) = -0.227 - 0.066 pH}, with an intersection point at pH ≈7.6, assigning a pK_a value of MOXI. This is in accordance with literature data about reduction scheme of some fluoroquinolones antibiotic hydrogenation of the carboxylic group [19, 20]. For analytical purposes, 0.04 mol l^{-1} Phosphate buffer solution at pH 8.0 was therefore chosen as best work conditions.

In continuity of the studies, the coordination number of the formed complex adsorbed on the electrode surface (m) and the stability constant of the complex (β) was determined as described for Zhang et al [12, 13], through the use of the following equation:

$$\frac{1}{i_p} = \frac{1}{i_{p,\max}} + \frac{1}{\beta . i_{p,\max} . C_L^m}$$

Where i_p is the measured peak current; $i_{p,max}$ is the peak current in the case of complete metal complexing and C_L is the concentration of the MOXI. A relationship linear was obtained for m = 1, indicating that the composition of the electroactive complex of MOXI-Cu(II) at pH 8.0 is 1:1 and the constant stability (β) is 3.10x10^4.

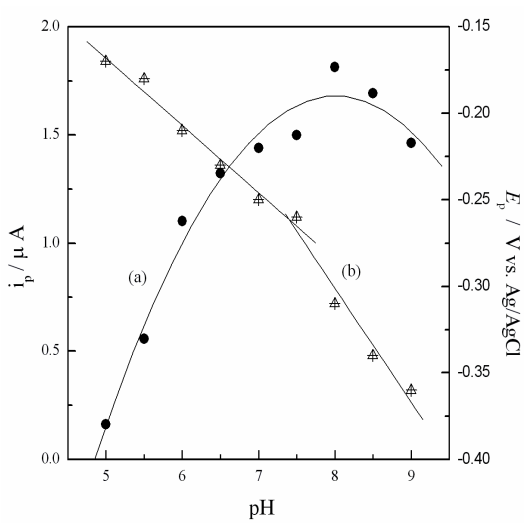

Figure 3. Influence of pH on the peak current (a) and peak potential (b) response for 5.00-10^{-6} mol l^{-1} MOXI in the presence of 5.00-10^{-6} mol l^{-1} Cu(II) in Phosphate buffers (pH 5.0–9.0). Other parameters: Fig. 2.

Effect of accumulation potential and accumulation time

The effect of accumulation potential ($E_{acc.}$) on the peak current response was investigated from +0.10 and -0.70 V for mixture of $4.00x10^{-6}$ mol l^{-1} of MOXI and Cu(II) in Phosphate buffer pH 8.0 using ($t_{acc.}$ = 10 s). The peak height increases when the accumulation potential increases from +0.10 to -0.40 V, but decreases abruptly up to -0.70 V. A potential of -0.40 V was adopted as the optimum accumulation potential for MOXI-Cu(II) complex detection.

The effect of accumulation time ($t_{acc.}$) for $4.00x10^{-6}$ mol l^{-1} MOXI and Cu(II) solutions at pH 8.0 is shown in Fig. 4. As expected, pre-concentration is a function of the accumulation time. The peak current was found to increase with increasing the accumulating time between 0 and 10 s. Above this time, the peak current decreases and it is almost constant up to 25 s, indicating that the adsorptive saturation of the drug onto the mercury electrode surface was achieved [21-23]. This phenomenon leads to an effective alternative for the increase of the method sensibility. Hence, an accumulation time of 10 s was chosen to evaluate the analytical parameters of the proposed method.

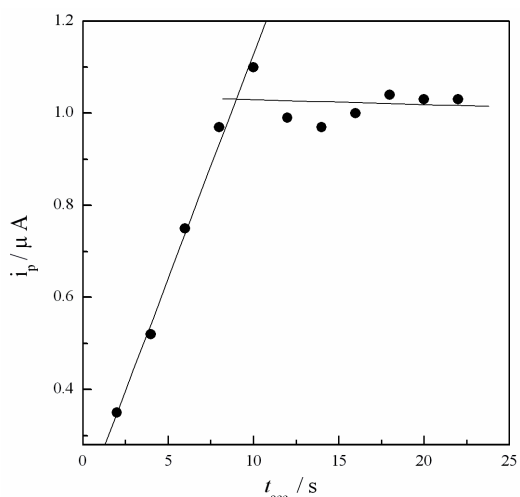

Figure 4. Effect of the accumulation time on the peak current in the response for a 5.00?10^{-6} mol l?1 MOXI in the presence of 5.00?$10^{?6}$ mol l?1 Cu(II) solution in Phosphate buffer (pH 8.0). Other parameters: Fig. 2.

Instrumental parameters

Several instrumental parameters, such as drop size, stirring rate, scan increment (ΔE_S) and pulse amplitude (E_{sw}) were examined. The chosen working conditions were: drop size of larger (drop area 0.52 mm^2), stirring rate of 1500 rpm, ΔE_S = 6 mV and E_{sw} = 25 mV. The current peak was not modified with rest period change. The chosen value 15 s is sufficient to allow the formation of a uniform concentration of the complex on the mercury drop.

Analytical parameters

In order to investigate the possibility of applying the proposed method to the determination of MOXI in pharmaceutical formulation by interaction of Cu(II) ion, calibration curves were constructed. Using the optimal conditions proposed previously, was found that the reduction peak of MOXI-Cu(II) complex is proportional to the increase of the concentration of MOXI from $1.00x10^{-7}$ to $3.50x10^{-6}$ mol l^{-1}, when the Cu(II) ion concentration was fixed at $5.00x10^{-6}$ mol l^{-1} in Phosphate buffer pH 8.0. Fig. 5 shown the calibration graphs and respective voltammograms obtained at ($t_{acc.}$ = 10 s) and ($E_{acc.}$ =-0.40 V). Concentration range and regression equations for obtained curves are listed in Table 1.

The limits of detection (LOD) and quantitation (LOQ) [24] were calculated using the statistic treatment ($3xS.D._a/b$) and ($10xS.D._a/b$), respectively, where, ($S.D._a$) is the standard deviation of the average arithmetic of ten voltammograms of the blank obtained in the same potential of MOXI-Cu(II) complex and (b) is the slope of the calibration curve. The LOD and LOQ values were of $3.60x10^{-8}$ mol l^{-1} and $1.20x10^{-7}$ mol l^{-1}, respectively. The obtained LOD and LOQ values using the proposed procedure were compared with two reported methods, spectrofluorimetric [17] and spectrophotometric (Table 1). Both LOD and LOQ values indicate the good sensitivity of the proposed method.

The repeatability and precision of the method was determined by making successive eight measurements for two solutions of MOXI ($1.00x10^{-7}$ and $3.00x10^{-6}$ mol l^{-1} in the presence of $2.00x10^{-7}$ and $6.00x10^{-6}$ mol l^{-1} of Cu(II), respectively) at pH 8.0, using ($t_{acc.}$ = 10 s) and

Table 1. Analytical parameters of the proposed and reported method.

Parameter	Methods		
	Electroanalytical	Spectrophotometric	Reported [17]
Conc. range (mol l^{-1})	$(0.10\text{-}3.50)\times10^{-6}$	$(0.44\text{-}6.50)\times10^{-5}$	$(0.75\text{-}7.50)\times10^{-7}$
Intercept (μA)	-0.1717	-0.0422	-
S.D. of intercept	0.0997	1.66×10^{-3}	-
Slope (μA l μmol^{-1})	0.2452	0.0451	-
S.D. of Slope	0.0869	1.80×10^{-4}	-
r[a]	0.996	0.999	0.999
LOD[b] (mol l^{-1})	3.60×10^{-8}	1.05×10^{-7}	2.50×10^{-8}
LOQ[c] (mol l^{-1})	1.20×10^{-7}	3.70×10^{-7}	7.50×10^{-8}

[a] coefficient correlation; [b] detection limit; [c] quantitation limit.

($E_{acc.}$ =-0.40 V). The relative standard deviation was 2.68 and 5.00%, respectively.

The interference of some metal ion was tested. It was found that small amounts, i.e. Zn(II), Ni(II), Pb(II), Fe(III), Mg(II) and Ca(II) at concentration smaller than $1.00\text{x}10^{-5}$ mol l^{-1} did not cause significant effect on the determination of MOXI by complexation with Cu(II) ion.

Analysis of tablets

The optimized procedure was successfully applied for determination of MOXI drug in tablets (Avelox®-400 mg) and the results obtained are shown in Table 2. The amount of MOXI in Avelox® tablets was determined by the standard additions method after dilution of the sample in 10 ml of Phosphate buffer and 10 ml of de-ionized water to avoid matrix effects. The quantitation was achieved by standard addition of the MOXI-Cu(II). The mean value of 408.33 mg was obtained (Table 2), which is in a good agreement with the reported method [17], so the proposed method could be recommended for MOXI determination in pharmaceutical formulation. These obtained results were also compared with those obtained by the spectrophotometric method (Table 2). As can be observed, a good agreement was achieved between both tested methods. Furthermore, excipients presents in the commercial tablet do not cause interference with MOXI determination. The accuracy and precision of the proposed procedure was also judged by applying the standard addition method. The precision was expressed as the relative standard deviation (R.S.D.) and accuracy as a mean relative error (Table 2). As can be seen from these results, the MOXI can be quantitatively determined using the proposed method in formulation products containing MOXI by interaction with Cu(II).

Analysis of tablets for UV-Vis

The UV spectrophotometric method was also developed with the objective to obtain comparative results for validation of the electroanalytical method. Absorption spectra obtained for MOXI exhibits one band at 297 nm (data not shown) and this was used for analytical purposes. The band exhibits a linear relationship between absorbance and drug concentration in the range of $4.40\text{x}10^{-6}$ to $6.50\text{x}10^{-5}$ mol l^{-1} (Table 1). For analytical applications, the standard addition method was used and the results are showed in the Table 2. As mentioned above, no significant difference was found for both methods. Moreover, the spectrophotometric method was less sensitive than the electroanalytical method.

Table 2. Spectrophotometric and electroanalytical assay of MOXI in pharmaceutical formulation.

Analysis method	Drug	Value labeled (mg)	Found (mg)	R.S.D. (%)	E_r (%)
Proposed method	Avelox®	400.00	408.30 [a]	1.00	2.08
Spectrophotometric method	Avelox®	400.00	402.00 [a]	2.62	0.50
	Octegra®	400.00	405.00	0.50	-
Reported method [b]	Actira®	400.00	402.00	0.30	-
	Profox®	400.00	400.00	0.40	-

[a] Average of five determinations; [b] Reference [17]; R.S.D. relative standard deviation; E_r relative error.

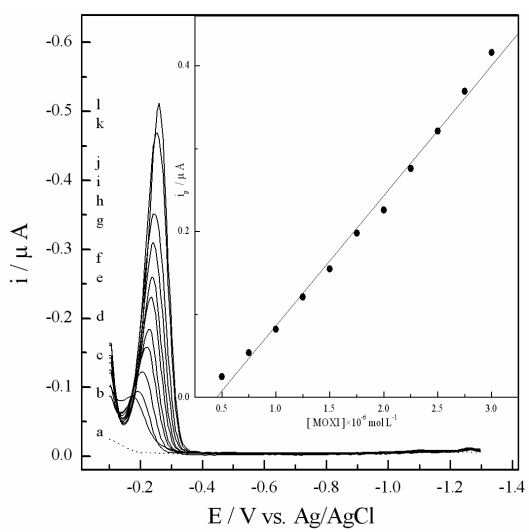

Figure 5. Adsorptive square-wave voltammograms obtained of the increasing concentration of MOXI on Cu(II) solution Phosphate buffers (pH 8.0): (a) blank, (b) 0.50x10^{-6}, (c) 0.75x10^{-6}, (d) 1.00x10^{-6}, (e) 1.25x10^{-6}, (f) 1.50x10^{-6}, (g) 1.75x10^{-6}, (h) 2.00x10^{-6}, (i) 2.25x10^{-6}, (j) 2.50x10^{-6}, (k) 2.75x10^{-6} and (l) 3.00x10^{-6} mol l^{-1}, respectively. Inset: Dependence of the peak current on the MOXI concentration. Parameter: $t_{acc.}$ = 10 s; $E_{acc.}$ = -0.40 V; f = 60 s^{-1}, ΔE_s = 10 mV and E_{sw} = 25 mV.

Conclusion

In this work was reported that the interaction of MOXI-Cu(II) resulted in a 1:1 complex that is reduced in a new well-defined peak at -0.21 V vs. Ag/AgCl and its the base was used for analytical determinations by square-wave voltammetry. Besides, the interference from excipients of the drugs does not interfere with the determination. Therefore, extraction procedures are not needed. Comparing these results with those obtained by the spectrophotometric and spectrofluorimetric [17] methods for the MOXI assay it is possible to see a good agreement between both results, confirming that the proposed procedure can be used for MOXI analysis of this antibiotic drug in pharmaceutical formulation.

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Estudo de interação de moxifloxacina com íon Cu(II) usando voltametria de onda quadrada e sua aplicação na determinação em formulação.

Resumo: Este trabalho apresenta um método eletroanalítico para a determinação de moxifloxacina em uma formulação farmacêutica a partir da interação com o íon Cu(II), monitorando a redução sobre elétrodo de gota de mercúrio pendente (HMDE). Um pico de redução bem definido em -0.21 V vs. Ag/AgCl foi observado após a interação da MOXI com o íon Cu(II) por voltametria de onda quadrada (SWV) em tampão fosfato 0.04 mol l^{-1} pH 8.0. Usando 10 segundos de pré-contração em -0.40 V um limite de detecção de 3.60 10^{-8} mol l^{-1} foi encontrado. A comparação dos resultados obtidos com um método espectrofométrico não mostrou diferença significativa entre as medidas.

Palavras-chave: moxifloxacina; eletroanálises; complexação de moxifloxacina

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