Research Article

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Fabrication of ultra-sensitive carbon paste electrode with nanocomposite CdS modification for electroanalysis of rafoxanide in dosage form and biological fluids

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Abstract: An anthelmintic, rafoxanide (RF), is frequently used in veterinary medicine to cure fascioliasis in cattle and sheep. A sensitive, quick, and selective detection of RF in its pharmaceutical preparation and in human urine was achieved through developing a new electrochemical sensor. The suggested method relied on the electro-oxidation of RF that used a modified carbon paste electrode in the presence of sodium dodecyl sulfate, which acts as an anionic surfactant. Voltammetric types were utilized in RF analysis, and these methods were cyclic voltammetry and differential pulse techniques. The suggested electro-analytical method’s validity is verified using the International Council on Harmonization (ICH/Q2) rules. The calibration curve for RF quantification was done in the concentration range from 2.9 × 10^{-6} to 3.1 × 10^{-4} M at cadmium sulfide modified carbon paste electrode. The limit of detection and the limit of quantification LOQ were found to be 6.7 × 10^{-7} M and 2.01 × 10^{-6} M, respectively. This study could be applied to the examined drug in QC-laboratory units, and also RF could be assayed in its pharmacokinetic studies.

Keywords: rafoxanide, voltammetric determination, modified electrode, spiked urine samples

1 Introduction

An anthelmintic, rafoxanide (RF), is frequently used in veterinary medicine to treat fascioliasis in cattle and sheep. IUPAC name of RF is N-[3-chloro-4-(4-chlorophenoxy)phenyl]-2-hydroxy-3,5 diido-benzamide (Figure 1) [1]. There are various published methods for quantifying RF that were examined in pure form, co-administered, and in combination. These methods included chromatographic methods such as gas chromatography, ultra-performance liquid chromatography (UPLC) [2–8], and also spectrophotometric methods [9,10]. The electro-analytical technique uses different types of voltammetric methods, such as cyclic voltammetry (CV) and differential pulse voltammetry (DPV). These types are simple, cost-effective, and rapid using low toxicity reagents (generally aqueous buffer solutions) [11–13]. In addition, voltammetric methods are informative and give more information about the active site of the studied drug based on oxidation–reduction behavior. Hence this technique is preferable compared to the above-mentioned classical method for RF analysis. In the present study, the carbon paste electrode (CPE) was fabricated to determine RF at different experimental conditions. CPE has good chemical reactivity in electroanalysis [14–19], good rigidity, simplicity, gives good linearity, high accuracy, fastness, inexpensive, low ohmic resistance, and an extreme potential window [12,20–27]. The modification of CPE was another strategy that was developed to increase electrode sensitivity. Furthermore, the resulting data is accurate, precise, selective, and robust. Different nanomaterials were utilized as a modifier to improve the performance of the carbon-based electrodes [5,28].
The main objective of the present work is to offer a valid, simple, economical, and excellent reproducibility and powerful electro-analytical method. Finally, the proposed voltammetric approaches, such as CV and DPV techniques, provided a way to improve the conditions for the accurate detection of RF in its commercial dosage forms and spiked urine samples.

2 Experimental material

2.1 Chemicals and reagents

The used reagents and solvents were of analytical grade-A. All chemicals were used without the need for further purification. Graphite (powdered, particle dimension 20 μm) was obtained from Sigma-Aldrich, Germany, and an anionic surfactant like sodium dodecyl sulphate (SDS), cadmium sulphide, ZnSO₄·7H₂O, and paraffin oil were purchased from El Nasr Co. for Intermediate Chemicals, Egypt. Flukanil® injection (B. no., 1509104) and RF (99.8% purity) was kindly supplied by Pharma Swede, Egypt. The selected supporting electrolyte was aqueous Britton Robinson (BR) buffer solutions from pH 2.0 to pH 10. The composition of BR buffer solutions (0.04 M of each phosphoric acid, boric acid, and acetic acid (Merck, Darmstadt, Germany) was adjusted by 0.2 M NaOH to reach the desired pH.

2.2 Instruments

Electrochemical measurements were done through a Potentiostat voltammetric analyzer, OrigaFlex OGF500. Origa Master software was used. Three electrodes were placed in an electrochemical cell namely the working electrode of 3.0 mm glassy carbon, platinum as auxiliary or counter electrode, and reference silver (Ag/AgCl) electrode. The diamond paste was used to polish the working electrode.

Analytical digital balance (Switzerland) has been used. pH measurements were done with an Adwa pH-meter, Model: AD1030.

2.3 Standard RF solution

An accurate amount (62.0 mg) of RF was weighed and mixed with 20 mL of methanol as a solvent in 100 mL calibrated flask, then completed to 100.0 mL with the same solvent. The final concentration was 1.0 × 10⁻³ mol·L⁻¹ and stored away from light.

2.4 Electrode preparation

The CPE was fabricated through mixing of 0.3 mL of paraffin oil with the mixture of graphite powder (0.5 g) and cadmium sulfide in glass mortar [29]. The obtained paste was placed into the hole of the electrode body and then smoothed to produce a shiny electrode appearance. The prepared modified electrode is carried in deionized water and under nitrogen conditions. Different concentrations of cadmium sulfide were added to obtain a cadmium sulfide modified carbon paste electrode (CCPE). After that, CCPE is washed and dried enough before being used.

2.5 Electrochemical measurement of CdS

The measurements were recorded after cyclic voltammetric measurements on CCPE for exactly 1.0 × 10⁻³ M RF at pH 5.0, upon successive additions of different percentages (2%, 3%, 5%, and 7%) of cadmium sulfide solution to the electrochemical cell.

2.6 Analysis of RF in its pure form

At pH 5.0, an aliquot of (1.0 × 10⁻³ M) RF solution was transferred to the electrochemical cell, with BR buffer provided as a supporting electrolyte. The resulting solution was stirred for 5 s at the CCPE working electrode under open circuit conditions. Anionic surfactant (SDS) solution, 4.0 × 10⁻⁵ M was used. All measurements were then recorded at a scan rate of 10 mV·s⁻¹.

Figure 1: Chemical structure of rafoxanide.
2.7 RF Analysis in dosage form

Flukanil® injection (75 mg·mL) yielded an exact volume equivalent to 1.0 × 10⁻³ M RF solution in a 100 mL volumetric flask containing 75 mL methanol. The mixture was then dissolved using sonication for 30 min before being completed to volume with methanol. The final solution was filtered. The electrochemical cell was filled with various aliquots of the produced solution (35 μL) and the standard RF solution (1.0 × 10⁻³ M) and voltammograms were observed [30].

2.8 Applications to human urine

400 μL of human urine samples were precisely spiked with aliquots of RF solutions into each centrifugation test tube accurately. For 5 min, the vortex was used to generate the combination. Following that 0.5 mL of methanol, 0.1 mL (0.1 M) of NaOH, and 0.5 mL of ZnSO₄·7H₂O (5% w/v) [31] were accurately added and centrifuged at 4,000 rpm for 10 min. A 0.45 μm cellulose acetate membrane filter was used to purify the supernatant. The supernatant liquor (0.1 mL) was placed into the electrochemical cell and filled to a total volume of 5 mL with BR buffer, pH 5. After that the proposed DPV procedure was performed [32].

3 Results and discussion

3.1 Influence of pH on RF electrochemical behavior

As shown in Figure 2, preliminary CV measurements for (1.0 × 10⁻³ mol·L⁻¹) RF were performed at CPE in BR buffer solutions. The pH range (2.0–12) was investigated, as well as two anodic peaks for the oxidation process of RF within the pH range of 3.0–7.0. In the suggested mechanism, first, the –OH group in RF gives one electron and oxidizes to phenoxy radical form (–O). Then, the protonated azomethyn (–NH₂⁺) group in the structure gives one electron and one proton and oxidizes to cationic radical form (–NH⁺). Finally, the formed diradical also loses one proton, and a new product is formed by the cyclization process [19] as shown in Scheme 1. This is based on the oxidation of the primary amino group, which becomes inactive in acidic media due to protonation (Figure 3). The anodic peak potential is affected by pH, which increases up to pH 3 before reaching a near-steady state at pH 5. The anodic peak potential increases from pH 7 to pH 10, and then decreases to pH 5.

![Figure 2](image1.png)

**Figure 2:** Cyclic voltammograms of the oxidation of RF solution (1.0 × 10⁻³ mol·L⁻¹) at CPE using BR buffer.

![Scheme 1](image2.png)

**Scheme 1:** The suggested mechanism of the studied electrochemical oxidation process for RF at CPE.
12. At pH values of 5.0 and 10.0, the anodic peak current \((I_p)\) has maximum values of 21.23 and 120.05 \(\mu\)A, respectively. Figure 4 illustrates the anodic peak currents of RF in the presence of CPE, different concentrations of CCPE, and SDS. At pH 10, the greatest anodic peak current value was 149.22 \(\mu\)A. While in the presence of \(4.0 \times 10^{-5}\) M SDS solution, a CPE containing 5% cadmium sulfide was changed. This suggested that the basic medium (pH 10) was preferable to any other medium for producing the assessment maximum anodic peak for the modified electrode with SDS.

3.2 Effect of scan rate \((u)\)

In the presence of SDS solution, scan rate \((u)\) had an effect on the anodic peak current \((I_p)\) of RF at both CPE and CCPE in the range of 10–150 mV·s\(^{-1}\). Figure 5 shows the relationship between the logarithm of oxidation peak current \((\log I_p)\) and the logarithm of scan rate \((\log u)\). The linear regression equation is

\[
\log I_p = -0.453 \log u + 6.7248
\]

with \(R^2 = 0.8644\). According to the slope values, the RF oxidation process is an adsorption-contributed process at CPE and CCPE in the presence of SDS solution [33]. The diffusion coefficient of RF can be calculated using the (Randles-Sevcik equation) and the square root of the scan rate (Figure 5) [33]

\[
I_{pa} = (2.69 \times 10^5)n^{3/2} \cdot A \cdot D^{1/2} \cdot C \cdot u^{1/2}
\]

where \(I_{pa}\) is the anode peak current \((A)\), \(n\) is the number of transferred electrons in a redox cycle, \(A\) is the active surface area of the electrode \((\text{cm}^2)\), \(D\) and \(C\) are the diffusion coefficients \((\text{cm}^2\cdot\text{s}^{-1})\) and concentration of redox-active species, respectively, and \(u\) is the applied scan rate in \(\text{V} \cdot\text{s}^{-1}\). The diffusion coefficients for RF are \(1.076 \times 10^{-6}\), \(1.155 \times 10^{-5}\), and \(7.911 \times 10^{-7}\) cm\(^2\)·s\(^{-1}\) at CPE, CCPE, and CCPE/SDS, respectively. The results showed that there was a quick mass transfer of RF molecules from the bulk solution to the surface of the CCPE when SDS solution was present.
3.3 Validation of an electro-analytical methodology

3.3.1 Linearity range, detection, and quantification limit

The proposed methods were validated based on International Council Harmonization (ICH/Q2) rules [34]. To provide the electro-analytical method for RF analysis, different quantitative measurements were performed using DPV at CCPE in the presence of SDS solution \((4.0 \times 10^{-5} \text{ M})\). The calibration plot was constructed through consecutive additions of RF solution \((1 \times 10^{-3} \text{ M})\) to the electrochemical cell at pH 10. The peak currents vs different RF concentrations were plotted within the linearity range. As shown in Figure 6, the anodic peak current \(I_p\) increases linearly with the increase in the RF concentration from \(2.9 \times 10^{-6}\) to \(3.1 \times 10^{-4} \text{ M}\) with a correlation coefficient of 0.9992, which can be seen in Table 1. The limit of detection (LOD) and limit of quantification (LOQ) are obtained according to the following equations:

\[
\text{LOD} = 3.3\sigma / S \\
\text{LOQ} = 10\sigma / S
\]

where \(S\) is the slope of the calibration curve, and \(\sigma\) is the standard deviation of the intercept [35,36]. Through the calibration graph, the calculated value of LOD and LOQ in μg/mL was converted to molar concentration using the molecular weight of rafoxanide. LOD and LOQ were found to be \(6.7 \times 10^{-7}\) and \(2.01 \times 10^{-6} \text{ M}\), respectively.

### Table 1: Statistical data and quantitative parameters for RF determination by the proposed method

| Parameter     | CCPE |
|---------------|------|
| \(E (V)\)    | 0.571|
| Linearity (M) | \(2.9 \times 10^{-6} - 3.1 \times 10^{-4}\) |
| \(A\)         | 1.32 |
| \(B\)         | 0.11 |
| \(s_a\)       | 0.014|
| \(s_b\)       | 0.01 |
| \(s_{y/x}\)   | 0.015|
| RSD           | 0.25–1.51%|
| LOD (M)       | \(6.7 \times 10^{-7}\) |
| LOQ (M)       | \(2.01 \times 10^{-6}\) |
| \(R^2\)       | 0.9992|

where \(A\) – intercept; \(B\) – slope; \(s_a\) – standard deviation of intercept; \(s_b\) – standard deviation of slope; \(s_{y/x}\) – standard deviation of regression; LOD – limit of detection; LOQ – limit of quantification; \(R\) – correlation coefficient; LR – linear range; \(n\) – number of data; \(R^2\) – coefficient of determination.

### Table 2: Standard addition method for the assay of 5 μg mL\(^{-1}\) at CCPE

| Added (μg·mL\(^{-1}\)) | % Recovery | Bias (%) | SD  | CV  |
|-------------------------|------------|----------|-----|-----|
| 1.0                     | 99.6       | -1.4     | 1.21| 1.41|
| 3.0                     | 100.2      | 0.6      | 1.33| 1.32|
| 4.0                     | 99.3       | -0.7     | 1.15| 1.10|

### Table 3: Precision data of the proposed method for determination of RF

| RF (M)   | Intraday precision | Interday precision |
|----------|--------------------|--------------------|
|          | % Recovery ± SD*   | CV                 | % Recovery ± SD* | CV    |
| \(3 \times 10^{-6}\) | 99.61 ± 0.37 | 1.02 | 99.61 ± 1.11 | 0.97 |
| \(3 \times 10^{-5}\) | 98.78 ± 0.91 | 0.92 | 98.95 ± 0.81 | 1.01 |
| \(3 \times 10^{-4}\) | 99.95 ± 1.12 | 0.81 | 99.54 ± 0.84 | 0.92 |

* Number of replicates \((n)\) = 5.
Different RF doses in the linear range that extends from $2.9 \times 10^{-6}$ to $3.1 \times 10^{-4}$ M were used to test the validity of the approach. The values of relative standard deviation (RSD) ranging from 0.25% to 1.51% were obtained (Table 1).

### 3.3.2 Accuracy and precision

For the analysis of Flukanil® injection, the suggested electro-analytical method’s accuracy was tested using the standard addition method, and aliquots of RF standard solution ($1.0 \times 10^{-3}$ M) were added. Five replicate trials produced the resulting data, expressed as estimated percent recoveries ranging from 99.95% to 100.8%, with RSD values between 0.493% and 1.338%. The obtained results were in excellent agreement with the labeled content (Tables 2 and 3). After studying the effect of various excipients accessible in Flukanil® injection, there are no interferences from the matrix. The estimated values in the current investigation of the DPV technique for the analysis of RF in bulk and pharmaceutical formulations were $1.0 \times 10^{-8}$–$1.0 \times 10^{-1}$ μM and $5.0 \times 10^{5}$–$1.0 \times 10^{-1}$ μM, respectively, indicating that it is more sensitive than HPLC and spectrophotometric approaches. After statistically comparing the computed and tabular data, it was discovered that there is no significant difference between the proposed approach and the published spectrophotometric method [10] at 95% confidence level [10] as shown in Table 4.

### 3.3.3 Reproducibility and Stability

Five DPV experiments at pH 5 were studied using the fabricated sensing for the same electrode, which was conducted in a row under similar conditions. The RSD value was found to be 3.22%, which proved the excellent reproducibility of the modified CCPE. Furthermore, the stability was tested in the fabrication of the modified CCPE. After 2 weeks of storing the CCPE in the refrigerator, the test was done using DPV at optimum experimental conditions and on every 5th day, the stability was checked. The results showed that the electrode remained stable by 98% of the current activity toward RF till 15 days, demonstrating the long-term stability of the CCPE.

### 3.4 RF testing in urine samples

To test the application of the proposed electro-analytical method of RF in biological fluids, urine samples were collected from healthy volunteers and processed as stated in (Section 2.8). Its calibration curve was a straight line with a correlation coefficient of 0.9995. According to the statistical regression data, the LOD and LOQ are $7.70 \times 10^{-7}$ and $2.57 \times 10^{-6}$ mol·L$^{-1}$, respectively. Also, mean %R and RSD were found to be 99.30–101.65% and 0.621–1.420%, respectively. Therefore, the proposed electro-analytical study can be successfully and easily used to determine RF in human urine (Table 5).

### 4 Conclusion

The proposed method produces ultra-sensitive, simple, selective, long-run stability, and the precise DPV method for determination of RF. The proposed electro-analytical method was fully validated based on the International Council Harmonization (ICH/Q2) rules. Based on the enhancing effect and formation of inclusion complexes with SDS, this approach may be used to detect RF in its
pure form, pharmaceutical formulations, and real urine samples using a modified CPE in presence of micellar SDS solution. Under optimized parameters, method validation demonstrated that the proposed electro-analytical method was linear and had a very low detection limit, good accuracy, and precision. The developed method can be used in routine work to analyze the cited drug in the pharmaceutical industry QC-units.

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Conflict of interest: The authors state no conflict of interest.

Precaution: Care must be taken when handling cadmium sulfide residues as they are toxic.

Data availability statement: All data generated or analyzed during this study are included in this published article.

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