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Voltammetric analysis of Cu (II), Cd (II) and Zn (II) complexes and their cyclic voltammetry with several cephalosporin antibiotics

N. Abo El-Maali*, A.H. Osman, A.A.M. Aly, G.A.A. Al-Hazmi

Chemistry Department, Faculty of Science, Assiut University, 71516-Assiut, Egypt

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Abstract

Both osteryoung square wave voltammetry and cyclic voltammetry have been utilized to elucidate and confirm the possible complexation reaction that occur between the various cephalosporin antibiotics and either the toxic, non-essential metal ion, viz. Cd (II), or the essential but toxic (when their concentration exceeds certain level in serum) metal ions, viz. Cu (II) and Zn (II).

Voltammetric measurements indicated the existence of 1:1 metal-to-ligand ratio (as in cephalexin and cephapirin complexes), 1:2 ratio (such as in cefamandole, cefuroxime and cefotaxime complexes) and 2:1 ratio in case of ceftazidime complexes. Adsorption behavior was evidenced for Cu (II)–cefuroxime or ceftazidime complexes as well as for those for Zn (II)–cephalexin or cephapirin. This phenomenon could be used for the determination of either the antibiotic or the metal ion using adsorptive stripping voltammetry. Detection limits down to 7×10^{-10} M have been easily achieved.

Keywords: Cephalosporin antibiotics; Complexes; Cyclic voltammetry; Osteryoung square wave voltammetry

1. Introduction

Cephalosporins are the second major group of β-lactam antibiotics [1], they are classified into four generations. The biological activity of these antibiotics is the β-lactam ring [2]. The possible interaction that may occur between metal ions and these antibiotics is of importance as this may affect the drug absorption through the human membrane [3]. This may help in understanding what is going in vivo when administrating an antibiotic. Since metal ions are known to accelerate the rates of chemical reactions [4], it may also "mask" a nucleophile and thus prevent an otherwise likely side reaction [4]. Metal ions also act as Lewis acid catalysts especially the transition ones like Zn, Fe, Mn and Cu because they have empty d electron orbitals that can act as electron sinks [5]. The functioning of a metal as a Lewis acid requires chelate formations with a ligand such as that occur with the enzymes in vivo [5]. Antibiotics also can behave as ligands [6–11]. Although few reports exist in the literature concerning this topic area, some are cited either using voltammetry [6–8] or other methods, e.g. spectrophotometry [9–11].

Various electroanalytical techniques have been used to study the polarographic activity [12–17], degradation products, and the electrode reaction of cephalosporins [18,19]. The electrochemical behavior of cephalexin has been studied by Li and Chen [20]. The electrochemical behaviors of cephalexin and cephapirin have been determined using differential pulse polarography in Britton–Robinson buffer (pH 7.3) by Fredrik et al. [21]. Bernacca et al. [22] have investigated a polarographic behavior of the β-lactam antibiotic cefuroxime and study of the reduction mechanism in acidic media. The electrochemical behavior and analysis of cefotaxime sodium have been studied by Raghavan et al. [23]. Cathodic

* Corresponding author.
E-mail address: nelmaali@yahoo.com (N. Abo El-Maali).

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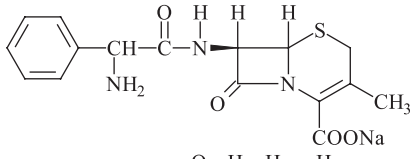
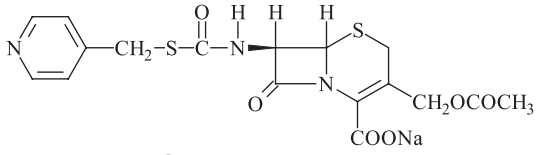
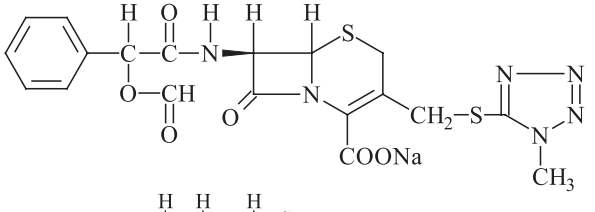
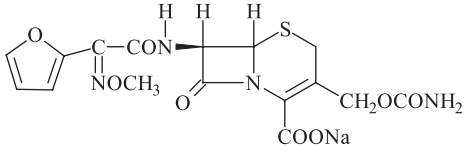
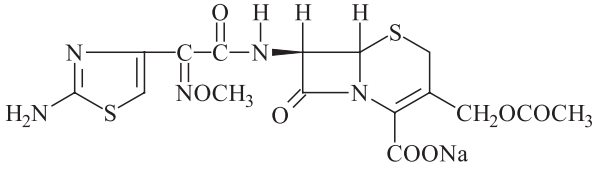
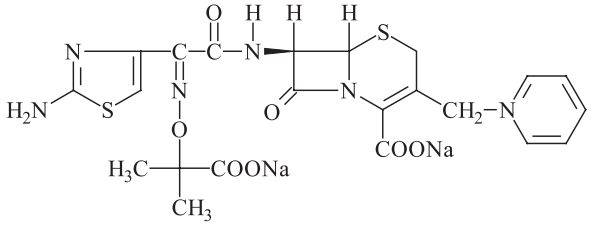
stripping voltammetric method has been described for determining cephalosporin antibiotic ceftriaxone by Abo El Maali et al. [12].

Cefotaxime and cefuroxime in Britton–Robinson or Clark–Lubs buffer solution as supporting electrolyte have been examined by d.c., sampled-d.c. and differential pulse polarography and cyclic voltammetry [24]. Cefotaxime and cefuroxime each gave two reduction waves ($E_{1/2}$=−0.6–0.8 V vs. Ag–AgCl). Each drug could be determined at weakly acid pH by Zhang et al. [25] have studied the voltammetric behavior of cefotaxime sodium and its determination by single-sweep oscillopolarography. Interference caused by Fe (II), Cu (II), Zn (II), and Cd (II) can be avoided by addition of 0.3 ml of 5% EDTA.

A differential pulse polarographic method has been described for determining ceftazidime in urine samples with and without prior extraction [26]. Ceftazidime also has been determined by cathodic-stripping voltammetry [27] in a supporting electrode containing 0.45 μg/ml poly-L-lysine in Britton–Robinson buffer of pH 10. Various types of electrodes have been utilized [28] for an electrochemical study of ceftazidime in aqueous and biological media.

Few reports are found in the literature concerning the identification and isolation of the metal ions–cephalosporin complexes [29]. The aim of the present work is to utilize our previous publications [30,31] for studying the electrochemical behavior of the isolated solid Cu (II), Cd (II) and Zn (II) cephalosporin antibiotics namely: Cephalexin (CEX), Cephapirin (CEP), Cefamandole (CML), Cefuroxime (CRX), Cefotaxime (CTX) and Ceftazidime (CFZ), with their use for quantifying either the antibiotic or the metal ions using the adsorptive stripping voltammetric method of analysis.

Table 1
Structure, name, generation, and notation of the antibiotics under investigation

Name	Generation	Notation	Structure
Cephalexin	First	CEX	
Cephapirin	First	CEP	
Cefamandole	Second	CML	
Cefuroxime	Second	CRX	
Cefotaxime	Third	CTX	
Ceftazidime	Third	CFZ	

2. Experimental

All chemicals were of analytical grade, cephalexin (CID, Assiut, Egypt) and the sodium form of cephapirin (Bristol-Myers Squibb, New York), cefamandole (Eli Lilly, Italia), cefuroxime (Glaxo Wellcome, U.K.), cefotaxime (Pharco Pharmaceutical, A.R.E.) and ceftazidime (Glaxo Wellcome) were used as purchased.

2.1. Apparatus

Voltammetric measurements were recorded using a BioAnalytical System BAS CV-50 W Voltammetric Analyzer (USA) electrochemical running under windows™ software.

Measurements were taken using Static Mercury Electrode (SME) as working electrode, the capillary used is the standard capillary (MF-2090) having a beveled tip with a 100-μm ID. A BAS silver/silver chloride (MF-2063) serves as reference electrode and a BAS platinum wire (MW-1032) serves as an auxiliary one. The cell was completely shielded from any perturbing noises by a faraday cage (EF-1425).

All voltammograms were collected using an hp Hewlett Packard Laser Jet 4L printer.

The pHs were measured using the Fischer Scientific Accment pH Meter Model 810 equipped with a combined

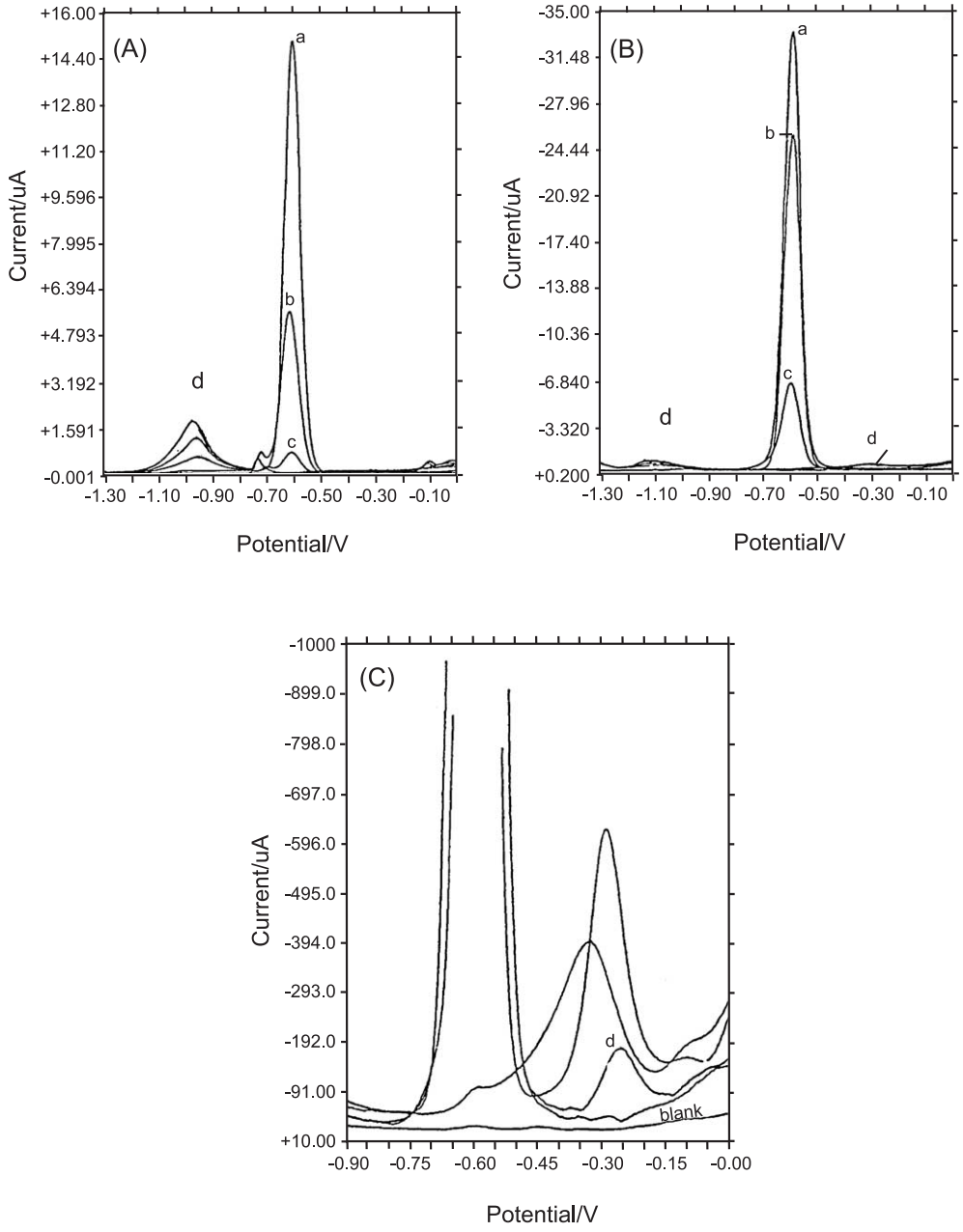


Fig. 1. Osteryoung square wave voltammograms of: (A) Cd–Cefuroxime, (B) Cd–Cefotaxime, (C) Cd–Cephapirin, (a) Cd (II), (b) Cd (II)+Cefuroxime, (c) solid synthesized complex and (d) Cefuroxime alone, pH 7.34 (1.7 M Ac/NaOH).

glass electrode, which is calibrated regularly with buffer solutions (pH 4.00 and 7.00).

For Osteryoung square wave voltammetry (OSWV), the experimental parameters used are:

Initial E (mV)=−1600 (variable), Final E (mV)=0 (variable) (anodic direction),
Initial E (mV)=0, Final E (mV)=−1600 (cathodic direction),
S.W. amplitude (mV)=25,
Frequency (Hz)=15,
Step E (mV)=4,
Quiet time (s)=0.

For Cyclic Voltammetry (CV), the parameters used are:

Initial E (mV)=−1600 (variable),
High E (mV)=0 (variable),
Low E (mV)=−1600,
Initial $P/N=P$,
Scan rate (mV/s)=100,
Sweep Segments=2,
Ampl Int (mV)=1,
Quiet time (s)=0.

V3 series HTL micropipettes (Germany) were used to pipette microliter volumes of solutions.

2.2. Reagents and solutions

A fresh solution was always prepared daily of each antibiotics by dissolving the appropriate weight in doubly distilled water. Antibiotics were used as received without any further purification.

The supporting electrolyte was 10 ml of acetic acid (Merck quality), the pH was adjusted to 7.34 using free carbonate sodium hydroxide solution.

All reagents were of analytical grade quality. All measurements were carried out at 25±1 °C. The solution was degassed with highly purified nitrogen for 8 min to remove oxygen.

2.3. Solutions of metal ions

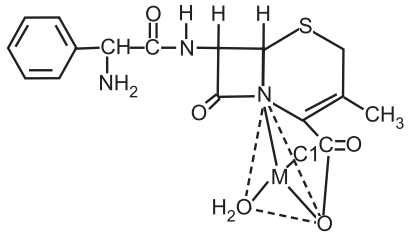
Stock solutions (0.01 M) used in complex formation of cadmium sulphate (Adwic Prolabo), zinc sulphate pentahydrate (Riedel-Dehan Seelze-Hannover) and copper nitrate (Arabic Laboratory Equipment) were prepared daily. The solutions were prepared and diluted as required for standard additions for quantitative analysis.

3. Results and discussion

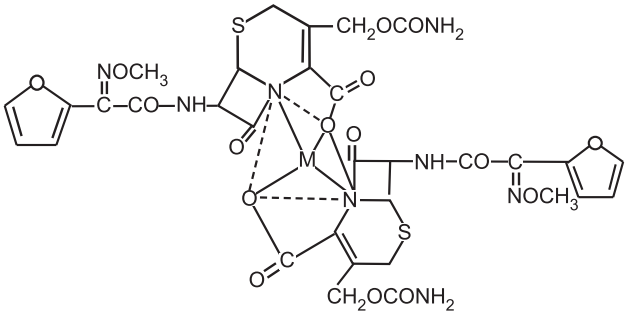
The possible complex formation reaction between either the toxic, non-essential metal ions, e.g. Cd (II) or the essential but toxic metal ions, e.g. Cu (II), Zn (II) with several cephalosporin antibiotics, is investigated. The antibiotics under investigation are cited in Table 1. Their solid complexes with Cu (II), Cd (II) and Zn (II) were prepared and isolated in our laboratory as mentioned in our previous publications [30,31].

3.1. Voltammetric behavior of Cd (II)–cephalosporin antibiotics

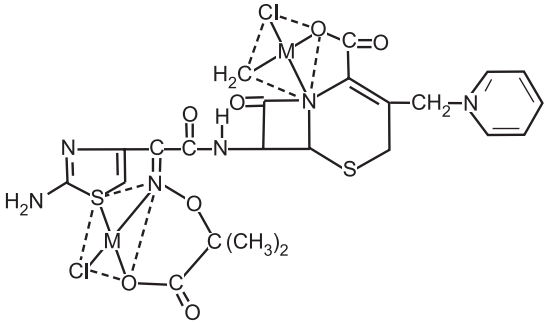
Fig. 1(A,B,C) shows the osteryoung square-wave voltammograms of three Cd-antibiotics (one representative for each generation). Evidence of a complex formation is established as a result of the decrease of the cadmium peak current (E_p at ~−0.6 V) such as the case of Cd–cefuroxime or Cd–cefotaxime complexes (Fig. 1A,B) and/or from the shift in the E_p of the first peak of the complexing agent such



1:1 Complexes $[MCl(CEX)(H_2O)].H_2O$



1:2 Complexes$[M(CRX_2].3H_2O$



2:1 Complexes $[M_2Cl_2(CFZ)(H_2O)].H_2O$

M= Cu(II), Zn(II) or Cd(II)

Scheme 1. Proposed structures for some representative complexes of the antibiotics.

that the case for Cd–cephapirin complex (Fig. 1C, curves d, e, f) or that shift occurs for the second peak of the complexing agent, e.g. cefuroxime and cefotaxime (see Fig. 1A,B, curves d, e, f). It is worthy, here, to mention that this is further elucidation and confirmation—with the proceeded results—for involvement of the different sites of these molecules during the complexation with Cd (II). (See Scheme 1 for complexation).

Anodic stripping voltammetry has been used to follow the concentration of unreacted metal titrant during the titration of organic ligands. After each aliquot of metal is added to the ligand, stripping analysis on the resulting solution is carried out. The result for given accumulation conditions and for mass transfer of the metal to the electrode by convective diffusion is a stripping current that depends only on the concentration of unassociated metal ions and an end point that is an estimate of the total free ligand concentration. However, the formation constant calculated from such method is a conditional one (K'_{ML}) [32,33]. In addition, a criterion that establishes whether a complex dissociates during accumulation, i.e. whether or not a complex is strictly "non labile" is also predicted.

3.2. Cyclic voltammetry of the investigated complexes

The electroreduction of the antibiotics—under investigation—along with their cadmium complexes solution equilibrium and those for the prepared solid complexes have been studied under the same experimental conditions. Fig. 2 shows a cyclic voltammogram for (1:1) Cd–cephalexin prepared solid complex after solubilization in the blank solution (acetic acid/NaOH). Two irreversible peaks, due to

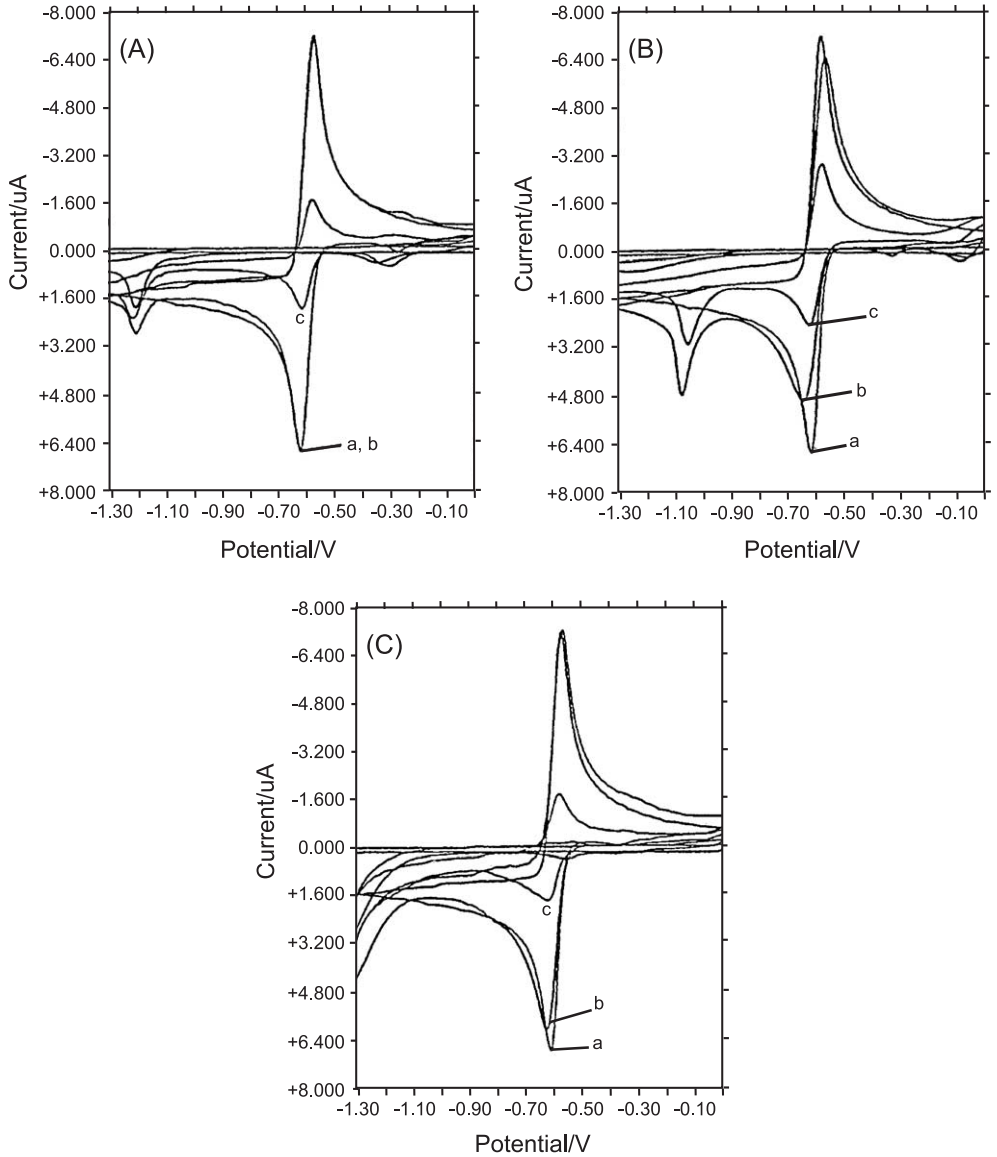


Fig. 2. Comparison between the cyclic voltammograms for 1:1 complex (Cd–Cephapirin) (A), 1:2 complex (Cd–Cefamandole) (B) and 2:1 complex (Cd–Ceftazidime) (C).

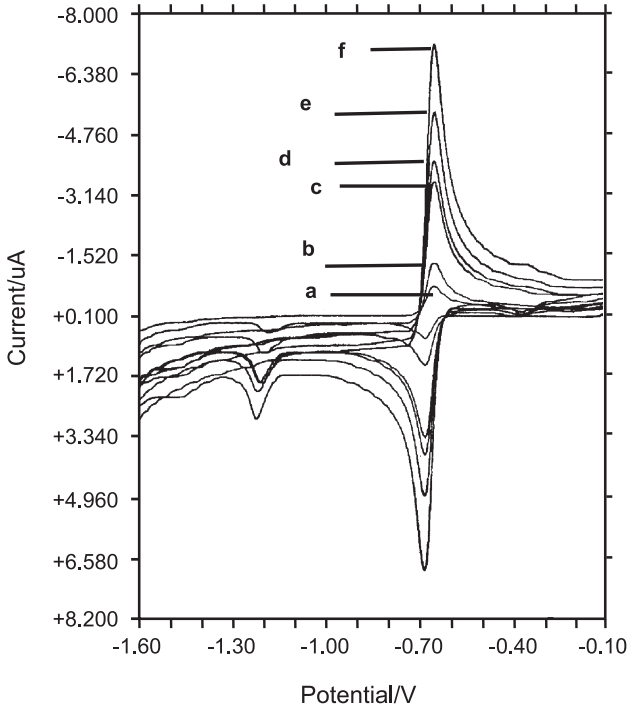


Fig. 3. Cyclic voltammograms of Cd (II)–Cephapirin, $t_{acc=}$, a=0, b=30, c=120, d=150, e=180 and f=240 s. pH 7.34.

the reduction of the drug and one reversible (at about −0.6 V), which is assumed to be due to the reduction of the cadmium in the complex. However, the peaks related to the drug are assumed to be due to two separate sites in the molecule as when the potential is held constant at a value between the two peaks, no alteration is seen in the height of the second peak. This is more confirmed when cyclic voltammograms are recorded as a function of the pH [19] where the first reduction process of ceftazidime (as an example) was attributed to two electron reduction of the >C=N-double bond in the methylethoxyimino group of the side chain, followed by the conventional reduction of the Δ^3 double bond in the cephm nucleus, activated by the pyridinium group (in the case of ceftazidime).

Cyclic voltammograms of cadmium alone, cadmium–cephapirin in solution, and cadmium–cephapirin prepared solid complex (pH 7.34) are shown in Fig. 2(A,B,C). It is worthy to mention that, in agreement with the foregoing results, evidence of 1:1 complex formation (for Cd–cephapirin and Cd–cephalexin) and 1:2 (for Cd–cefuroxime, Cd–cefotaxime and Cd–cefamandole) but 2:1 complex for Cd–ceftazidime is elucidated as a result of the values obtained for the cadmium reduction peak in these prepared complexes (I_p). In other words, the diffusion coefficient of cadmium (Fig. 2B, curve b) in Cd–cefamandole complex (1:2) is one-half that for either Cd–cephapirin or Cd–ceftazidime (1:1 or 2:1). This is—of course—due to the bulky structure when one mole of cadmium metal ion is complexed by two of the ligand (cefamandole, cefuroxime or cefotaxime in our study). Compare curve b in Fig. 2(A,B,C).

When stripping voltammetry is applied for such complex equilibria, adsorption behavior of these complexes is observed (Fig. 3) as the peak current was found to increase with increasing the accumulating time up to 300 s. This phenomenon has been used for quantitation of these drugs.

3.3. Voltammetric behavior of Zn (II)–cephalosporin antibiotics

Fig. 4 shows comparative voltammograms for (a), blank solution (1.7 M acetic acid/NaOH), (b) cephalexin alone, (c) the metal ion alone, then the metal ion and the complexing agent (cephalexin), curve (d) and that for the synthesized solid complex, curve (e). As indicated from the figure, there is an evidence of a complex formation reaction between Zn (II) and cephalexin. This is obvious from the appearance of a new peak at about −0.35 V and another one at −0.45 V.

Cyclic voltammetry of the synthesized complex (Fig. 5A) shows that the reduction of the two peaks—due to complex formation—occurs via irreversible (peak a), or reversible manner (peak b). The irreversible one is assumed to be a pre-peak due to adsorption process; this is confirmed as a straight line is obtained when I_p is drawn as a function of the scan rate (Fig. 5B).

Fig. 6 shows such adsorption behavior for Zn–cephapirin complex. Although an evidence of the complex formation is

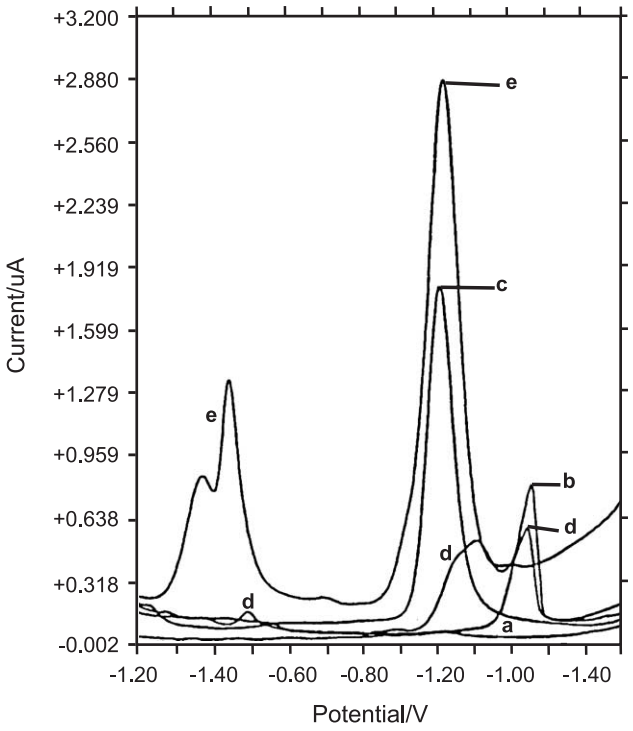


Fig. 4. Osteryoung square wave voltammograms of: a: blank solution (1.7 M Ac/NaOH), b: (a)+1×10^{-4} M Cephalexin, c: (a)+1×10^{-4} M Zn (II), d: (a)+(b)+(c) and e: (a)+solid synthesized complex. All measurements were taken at pH 7.34. Other experimental parameters are cited in the experimental part.

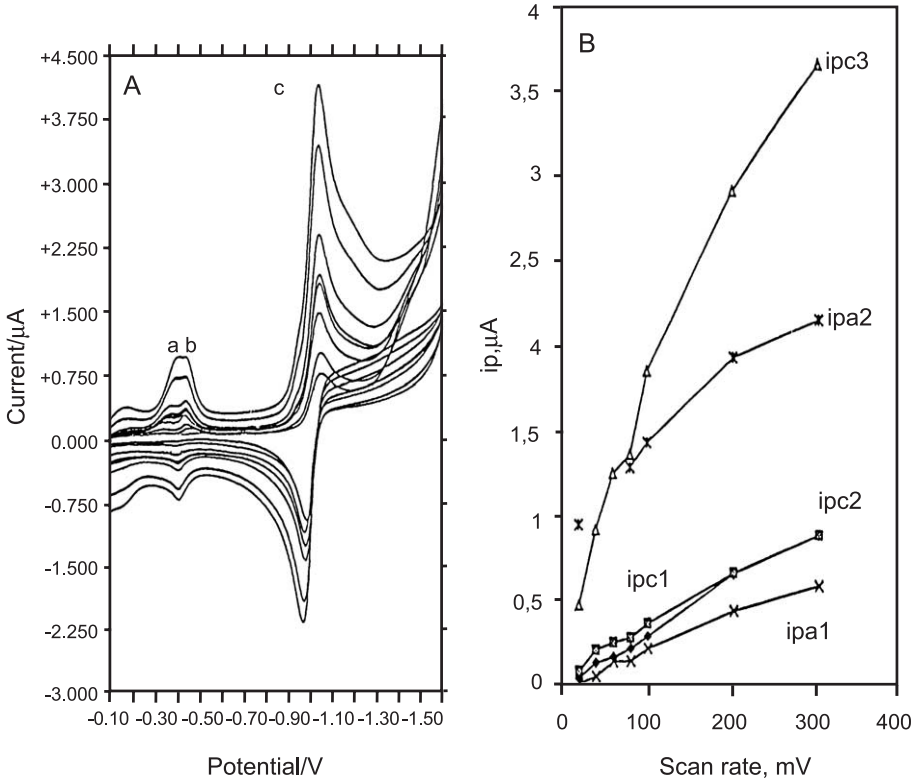


Fig. 5. (A) Cyclic voltammograms of Zn–cephalexin solid complex, pH 7.34, at different scan rates. (B) Effect of the scan rate on the peak height of Zn–cephalexin, pH 7.4. ipc_1: current due to reduction of peak b in (A). pa_1: current due to oxidation of peak b in (A). ipc_2: current due to reduction of peak c in (A). ipa_2: current due to oxidation of peak c in (A). ipc_3: current due to reduction of the adsorption peak (pre-peak) a in (A).

clear from the shift in the E_p (~−1.18 V) of cephapirin when tracing either the complex-solution equilibrium or the solid complex, a new phenomenon is appeared in the potential range corresponds to the reduction of the metal ion, that is, an increase in the I_p for Zn is obtained for either the solution complex or the prepared solid complex (compare peaks c, d, e, in Fig. 6A). This phenomenon may be attributed to the fact that Zn–cephapirin complex is adsorbed on the electrode surface. Further confirmation of this behavior has been elucidated using adsorptive stripping voltammetric techniques (Fig. 6B) allowing the drug quantitation down to 2×10^{-9} M. A detection limit of 7×10^{-10} M has been easily achieved.

When cefotaxime, cefamandole or cefuroxime are introduced to Zn (II), a complex formation reaction is assumed to occur as a result of the appearance of a new peak (Fig. 7) at about (−0.45 V). Besides, a negative shift in the Zn (II) reduction peak potential is also observed, whereas that due to the ligand is not altered. This behavior may be attributed to the fact that as for these complexes of stoichiometry 1:2 (Refs. [30,31]), Zn atom is restricted by two moles of the ligand, so energy is required to reduce such restricted atom in the complex structure, therefore a negative shift in the Zn (II) peak potential is noticed.

Fig. 8 is the osteryoung square wave voltammograms of Zn–ceftazidime complexes for the complex formed in solution (curve d) and that of the prepared solid complex (curve e). It is obvious from the figure that evidence of the complex formation due to the appearance of new peak (at about −1.15 V), the appearance of this new peak at such potential shows that a new stoichiometry is happened between Zn (II) and ceftazidime, also the noticeable decrement in the I_p for Zn (II) beside its small shift in potential. However, as it is elucidated from the previous study in this work, 2:1 stoichiometry is found for such complexation. Our voltammetric data agreed with this as the diffusion current for Zn (the reoxidation peak in Fig. 8) is much higher than that complexed to the ligand. This proves that either Zn–ceftazidime complex is not adsorbable at the electrode surface as it was the case for cephapirin and cephalexin complexes or due to the fact that the involvement of two metal ions (2:1 stoichiometry) gave rise to double value for the diffusion coefficient of Zn.

3.4. Voltammetric behavior of Cu (II)–cephalosporin antibiotics

The osteryoung square wave voltammograms for Cu (II)–cephalexin complex (formed in solution) and that for the prepared solid complex were traced, appearance of a new peak at about −0.8 and −0.67 V for the solution and solid complex, respectively, is an evidence of the complex formation reaction between Cu (II) and cephalexin. Also, a shift of the cephalexin reduction peak (in case of solution

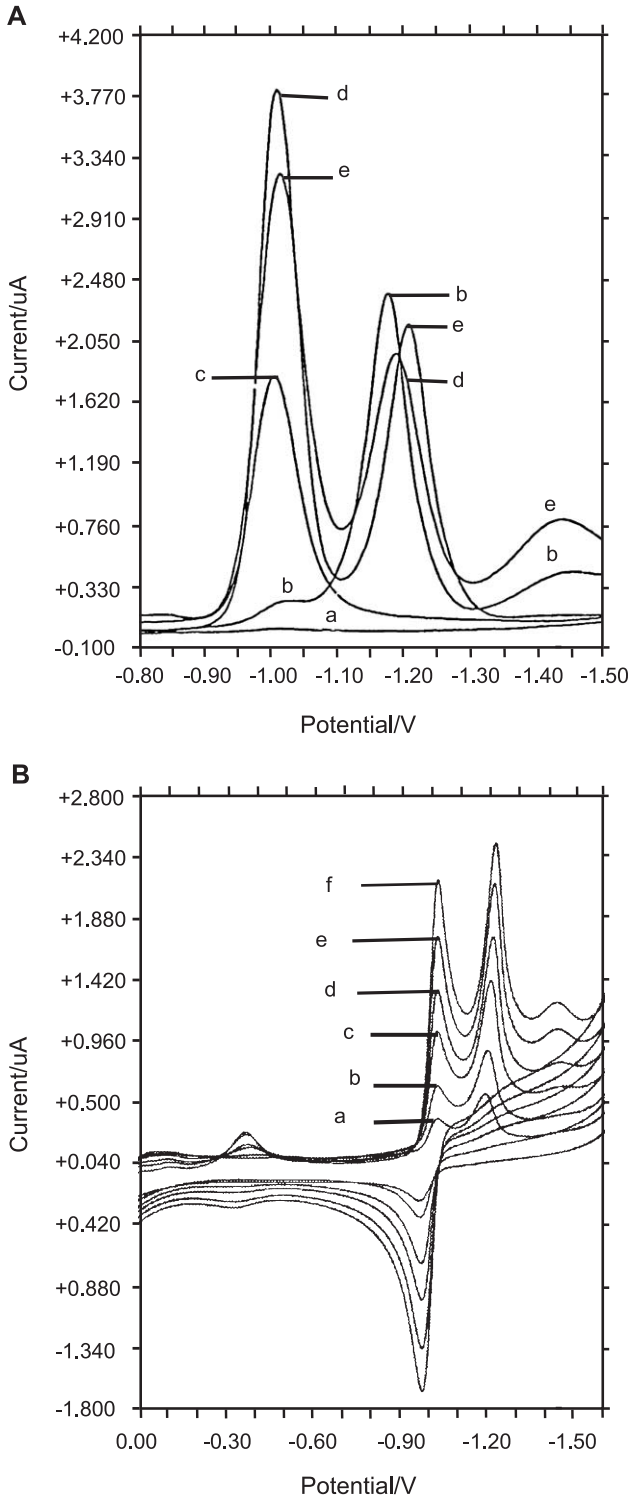


Fig. 6. (A) Osteryoung square wave voltammograms of: a: blank solution (1.7 M Ac/NaOH), b: (a)+1×10^{-4} M Cephapirin, c: (a)+1×10^{-4} M Zn (II) d: (a)+(b)+(c) and e: (a)+solid synthesized complex. All measurements were taken at pH 7.34. (B) Cyclic voltammograms of Zn–cephapirin solid complex applying different accumulation times, *a*=0, *b*=30, *c*=60, *d*=120, *e*=180 and *f*=240 s. pH 7.34.

complex) is observed and almost its disappearance (in case of the solid complex) confirming a complex formation reaction.

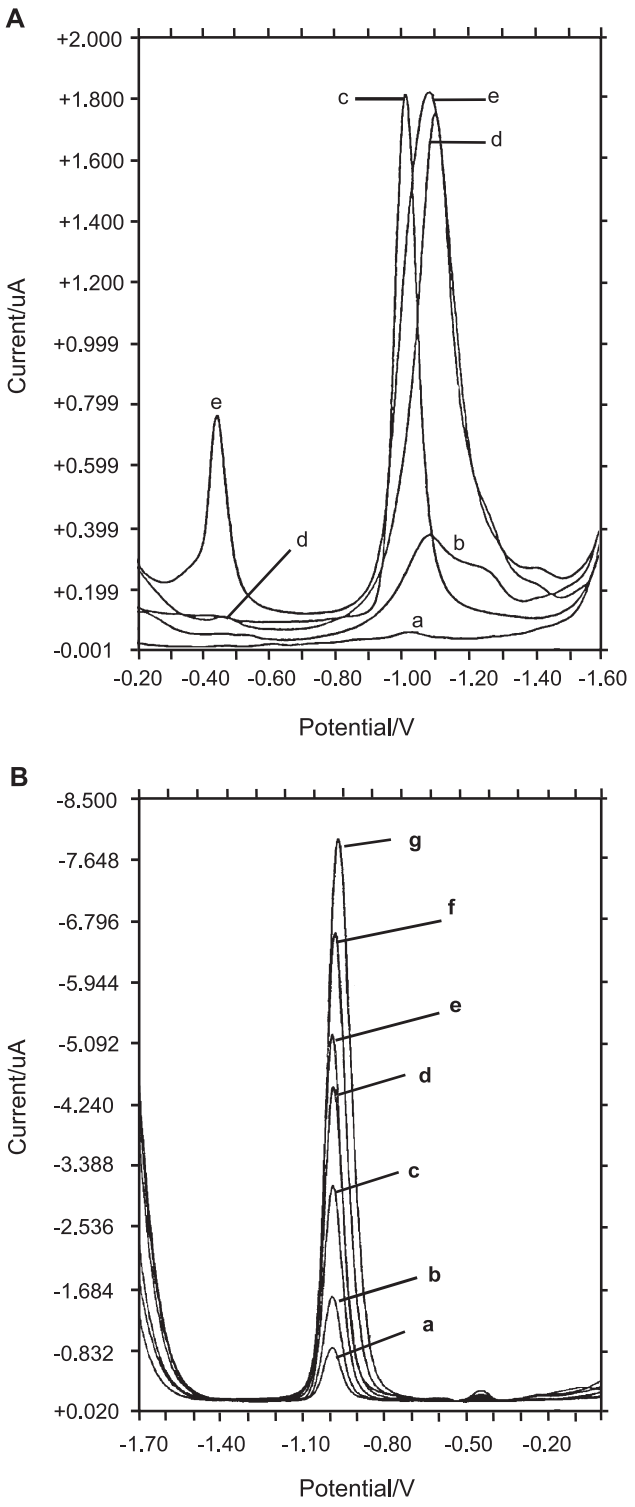


Fig. 7. (A) Osteryoung square wave voltammograms of: a: blank solution (1.7 M Ac/NaOH), b: (a)+2×10^{-4} M Cefamandole, c: (a)+1×10^{-4} M Zn (II) d: (a)+(b)+(c) and e: (a)+solid synthesized complex. All measurements were taken at pH 7.34. Other experimental parameters are cited in the experimental part. (B) Osteryoung square wave voltammograms of Zn–Cefamandole, pH 7.34 at accumulation times, *a*=0, *b*=30, *c*=60, *d*=120, *e*=180, *f*=240 and *g*=300 s. Other experimental conditions are cited in the text.

Cu (II)–cephapirin complex formation reaction has been also tested utilizing cyclic voltammetric technique. Appearance of new peaks at about −0.55 V for both the solid complex or the solution one while disappearance of the first one for the ligand (cephapirin in this case) and also decrease observed in the second ligand peak (at about −1.1 V) are all together a good evident for a complex formation reaction between Cu (II) and cephapirin.

Cu (II)–cefamandole complex is also evidenced using both osteryoung square wave and cyclic voltammetry. Cyclic voltammetry of the Cu (II)–cefamandole system shows reversible peak for the reduction of the free Cu (II) (Fig. 9) another one for the complex formed in solution (peak b) and (peak c) for the prepared solid complex.

For cefuroxime complexation system with Cu (II), again an adsorption behavior is observed as that obtained for Zn–cephalexin and cephapirin complexes, as the reduction peak of the ligand (cefuroxime) is enlarged in presence of Cu (II). The shift in the peak potential for the reduction peak obtained at about −0.70 V is another evidence for the complex formation reaction.

Cu (II) could also be complexed by cefotaxime. This complex formation reaction leads to appearance of a new peak at about −0.4 V and another one at about −0.7 V.

Ceftazidime shows a reduction peak at about −1.0 V (pH 7.34). In the presence of Cu (II), new peak at about −0.7 V appeared, its E_p is shifted with the increase of the concentration. Therefore, it is concluded that the Cu (II)–ceftazidime complex is adsorbed onto the electrode surface. However, this peak that is due to complex formation reaction could be successfully used for analytical studies for the determination of either Cu (II) or ceftazidime.

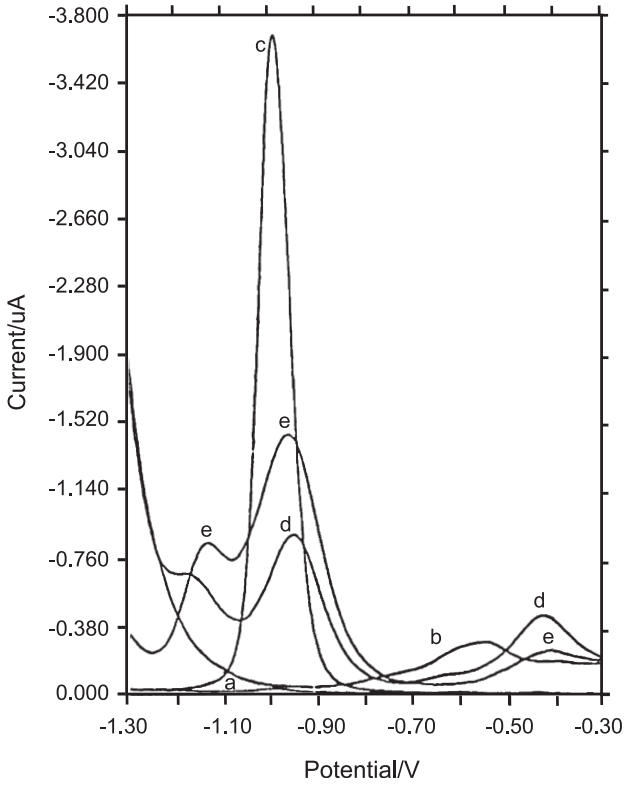


Fig. 8. Osteryoung square wave voltammograms of: a: blank solution (1.7 M Ac/NaOH), b: (a)+1×10^{-4} M Ceftazidime, c: (a)+2×10^{-4} M Zn (II) d: (a)+(b)+(c) and e: (a)+solid synthesized complex. All measurements were taken at pH 7.34.

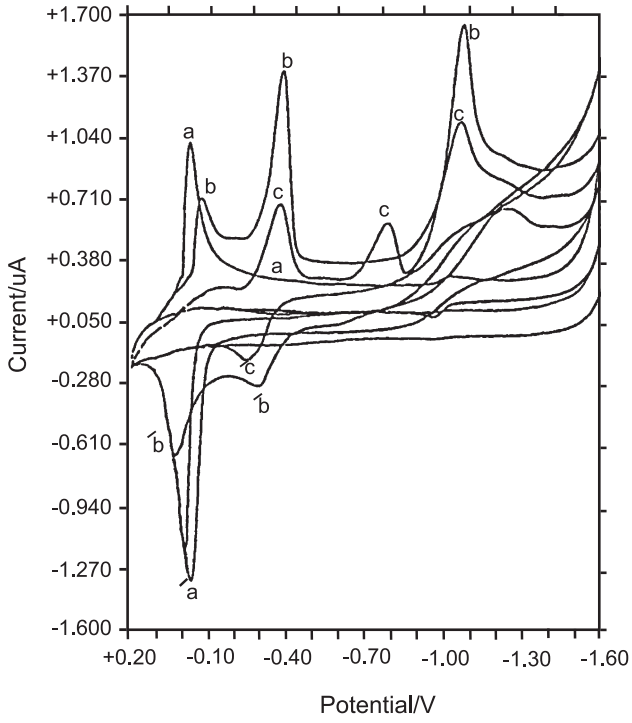


Fig. 9. Cyclic voltammograms of a: 1×10^{-4} M Cu (II), b: 1×10^{-4} M Cu (II)+2×10^{-4} M Cefamandole, c: prepared Cu–Cefamandole solid complex (stoichiometry 1:2), pH 7.34.

4. Conclusion

As it is well-known that deficiencies of trace elements can occur for the same general reasons as vitamin deficiencies [34], the possible complex formation reaction that may occur between metal ions and the antibiotics under investigation may give an image of what will happen when administrating an antibiotic. For this purpose, both osteryoung square wave voltammetry and cyclic voltammetry have been utilized to elucidate and confirm the possible complexation reaction which occur between the various cephalosporin antibiotics and either the toxic, non-essential metal ion, viz. Cd (II), or the essential but toxic (when their concentration exceeds certain level in serum) metal ions, viz. Cu (II) and Zn (II).

In a good agreement with the stoichiometries of the isolated solid complexes [30,31], the voltammetric measurements indicated the existence of 1:1 metal-to-ligand ratio (as in cephalexin and cephapirin complexes), 1:2 ratio (such as in cefamandole, cefuroxime and cefotaxime complexes) and 2:1 ratio in case of ceftazidime complexes. Adsorption

behavior was evidenced for Cu (II)–cefuroxime or ceftazidime complexes as well as for those of Zn (II)–cephalexin or cephapirin. This phenomenon could be used for the determination of either the antibiotic or the metal ion using adsorptive stripping voltammetry.

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