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Short communication

# Voltammetric behavior and assay of the antibiotic drug cefazolin sodium in bulk form and pharmaceutical formulation at a mercury electrode

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**Abstract**

The electrochemical behavior of the antibiotic drug cefazolin sodium (CFZ) in Britton–Robinson buffers (pH 2–11) at the mercury electrode was studied by means of dc-polarography, cyclic voltammetry, controlled-potential coulometry and square-wave adsorptive stripping voltammetry techniques. A validated square-wave adsorptive cathodic stripping voltammetric procedure was described for the trace determination of cefazolin in bulk form up to limits of detection and quantitation of $2.6 \times 10^{-10}$ M and $8.6 \times 10^{-10}$ M, respectively. The method was successfully applied for determination of cefazolin in pharmaceutical preparation without the necessity for samples pretreatment or any time-consuming extraction or evaporation steps prior to the analysis.


*Keywords:* Cefazolin; Dc-polarography; Cyclic voltammetry; Square-wave stripping voltammetry; Assay

## 1. Introduction

Cefazolin sodium: 3-[(5-methyl-1,3,4-thiadiazol-2-yl) thiomethyl]-7-(tetrazol-1-ylacetamido)-3-cephem-4-carboxylic acid; is a semi synthetic cephalosporin antibiotic. Cefazolin (CFZ) is classified as a first generation cephalosporin having a broad spectrum of activity and exhibits somewhat greater activity against *klebsiella pneumoniae* [1]. It is active in vitro against many Gram-positive aerobic cocci but has a limited activity against Gram-negative bacteria [2].

Numerous analytical procedures were reported for the determination of CFZ including the use of fluorimetry [3], colourimetry and AAS [4], spectrophotometry [5–7], radiosensitivity [8], capillary zone electrophoresis [9], densitometry [10], liquid chromatography [11–13], high-performance liquid chromatography [14–18], and voltammetry [19–21]. Most of these methods required formation of CFZ-metal complexes [3–5] or samples pretreatment and time-consuming extraction steps prior to analysis of the drug [6–18]. The reported voltammetric methods achieved the detection limits of $1.5 \times 10^{-5}$–$1 \times 10^{-6}$ M CFZ [19–21], which are not sensitive enough for the trace assay of cefazolin.

The aim of this study was to investigate the electrochemical behavior of cefazolin at a mercury electrode and to describe a validated sensitive and precise square-wave adsorptive stripping voltammetric procedure for trace assay of cefazolin in bulk form and pharmaceutical formulation.

## 2. Experimental

### 2.1. Solutions

A standard solution ($1 \times 10^{-3}$ M) of cefazolin sodium was prepared daily in deionized water from the pure compound (Sigma, St. Louis, MO, USA). A series of Britton–Robinson (B-R) buffer of pH 2–11 was prepared [22] and used as a supporting electrolyte. Deionized water was obtained from a

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Purite Still Plus Deionizer attached to an Aquamatic bidistillation water system (Hamilton Laboratory Glass Ltd., Kent, UK). A Mettler balance (Toledo-AB 104, Switzerland) was used for weighing the solid materials. All the chemicals (Merck) were of analytical-reagent grade and were used without further purification.

### 2.2. Instrumentation

A polarograph Model 4001 (Sargent-Welch) was used for studying the polarographic behavior of CFZ. A polarographic cell with a dropping mercury electrode as a working electrode ($m = 1.03\ \text{mg s}^{-1}$, $t = 3.3$ s at mercury height = 60 cm) and a saturated calomel electrode (SCE) as a reference electrode was used. A computer-controlled Electrochemical Analyzer Model 394-PAR (Princeton Applied Research, Princeton, NJ, USA) with the software package 270/250 (PAR) was used for cyclic and square-wave measurements. The electrode assembly 303A (PAR) incorporated with a micro-electrolysis cell comprising of a hanging mercury drop electrode (HMDE) as a working electrode, an $Ag/AgCl/KCl_s$ as a reference electrode and a platinum wire as a counter electrode was used.

A potentiostat/galvanostat Model 173-PAR incorporated with a digital coulometer Model 179-PAR was used for the controlled-potential coulometric measurements at a mercury pool electrode. The number of electrons transferred per CFZ molecule in the B-R buffer of pH 2–11 was found to equal 2.

### 2.3. Procedures

#### 2.3.1. Assay of bulk CFZ

A known volume of cefazolin sodium solution was pipetted into 10 ml calibrating flask and made up to the mark with a B-R buffer of pH 6. The solution was introduced into the electrolysis cell, and then deoxygenated with pure nitrogen for 10 min in the first cycle and 30 s for each successive cycle; the nitrogen was then kept over the solution. Preconcentration of CFZ onto the HMDE was performed at −0.6 V for 90 s while stirring the solution at 400 rpm with a magnetic stirrer. After an equilibrium time of 5 s was allowed for the solution to become quiescent, the stripping voltammogram was recorded by scanning the potential toward the negative direction using the square-wave waveform under the optimized conditions.

#### 2.3.2. Assay of CFZ in formulation

Constitute sterile powder of the CFZ preparation (Cefazolin, 1 vial/1 g, produced by October Pharma S.A.E Egypt under license of Biochemie Austria) was dissolved in a volume of deionized water accurately measured corresponding to the volume specified in the labeling. An accurately measured volume of the prepared injection solution was diluted quantitatively with deionized water to obtain a $1 \times 10^{-3}$ M. Cefazolin solution was then analyzed using the optimized voltammetric procedure.

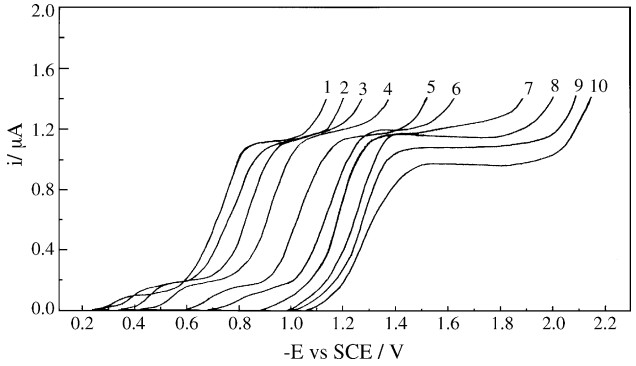


Fig. 1. Dc-polarograms of $2.5 \times 10^{-4}$ M cefazolin in (1) 0.1 M HCl solution (pH 1) and in B-R buffers of various pH values: (2) 1.8; (3) 3.0; (4) 4.0; (5) 5.0; (6) 6.0; (7) 7; (8) 8.0; (9) 10.0; and (10) 11.0.

## 3. Results and discussion

### 3.1. Dc-polarography

Polarograms of CFZ in B-R buffers of pH 2–11 exhibited a single 2-electron irreversible cathodic wave with almost pH-independent limiting current which could be due to the reduction of the $–CH_2–S–$ moiety of CFZ molecule [21,23–26]. In addition a pre-wave was appeared at less negative potential in solutions of pH <7 (Fig. 1). A similar behavior was obtained in 0.1 M HCl solution (pH 1), Fig. 1, curve 1. The pre-wave may be an adsorption one due to the reduction of the adsorbed CFZ species. Gibbs energy of adsorptive CFZ species makes the reduction of the adsorbed species easier than that of CFZ species in bulk solution [27]. Sulfur atoms of CFZ molecule play a crucial role in the adsorption phenomena of the analyte onto the mercury electrode surface [28]. Plots of $E_{\text{d.e.}}$ against $\log(i/i_d - i)$ [29] at the various pH values were straight lines with the slope values reported in Table 1 (slope, $\text{mV} = S_1 = 59/\alpha n_a$, where $\alpha$ is the transfer coefficient and $n_a$ is the number of electrons involved in the rate—determining step). The estimated values of $\alpha n_a$ and $\alpha$ indicated the irreversible nature of the reduction process of CFZ at the mercury electrode and the number of electrons ($n_a$) involved in the rate-determining step equals 2. The half-wave potential ($E_{1/2}$) of the polarographic wave of CFZ shifted to more negative values with the increase of pH up to 8, which indicated the involvement of protons in the rate-determining step of the reduction process [30] within this pH range.

The $E_{1/2}$–pH plot (Fig. 2, curve *a*) composed of two segments; the linear segment (pH ≤8) follows the equation: $E_{1/2} = -0.50 - 0.086$ pH while at higher pH values the effect of pH is almost negligible. From slope values ($S_2$) of the linear segment of the $E_{1/2}$–pH plot $\{\delta E_{1/2}/\delta\ \text{pH} = S_2, \text{mV} = (59/\alpha n_a)\ Z_H{}^+\}$, where $Z_H{}^+$ is the number of protons participated in rate-determining step of the reduction process}, and those ($S_1$) of the $E_{\text{d.e.}}$ versus $\log(i/i_d - i)$ plots at various pH values, the number of protons ($Z_H{}^+$) participated in the rate-determining

Table 1
Data of dc-polarographic and cyclic voltammetric measurements for $2.5 \times 10^{-4}$ M CFZ in B-R buffers of various pH values at 25 °C

| Dc-polarography | | | | | | Cyclic voltammetry | | | |
|---|---|---|---|---|---|---|---|---|---|
| pH | $S_1$ (mV) | $\alpha n_a$ | $\alpha$ ($n_a = 2$) | $S_2$ (mV) | $Z_H^+$ | $S_3$ (mV) | $S_4$ (mV) | $\alpha n_a$ | $\alpha$ ($n_a = 2$) |
| 1.0 | 55.9 | 1.06 | 0.53 | 86.1 | 1.5 | 87.8 | 45.5 | 1.29 | 0.64 |
| 1.8 | 57.1 | 1.03 | 0.52 | | 1.5 | | 46.1 | 1.28 | 0.64 |
| 3.0 | 60.7 | 0.97 | 0.49 | | 1.4 | | 48.4 | 1.22 | 0.61 |
| 4.0 | 62.8 | 0.94 | 0.47 | | 1.4 | | 50.0 | 1.18 | 0.59 |
| 5.0 | 60.2 | 0.98 | 0.49 | | 1.4 | | 57.5 | 1.03 | 0.51 |
| 6.0 | 63.7 | 0.93 | 0.47 | | 1.4 | | 61.6 | 0.96 | 0.48 |
| 7.0 | 64.6 | 0.91 | 0.46 | | 1.3 | | 63.1 | 0.94 | 0.47 |
| 8.0 | 61.4 | 0.96 | 0.48 | | 1.4 | | 72.4 | 0.81 | 0.41 |
| 9.0 | 64.6 | 0.91 | 0.46 | – | – | – | 83.5 | 0.71 | 0.35 |

$S_1$: slope of $E_{d.e.}$–log $(i/i_d - i)$ plots, $S_2$: slope of $E_{1/2}$–pH plot; $S_3$: slope of $E_p$–pH plot $S_4$: slope of $E_p$–log $\nu$ plots.

step was determined by applying the relation: [29,31]:

$$Z_H{}^+ = \frac{\delta E_{1/2}/\delta \text{pH}}{59/\alpha n_\alpha} = \frac{S_2}{S_1}$$

and was found to equal one (Table 1). The data reported in Table 1, indicated that the most probable values of α-parameter were obtained at the ratio $(Z_H{}^+/n_a) = 0.5$.

### 3.2. Cyclic voltammetry

Cyclic voltammograms of $2.5 \times 10^{-4}$ M CFZ in B-R buffers of pH 2–11 showed a single 2-electron irreversible cathodic peak over the entire pH range, in addition to a pre-peak at less negative potentials in solution of pH values <7. The peak potential shifted to more negative values with the increase of pH up to 8. Plot of $E_p$ versus pH (slope $S_3$, Table 1) showed two segments (Fig. 2, curve *b*) similar to that observed for the $E_{1/2}$ versus pH plot (Fig. 2, curve *a*). Over the linear segment (pH ≤8) the peak potential shifted to more negative values according to the equation: $E_p = -0.67 - 0.0878$ pH, while over the pH range >8 the effect of pH is almost negligible. Moreover, the peak potential ($E_p$) shifted linearly to more negative values with increase of scan rate ($\nu$) that confirmed the irreversible nature of the electrode reaction. Values of $\alpha n_a$ and $\alpha$ (Table 1) obtained from slope ($S_4$) of $E_p$ versus log $\nu$ plots agree well with those obtained from polarographic measurements.

The interfacial adsorptive character of CFZ onto surface of the mercury electrode was identified by recording cyclic voltammograms of $4 \times 10^{-6}$ M CFZ in a B-R buffer of pH 6 at open circuit and following preconcentration onto the HMDE in a stirred solution for a period of 30 s at −0.6 V (Fig. 3). The preconcentration of CFZ gave substantial enhancement of the cathodic peak (curve *b*) compared with those at open circuit (curve *a*) and subsequent second scan at the same mercury drop (curve *c*), confirming the interfacial adsorptive character of CFZ onto surface of the HMDE.

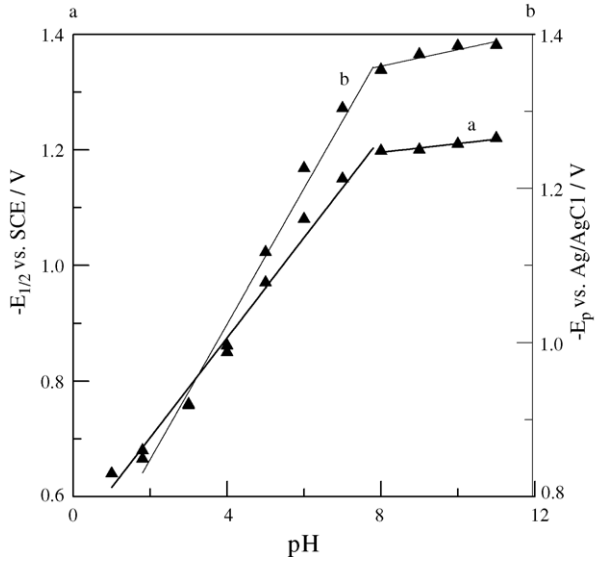


Fig. 2. Plots of $E_{1/2}$–pH (a) and $E_p$–pH (b) for $2.5 \times 10^{-4}$ M CFZ in B-R buffers.

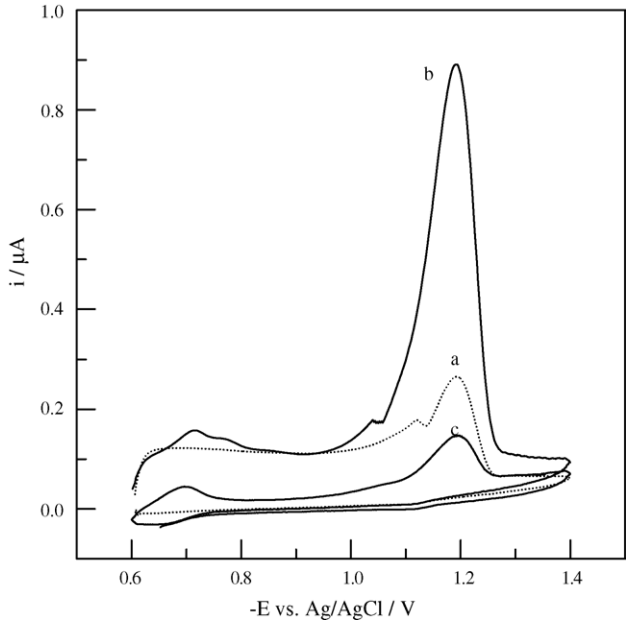


Fig. 3. Cyclic voltammograms for $4 \times 10^{-6}$ M CFZ in a B-R of pH 6 at scan rate $\nu = 200$ mV s$^{-1}$: (a) at open circuit; (b) following preconcentration for 30 s at $E_{acc.} = -0.6$ V; and (c) repetitive cycle at the same mercury drop.

The electrode surface coverage $\Gamma$ (mol cm$^{-2}$) was calculated from the amount of charge ($Q$) consumed by the surface process (as calculated by the integration of the area under the peak of the cyclic voltammogram corrected to residual current) using the equation: $\Gamma = Q/nFA$, where $n$ is the number of electrons consumed in the overall reduction process of CFZ ($n = 2$) and $A$ is the electrode surface area (0.026 cm$^2$). On dividing the number of coulombs transferred, 0.8755 μC, by conversion factor $nFA$ (5017.3 C) yielded a monolayer surface coverage of $1.745 \times 10^{-10}$ mol cm$^{-2}$. Each adsorbed CFZ molecule therefore occupies an area of 0.951 nm$^2$.

### 3.3. Square-wave stripping voltammetry

Square-wave voltammograms of $5 \times 10^{-7}$ M CFZ in B-R buffers of pH 2–11, following preconcentration onto the HMDE for 60 s at −0.4 V, showed a single irreversible cathodic peak. The response proceeded by preconcentration increases extensively at pH 5–6 (Fig. 4). The dependence of stripping peak current on the preconcentration potential was evaluated over the range −0.2 to −0.8 V for $5 \times 10^{-7}$ M CFZ in a B-R buffer of pH 6 following preconcentration for 60 s. A potential of −0.5 V was chosen as a preconcentration potential that has given the best-defined peak and more developed current. The extent of adsorption of CFZ onto surface of the HMDE was studied for $5 \times 10^{-8}$, $1 \times 10^{-7}$ and $5 \times 10^{-7}$ M CFZ solutions. Preconcentration duration of 60–90 s corresponding to a more developed peak current was chosen to evaluate the analytical characteristics of the developed procedure.

The peak current for $1 \times 10^{-7}$ M CFZ in a B-R buffer of pH 6 following preconcentration for 60 s at $E_{acc.} = -0.5$ V was optimized by changing the pulse-amplitude ($a$), scan increment ($\Delta E_s$) and frequency ($f$) within the range 10–100 mV, 2–10 mV, and 10–120 Hz, respectively. Dependence of the peak current ($i_p$) on the square-wave frequency ($f$) was found to be linear according to the equation: $i_p$ ($\mu A$) = 0.4 $f$ (Hz) −0.16 ($r = 0.999$). Also the peak current increased with the increase of pulse-amplitude; however pulse-amplitude of 50 mV was chosen since at higher values peak broading was observed. With increasing scan increment the peak intensity increased linearly. The influence of the working electrode area on the peak current was also studied. As expected, an increase of the electrode area yields an increase in the peak current, so a large area (0.026 cm$^2$) was considered suitable for the present analytical study. A rest period of 5 s was found to be sufficient to allow the formation of a uniform concentration of the analyte onto the mercury drop. Thus, the achieved optimal operational parameters of the proposed square-wave adsorptive cathodic stripping (SWAdCS) voltammetric procedure were: $E_{acc.} = -0.5$ V, $t_{acc.} = 60 - 90$ s, $\Delta E_s = 10$ mV, $a = 50$ mV, $f = 120$ Hz, electrode area = 0.026 cm$^2$ and a rest period = 5 s.

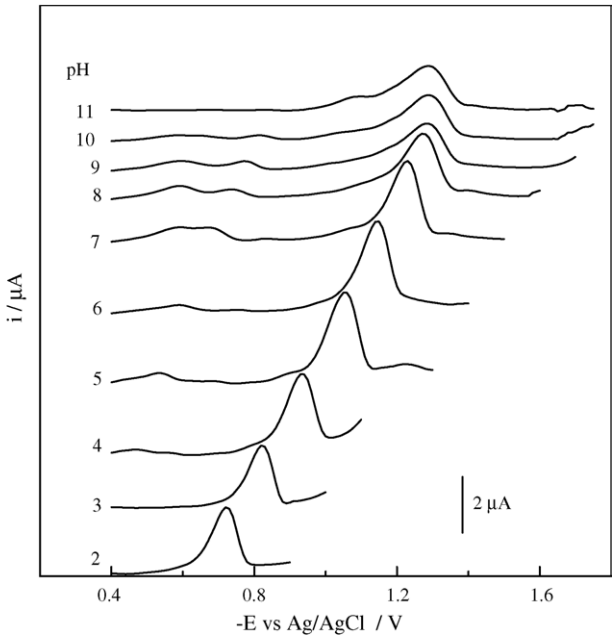


Fig. 4. SWAdCS voltammograms for $5 \times 10^{-7}$ M CFZ in B-R buffer of various pH values; $t_{acc} = 60$ s, $E_{acc} = -0.4$ V, $f = 120$ Hz, $\Delta E_s = 10$ and $a = 25$ mV.

### 3.4. Method validation

Following preconcentration of CFZ onto the HMDE for 90 s linear calibration graph (regression equation $i_p = 0.0152\ C + 0.07$, $r = 0.997$) was obtained within the concentration range $8.6 \times 10^{-10} - 2 \times 10^{-7}$ M. Limits of detection (LOD) and quantification (LOQ) of CFZ were calculated using the following equations [32]: LOD = 3 $S_b/m$ and LOQ = 10 $S_b/m$, where $S_b$ is the standard deviation of the blank and $m$ is the slope of the calibration curve. The obtained results of LOD = $2.6 \times 10^{-10}$ M and LOQ = $8.6 \times 10^{-10}$ M indicated the reliability of the proposed SWAdCS voltammetric procedure for the trace assay of CFZ.

Repeatability of results was evaluated by performing six measurements for 5, 10 and 20 nM CFZ, following precon-

Table 2
Analytical precision and accuracy of CFZ determination in bulk form by the proposed SWAdCS voltammetric procedure ($n = 5$) following preconcentration for 90 s

| Concentration (taken) (nM) | Intra-day | | | Inter-day | | |
|---|---|---|---|---|---|---|
| | $R$% | Accuracy bias% | Precision R.S.D.% | $R$% | Accuracy bias% | Precision R.S.D.% |
| 5 | 98.6 | −1.4 | 2.6 | 98.3 | −1.8 | 2.1 |
| 10 | 100.7 | 0.7 | 0.8 | 101.3 | 1.3 | 0.9 |
| 20 | 99.2 | −0.8 | 1.3 | 100.2 | 0.2 | 1.5 |

centration onto the HMDE for 90 s at −0.5 V (Table 2). Mean recoveries of 98.6–100.7% with R.S.D. of 0.8–2.6% were achieved. The precision and accuracy of the proposed procedure were investigated by intra- and inter-day determinations of CFZ for three concentrations ($n = 6$) within the linear range. Accuracy of the procedure was expressed as bias% within and between days was less than (1.3%) at low and high concentrations (Table 2).

The specificity [33] of the proposed stripping procedure was tested by analysis of a $5 \times 10^{-7}$ M bulk CFZ solution, then a standard CFZ injection real solution corresponding to a $5 \times 10^{-7}$ M CFZ, following preconcentration onto the HMDE for 60 s in both cases. No significant differences in the recoveries or the standard deviations were observed in the absence ($100.2 \pm 0.6\%$) and presence ($101.1 \pm 0.6\%$) of excipients, thus the proposed procedure can be considered specific.

The robustness [33] of the proposed procedure was examined by analysis of $5 \times 10^{-8}$ M bulk CFZ in B-R buffers of pH 5–6, $E_{acc.} = -0.4$ to $-0.6$ V and $t_{acc.} = 85$–$95$ s. The obtained mean recoveries and standard deviations were not significantly affected within the studied range of variation of the procedural operational conditions, and consequently the proposed procedure can be considered robust [33].

The intermediate precision [33] of results was examined in our laboratory by application of the proposed procedure to assay of $5 \times 10^{-8}$ M bulk CFZ at varying time, analyst and instrument (Potentiostat Models 263A and 394-PAR). The results were found reproducible, since no significant difference in the recovery or the standard deviation values were obtained.

### 3.5. Assay of CFZ in injections

The proposed SWAdCS voltammetric procedure was successfully applied for the direct determination of CFZ in pharmaceutical dosage form (cefazolin injection) and the validity was assessed by applying both the calibration curve and the standard additions methods. A mean percentage recovery of $99.57 \pm 0.63$ to $100.8 \pm 1.6$ was obtained. The calculated *t*-test and *F*-value are less than the corresponding theoretical values indicating that there is no significant difference between the results obtained by the proposed procedure and those of a reported spectrophotometric one [3] with respect to accuracy, precision and repeatability.

## 4. Conclusion

The electrochemical behavior of CFZ at the mercury electrode was studied and a fast, simple, sensitive and precise square-wave adsorptive cathodic stripping voltammetric procedure was described for its trace assay in bulk form and pharmaceutical preparation without the necessity for samples pretreatment or time-consuming extraction steps prior to analysis of the drug. The achieved quantitation limit of CFZ was low enough to reach its concentration at trace levels.

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