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Bismuth-coated screen-printed carbon electrodes for quantitative voltammetric determination of formaldehyde in urotropin

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Abstract

For the first time, a bismuth-modified electrode is used for the quantitative voltammetric determination of formaldehyde (FA) in urotropin. The well-established method of forming formaldehyde hydrazone (FAH) in the presence of hydrazine sulphate (HRZ) was employed to transform the hydrated form of FA into its electrochemically active derivative. The reduction current of FAH was recorded in a phosphate buffer solution (PBS, *p*H 5.2±0.1) in the presence of 0.09 M HRZ on a screen-printed carbon electrode that had been preliminarily modified with a bismuth film. A 20-second electrolysis at an applied potential of –0.28 V in a solution comprising 1 M HCl, 0.5 M NaBr, and 4 g/L Bi(III) resulted in the formation of a well-developed metal layer with an active surface. The determination of FA in technical urotropin yielded satisfactory results, indicating the potential for further applications of Bi/SPCE in pharmaceutical analysis.

Keywords

screen-printed carbon electrodes
bismuth film
formaldehyde
urotropin
voltammetry

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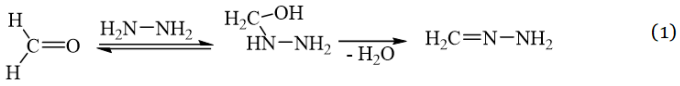
1. Introduction

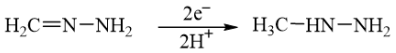
Urotropin (also known as methenamine, hexamine, hexamethylenetetramine) is a tertiary amine that is highly soluble in water and polar solvents, including alcohol, chloroform, methanol, and acetone. This compound was first synthesised by Butlerov in 1859 from formaldehyde (FA) and ammonia [1]. It is noteworthy that only 35 years after its discovery, the first medical use of methenamine was recorded, which demonstrated its exceptional efficacy as an antiseptic for urine, including sterilization of urine in patients with typhoid fever [1].

The recent emergence of antibiotic-resistant bacteria that cause urinary tract infections has led to a resurgence of interest in urotropin as a potential therapeutic agent. Its mechanism of action is due to the formation of bactericidal formaldehyde, which has non-specific antimicrobial activity due to the denaturation of bacterial proteins and nucleic acids. Furthermore, there is compelling evidence that warrants further investigation into the potential of urotropin as an antitumor agent in systemic cancers and glioblastomas [1]. In accordance with FS 2.1.0131.18 of the State Pharmacopoeia of the Russian Federation, XIV edition [2], the free FA content of the substance urotropin is subject to control. The maximum permitted concentration of FA is 0.005%. FA is toxic and has been linked to the development of serious diseases. A multitude of cases of poisoning, allergy, asthma, pulmonary damage, cancer, and even death linked to FA exposure from various sources have been documented. Additionally, it has been demonstrated that FA exhibits mutagenic and genotoxic effects in several experimental models in vivo and in vitro [3]. However, the method of visual assessment of FA content by the color of solutions proposed in FS 2.1.0131.18 is semi-quantitative.

It is established that FA is present in aqueous solutions predominantly in its hydrated form ($CH_2(OH)_2$), which is electrochemically inactive. The complete conversion of FA into its electrochemically active derivative is achieved through a chemical reaction with an amino compound, such as the formation of formaldehyde hydrazone (FAH) by interaction with hydrazine sulfate (HRZ), Equation 1 [4].



(1)



(2)

The current of the FM reduction on the surface of the toxic mercury electrode corresponds to the electroreduction of the double bond of the FAH [4] (equation 2).

In voltammetry (VA), "green" electrodes based on bismuth/antimony have been developed as low-toxic, environmentally friendly working electrodes for the detection of heavy metal ions and electroactive organic compounds. These electrodes exhibit suitable electrochemical properties such as a wide cathodic potential window due to the negative overpotential of hydrogen evolution, low background currents, high electrocatalytic activity, the ability to adsorb organic compounds and insensitivity to dissolved oxygen [5].

Screen-printed carbon electrodes (SPCEs) are a widely used substrate for "green" metal-based electrodes due to their simple modification process and favorable electroanalytical properties. Fabricated from carbon inks and pastes, SPCEs offer several advantages, including low cost, easy mass production capability, high versatility in modification, and excellent surface reproducibility. In contrast to glassy-carbon electrodes, SPCEs do not require multi-stage mechanical surface regeneration [6].

In this paper, we propose a novel quantitative voltammetric method for the determination of formaldehyde in urotropin, utilizing a bismuth-modified SPCE as the working electrode.

2. Experimental

All chemicals of analytical grade were used as received without further purification. Acids, salts, and alkali were obtained from Russian manufacturers. Phosphate solutions were prepared with 3.6 g Na_2HPO_4 and 27.2 g KH_2PO_4, using deionized water, in two separate volumetric flasks of 100 ml and 1000 ml, respectively. The concentration of both solutions was 0.2 M. Phosphate buffer solutions (PBS) of certain pH were prepared by mixing both phosphate solutions in appropriate volumetric ratios. Acetate buffer solution (0.1 M, *p*H 4.5) was prepared by mixing acetic acid and sodium acetate. A freshly prepared acidic solution of hydrazine sulfate (HRZ) was treated with a sodium hydroxide solution of concentration 10 M to reach a *p*H value of 5.95±0.1. State standard sample (GSO) of FA (8639-2004) with mass concentrations of 1 mg/mL as a stock solution was purchased from “Prime Chemicals Group” (Moscow, Mytishchi, RF). Working solutions were prepared by dilution of stock solution with water. The Bi(III) plating solutions of concentrations 80 g/L were prepared by dissolving $Bi(NO_3)_3{\cdot}5H_2O$ (≥ 98%) in 0.1 M HNO_3 solution. Deionized water obtained on device DVS-M/1HA(18)-N ("Mediana filter", Russia) was used throughout.

The samples of technical urotropin grades C and CT from PJSC “Metafrax” (RF) were used for determination of FA. For voltammetric determination, the accurate mass of the technical urotropin samples (1.00±0.01 g) in its original powder form was transferred to a 100 mL volumetric flask, and the volume was filled with deionized water. A solution of 0.8 mL of the sample, 4 mL of 0.2 M PBS (*p*H 5.0±0.2), 9 mL of 0.2 M hydrazine sulphate solution (*p*H 5.95±0.10) and 6 mL of deionized water was added to the voltammetric cell.

The electrochemical research was conducted using a PC-controlled 884 Professional VA (Metrohm, Switzerland) with a standard three-electrode cell. SPCEs based on carbon-containing paste DuPont 7102 from DuPont (USA) were manufactured in a laboratory setting, as detailed in reference [7]. The SPCEs were subjected to *ex situ* modification in a potentiostatic mode with bismuth (Bi/SPCE) or antimony (Sb/SPCE), in accordance with established procedures [8, 9], and served as the working electrodes. Following modification, the electrodes were rinsed with water and were subsequently ready for use. An Ag/AgCl (3 M KCl) electrode was used as the reference electrode, while a glassy carbon rod was employed as the auxiliary electrode in the measurement process. The *p*H of the solutions was determined using an Expert-pH ionomer (Econiks-expert, Russia).

3. Results and Discussion

FAH electro-conversion process was investigated on the surfaces of bare-SPCE and those modified with bismuth (Bi/SPCE) and antimony (Sb/SPCE) using cyclic voltammetry in PBS containing HRZ. The Bi/SPCE and Sb/SPCE electrodes were prepared at the potentiostatic preplating conditions from 0.1 M acetate buffer solution (*p*H 4.5), containing 100 mg/L Bi(III) ions according to [10] or from 0.01 M HCl after adding 50 mg/L Sb(III) [9] under constant electrodeposition potential (E_{el}) during electrodeposition time (t_{el}).

As illustrated in Figures 1 a, b, the cyclic voltammograms recorded at the bare SPCE and Sb/SPCE, respectively, exhibit no discernible anodic or cathodic peaks, indicating that these electrodes are electrochemically inactive with respect to FAH. In contrast, the Bi/SPCE electrode exhibited a cathodic peak at −0.97 V (Figure 1c). The absence of a corresponding anodic peak in the CV (Figure 1c) attributable to the FA and hydrazine sulfate adduct (FAH) on the bismuth surface indicates that the electrochemical reduction of FAH is an irreversible process, similar to that observed on HMDE [11].

Our investigation [12] revealed that the degree of antimony coverage of the substrate was 12% for Sb/SPCE, whereas in the case of Bi/SPCE, the substrate was found to be half covered with the metal. The electrochemical inactivity of bare SPCE and Sb/SPCE towards FAH can be attributed to the preferential reduction of FA on the metals

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rather than on the carbon substrate. Unfortunately, the formation of thicker antimony films results in a lack of adhesion between the metal and the carbon substrate.

It is well established that the electroanalytical properties of bismuth films are significantly influenced by their intrinsic characteristics, including structure, morphology, and adherence. To enhance the analytical performance of the electrodes, it is essential to achieve a highly developed bismuth surface. Additives are employed with the aim of modifying various aspects of the electrodeposition process, including particle aggregation, volume fraction, and crystallite dispersion [13]. The incorporation of bromide ions into the plating solution has been demonstrated to exert a pronounced influence on the morphology of the bismuth film on the carbon substrate electrode, through the formation of complexes with Bi(III) ions [14]. The bromide ions exhibit a preference for adsorption onto the developing bismuth deposit, forming a non-uniform blocking layer that inhibits crystal growth. This results in the formation of denser films with smaller, more uniformly distributed bismuth particles [15]. Furthermore, the complexation of Br^- enhances both the physical and electrochemical stability of the deposited film. The formation of a significantly improved bismuth film on a glassy carbon electrode from an unstirred acid solution with an extremely high concentration of Bi(III) in the presence of bromide ions has been demonstrated [14].

The Bi/SPCE for FA determination in urotropin samples was prepared ex situ in the presence of Br^-, in accordance with the methodology outlined in work [14]. The electrode was positioned within a plating solution comprising 1 M HCl, 0.5 M NaBr and 4 g/L Bi(III). A potential of –0.28 V was applied to the working electrode for a period of 20 sec, without stirring the solution. The area of the FA reduction peak demonstrates a linear increase in relation to its concentration, within the range of 0.2–1.0 mg/L (Figure S1, a). The limit of detection (LOD) was calculated from the corresponding equation for the calibration curve, resulting in a value of 0.02 mg/L FA. The LOD value was calculated using the formula $3\sigma/k$, where σ is the standard deviation of the free term of the linear relationship, and k is the sensitivity. The quantification concentration of FA is 0.07 mg/L. The operating conditions for recording differential pulse (DP) FA voltammograms on Bi/SPCE, as previously reported [8], were used (Figures S1, b).

The technical urotropin grades were subjected to analysis using the standard addition method. The DP voltammograms recorded for the samples exhibited well-defined reduction peaks of FA (Figure 2, inserts). The area of these peaks demonstrated a linear increase with varying additions of FA from the working solutions (Figure 2). The sensitivities of Bi/SPCE to FA in both the technical urotropin test solutions exhibited values close to 2.05 for pure solutions (Figure S1, a), indicating the absence of an interfering effect of the matrix of the studied samples on the determination of FA.

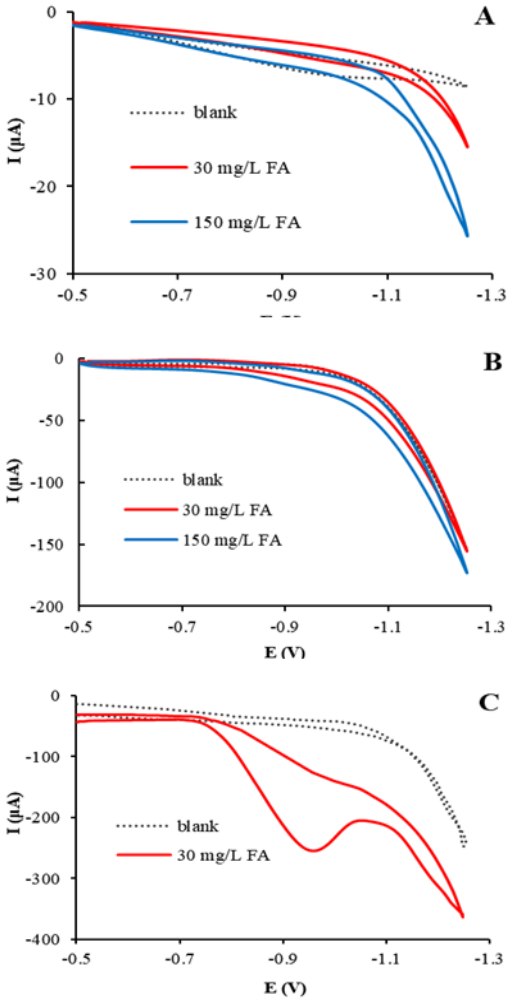

Figure 1 CVs registered on: bare-SPCE (A); Sb/SPCE (B) and Bi/SPCE (C) in 0.04 M PBS + 0.09 M HRZ (*p*H 5.2±0.1) without adding (blank) and after adding FA at a υ of 0.1 V/s. The deposition condition for metal films: 0.1 M acetic buffer, *p*H 4.5+100 mg/L Bi(III), E_{el} = –1.0 V, t_{el} = 480 s (B); 0.01 M HCl + 50 mg/L Sb(III), E_{el} = –0.5 V, t_{el} = 300 s (C).

The results of the FA determination in technical urotropin grades C and CT are presented in Table 1. The obtained results for both grades are highly similar. The relative standard deviation (RSD) does not exceed 5% for both grades, indicating that the method developed is precise.

The content of FA in technical urotropin of both grades does not exceed the permissible values specified by the manufacturer (0.02–0.2% on a dry weight basis). It is of great importance for the manufacturer to control the FA content in technical urotropin, as it has a significant impact on the quality of the produced urotropin pharmaceutical substance, which serves as an active ingredient in finished dosage forms.

The accuracy of the developed methods for the quantitative determination of FA in the specified samples was evaluated by comparing the obtained results with those obtained by an independent analysis method recommended by the State Pharmacopoeia of the Russian Federation, 14th edition [2].

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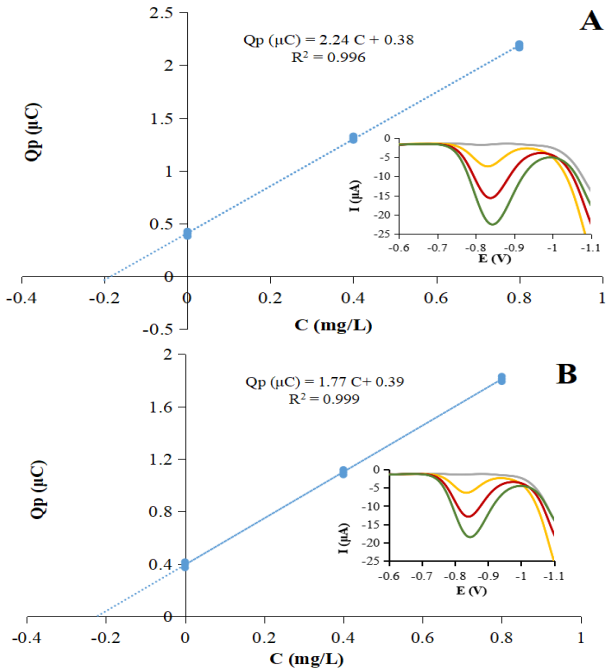

Figure 2 Calibration curves for technical urotropin grades C (A) and CT (B) and additions of 0.4 and 0.8 mg/L FA. Insert: corresponding DP voltammograms for blank (gray line), additions of urotropin grades C and CT (yellow line) and additions of FA 0.4 mg/L (red line) and 0.8 mg/L (green line) recorded at Bi/SPCE in 0.04 M PBS + 0.09 M HRZ (*p*H 5.2±0.1).

Table 1 Results of voltammetric determination of FA content in technical urotropin grades C and CT from PJSC "Metafrax"; (n = 6, P = 0.95).

Urotropin grades	Found FA		RSD, %
	urotropin test solution, mg/L	technical urotropin, %	
C	5.0	0.050	
	4.7	0.047	
	4.5	0.045	
	5.1	0.051	
	4.6	0.046	
	4.8	0.048	
$\bar{C} \pm \Delta C$, %	4.8±0.2	0.048±0.002	4.8
CT	5.0	0.050	
	5.2	0.052	
	5.5	0.055	
	5.1	0.051	
	5.0	0.050	
	5.0	0.049	
$\bar{C} \pm \Delta C$, %	5.1±0.2	0.051±0.002	4.2

In accordance with FS 2.1.0131.18, the semi-quantitative determination of FA content in the substance urotropin is conducted through visual assessment. The method is based on the formation of silver as a result of the interaction of silver nitrate with FA in the presence of ammonium hydroxide. To this end, 2 ml of a 2.5% silver ammonium nitrate solution is added to the test solution of the samples and the FA standard solution. The resulting gray color of the test solution after 5 minutes should not be more intense than the color of the comparison reference solution (RS) with 5 mg/L FA.

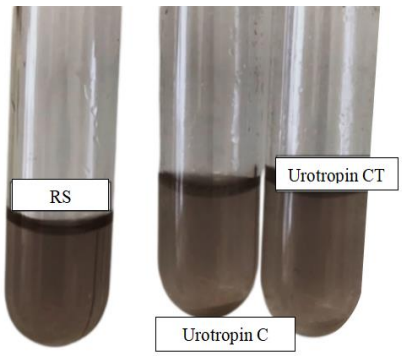

Figure 3 Colors of FA reference solution (RS) and 1% test solutions of commercial urotropin grades C and CT.

Figure 3 illustrates the identical colors of the RS and commercial urotropin test solutions, corresponding to a 5 mg/L FA concentration, which, in terms of dry weight, is approximately 0.05% FA for both samples. The FA content of the urotropin test solution was found to be 4.8±0.2 mg/L for the C sample and 5.1±0.2 mg/L for the CT sample, according to the VA method (Table 1). In terms of dry weight, the FA content in urotropin is 0.048±0.002% for the C sample and 0.051 ± 0.002% for the CT sample. This indicates that the results of both methods, the developed VA and the pharmacopeial, are in acceptable agreement.

4. Limitations

To extend the applicability of the developed methodology in pharmacological analysis, we intend to ascertain the concentration of FA in its pharmaceutical formulation and in finished dosage forms containing urotropin as the active ingredient. In order to gain a more comprehensive understanding of the subject matter, it is deemed appropriate to employ a combination of analytical techniques, in addition to the semi-quantitative pharmaceutical poetical, for the determination of FA in urotropin-containing pharmaceuticals. This approach will facilitate the investigation of potential interferences arising from excipients present in finished dosage forms, with a view to identifying the most effective methods for their elimination.

5. Conclusions

This paper presents, for the first time, a low-cost, straightforward, rapid and reliable voltammetric method for the determination of FA in urotropin in the form of electrochemically active formaldehyde hydrazone (FAH). The electroconversion process of FAH was investigated on the surfaces of three types of SPCE electrodes: bare SPCE, Sb/SPCE and Bi/SPCE. Cyclic voltammetry was used in PBS containing HRZ to examine the behaviour of FAH on these electrodes. It was demonstrated that the bare SPCE and Sb/SPCE electrodes exhibited no discernible anodic or cathodic peaks, indicating that they are electrochemically inactive with respect to FAH. In contrast, the Bi/SPCE electrode exhibited irreversible reduction of FAH, which was

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found to be a response-forming process. To obtain a bismuth film with a well-developed active surface, the bare SPCE was modified using a plating solution containing an extremely high concentration of Bi(III) in the presence of bromide ions.

The results of the FA determination in technical urotropin grades with direct differential pulse voltametry demonstrated the efficacy and reliability of the employed methodology, as well as the absence of any confounding effects associated with the matrix of the studied samples on the determination of FA. The accuracy of the developed methods for the quantitative determination of FA in the specified samples was evaluated by comparing the obtained results with those obtained from independent analytical methods recommended by the State Pharmacopoeia of the Russian Federation (FS 2.1.0131.18). The content of FA in the commercial urotropin of both grades is approximately 0.05%, which is within the permissible range of 0.02–0.2% by dry weight as specified by the manufacturer. The developed method has the potential for application in the determination of FA in urotropin pharmaceutical substances and finished dosage forms containing urotropin as an active ingredient.

• Supplementary materials

This manuscript contains supplementary materials, which are available on the corresponding online page.

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• Conflict of interest

The authors declare no conflict of interest.

• Additional information

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