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Original scientific paper

Fast and sensitive metronidazole determination by means of voltammetry on renewable amalgam silver-based electrode without the preconcentration step

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Abstract: Application of cyclic renewable amalgam silver-based electrode (Hg(Ag)FE) for sensitive metronidazole detection by the differential pulse voltammetry (DPV) is described. The unique properties of the Hg(Ag)FE such as the relative large surface area and its fast and very simple renewal were fully utilized for sensitive measurements. Compared with the classical hanging mercury drop electrode (HMDE), the renewable Hg(Ag)FE significantly increases the reduction peak current of metronidazole because of its large surface area. The effects of various factors for the metronidazole determination such as: pulse height and width, step potential, surface area of the working electrode, and basic electrolyte composition are optimized. The obtained calibration graph is linear from 0.1 (17 μg L^{-1}) to 2 μM (342 μg L^{-1}) with correlation coefficient 0.999. For the Hg(Ag)FE with the surface area of 10.1 mm^2 the limit of detection (*LOD*) is 20 nM (3.4 μg L^{-1}). The repeatability of the method at a concentration of the analyte of 0.5 μM (5.6 μg L^{-1}), expressed as relative standard deviation (*RSD*) is 2.1 % (n = 7). The proposed method was successfully applied and confirmed by studying recovery of metronidazole from spiked samples.

Keywords: metronidazole; drugs; amalgam film electrodes; voltammetry.

INTRODUCTION

One of the most important nitroimidazole compounds, metronidazole (1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole) is one of the most significant prodrugs, with a wide spectrum of action.[1–3] Due to its high activity against the anaerobic protozoa, metronidazole (MNZ) is commonly used for the protozoan infection treatment since 1960.[4] According to the later studies, it was proven that metronidazole exhibits not only an anti-protozoal action, but it is also active

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against a variety of anaerobic pathogens, including both Gram-negative and Gram-positive bacteria. It is also effective for the treatment of infections caused by anaerobic organisms such as Clostridium and amebiasis or fungus infection.[5] Considering the wide range of metronidazole activity, it is extensively used in the treatment of diseases such as pelvic inflammatory disease, endocarditis, bacterial vaginosis, rosacea, lung abscess, periodontitis, and trichomoniasis. It is also often exploited either alone or with other antibiotics to eradicate Helicobacter pylori bacteria, and to prevent infection after recovering from surgery.[6–8] MNZ may be taken orally, intravenously or transdermal and it is one of the most important medication according to the World Health Organization.[9]

Considering the numerous applications of MNZ as a medication, the new method of its determination has been developed. In order to achieve lower limits of detection, analytical methods such as spectrophotometry[10–14], chromatography[15–19] or mass spectrometry[20–22] were used. Among the proposed ways of obtaining high sensitivity of MNZ, wide variety of voltammetric techniques have been proposed. Not only classical mercury electrode was involved in researches[23], but also lots of solid state sensors such as boron doped diamond film electrode[24,25], gold[26,27] and carbon paste electrode[28,29] or glassy carbon electrodes modified with carbon nanotubes[30,31], conducting polymers[32,33] or other nanomaterials.[34–36]

The most popular working electrodes in voltammetry, according to its almost ideal surface parameters, are hanging drop mercury electrodes. Repeatability and reproducibility obtained with these electrodes is better when compared to solid electrodes and limits of detections are lower. However, due to its toxicity and the strict limits of mercury usage, the new constructions of classical electrodes are proposed. Among them are the film electrodes with renewable surface, based on different metals, *e.g.*, bismuth, lead, copper or mercury.[37] This type of electrodes was successfully applied for highly sensitive determination of elements,[38–42] organic and inorganic compounds[43–45] or pharmaceuticals.[46–49] Another solution is to use a solid silver amalgam for voltammetric electrodes. Their fabrication, properties, characteristic and applications were widely studied by Barek and coworkers.[50–57]

In this work the differential pulse voltammetry (DPV) is applied for the determination of low concentration of MNZ using silver based amalgam electrode (Hg(Ag)FE). The validation and recovery of the proposed method was done using spiked samples. The potential interferences from selected cations, organic compounds, and surface-active substances were checked. New procedure was successfully applied for MNZ sensitive determination in pharmaceutical formulations.

EXPERIMENTAL

Measuring apparatus and software

A multifunctional electrochemical analyzer M161 with the electrode stand M164 (both MTM-ANKO, Poland) were used for all voltammetric measurements. The classical three--electrode cell consisting of a cylindrical silver based mercury (amalgam) film electrode (Hg(Ag)FE)[37], refreshed before each measurement and with a surface area of 1–12 mm^2, as the working electrode, a double-junction Ag/AgCl/KCl (3M) reference electrode and a platinum wire as an auxiliary electrode. All potentials in the paper are given on Ag/AgCl/KCl (3M) scale. The results obtained with the amalgam film electrode were then compared with the corresponding values obtained using the hanging mercury drop electrode M163 (MTM--ANKO). pH Measurements were performed with laboratory pH-meter (n-512, Elpo, Poland). Magnetic Teflon-coated bar (Aldrich) was used for stirring the measured solution (with approximately 500 rpm). All experiments were carried out at laboratory temperature.

Chemicals and glassware

All reagents used in the work were of the analytical grade. Acetic acid, sodium acetate (Suprapur®) and mercury GR for polarography were obtained from Merck. Standard stock solution of MNZ (0.01 M) was prepared by dissolving crystalline $C_6H_9N_3O_3$ (Aldrich) in water and stored in refrigerator at 4 °C. Solutions with lower MNZ concentrations were made daily by appropriate dilution of the stock solution. The silver base for the electrode was prepared from polycrystalline silver wire with a diameter of 0.5 mm, and of 99.99 % purity (Goodfellow Science Park, England). Prior to use, glassware was cleaned by immersion in a 1:10 aqueous solution of HNO_3, followed by copious rinsing in distilled water.

Standard procedure of measurements

Quantitative measurements of MNZ were performed using differential pulse voltammetry (DPV) and the standard addition procedure. The procedure of refreshing the amalgam film Hg(Ag)FE electrode was carried out before each voltammogram registration. The Hg(Ag)FE electrode renovated in this way was used to determine MNZ in the base electrolyte: 0.1 M acetate buffer (pH 4.4), total volume 10 ml contained in a voltammetric cell. The DPV procedure was performed with the following steps in a continued sequence:

a) Conditioning of the Hg(Ag)FE: $E^{I}_{cond} = -1100$ mV, $t_{cond} = 5$ s (removal of oxides from electrode, lower background current).

b) Rest period 5 s.

c) Recording of voltammogram in the potential range from 25 to –950 mV.

Conditions for the DP mode were as follows: pulse amplitude (dE), 50 mV; potential step (E_s), 4 mV; time step potential (t_w, t_p), 20 ms (10 ms waiting + 10 ms current measuring time). Measured solutions were deaerated by 5 min bubbling with argon. The determinations were performed using the standard additions method (based on three additions).

Sample preparation

Pharmaceutical products and urine. For *DPV* determination of MNZ in tablet, 3 tablets, obtained from pharmacies (Metronidazol Polpharma, 250 mg MNZ per tablet) were grinded into a fine powder with a mortar and pestle. The powder (25 mg) was transferred through a funnel into a 10 mL volumetric flask by washing with water and filling up to the mark. The obtained solution was sonicated for 10 min. Next 500 μL of the sample was pipetted into the voltammetric cell containing 2 mL (0.5 M) of acetate buffer (pH 4.4) and 7.5 mL of water.

In the case of metronidazole for injection (Metronidazole Fresenius, 500 mg per 100 mL) the whole drug (100 ml) was diluted in 1000 mL volumetric flask. Next 250 μL of the sample was pipetted into voltammetric cell containing 2 mL (0.5 M) of acetate buffer (pH 4.4) and 7.75 mL of water.

In the case of MNZ determination in urine, the urine sample was centrifuged at 5000 rpm for 10 min with addition of methanol (10 vol. %). Next, the solution was filtrated and the clear supernatant was transferred into a 10 mL volumetric flask. Next, 100 μL of the fresh sample of the urine from volunteer was added directly into voltammetric cell with the supporting electrolyte (2 mL (0.5 M) acetate buffer (pH 4.4), 7.9 mL water – total volume: 10 mL).

RESULTS AND DISCUSSION

Metronidazole on renewable amalgam film electrode Hg(Ag)FE

Differential pulse voltammetry is appropriate for measuring the traces of metronidazole. This is due to its high sensitivity, relatively low background current, good reproducibility, and linearity. The use of mercury as the working electrode material should be greatly reduced because of its high toxicity, especially in the case of laboratory analysis. It is possible to reduce significantly the use of mercury from the analytical procedure of MNZ determination by means of Hg(Ag)FE. Typical signals obtained for Hg(Ag)FE as compared to hanging mercury drop electrode (HMDE) for 5 μM MNZ are presented in Fig. 1.

MNZ peak current is about 20 % higher for the Hg(Ag)FE *vs.* the HMDE electrode (for similar geometrical sizes of surfaces of working electrodes). The measured peak potentials were: −283 and −252 mV for Hg(Ag)FE and HMDE, respectively. The MNZ peak half width was 88 mV for Hg(Ag)FE and 84 mV for

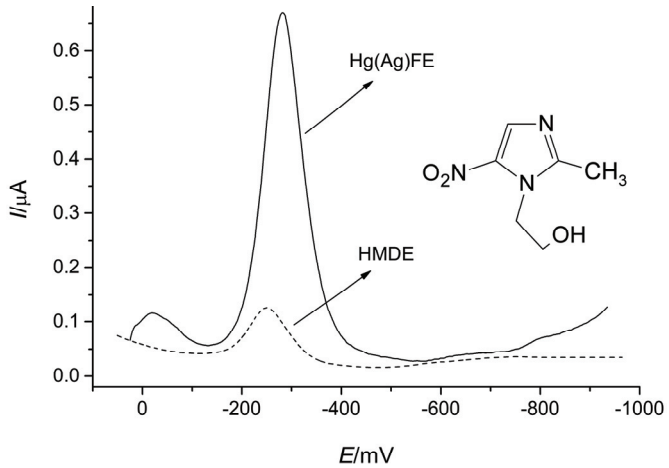

Fig. 1. Juxtaposition of DP voltammograms measured for 5 μM MNZ in 0.1 M acetate buffer (pH 4.4) for HMDE and Hg(Ag)FE electrode. The electrode areas were 10.1 mm^2 for the (Hg(Ag)FE) and 1.7 mm^2 for the HMDE, respectively. DP instrumental parameters: dE = 50 mV, E_s = 4 mV, t_w and t_p = 10 ms (inset – chemical structure of MNZ).

HMDE electrode. The achieved reproducibility at (Hg(Ag)FE) for n = 7 and 0.5 μM of metronidazole was 2.1 %. The surfaces of solid electrodes are frequently much larger than those of mercury drop electrodes. When using the Hg(Ag)FE electrode the surface of the working electrode may be simply changed in a wide range. For the surface area of 2.1 mm^2, the MNZ peak current (5 μM) was 0.13 μA and grew with the increasing electrode area. For the surface area of 12.1 mm^2, the peak current was 0.73 μA (Fig. 2).

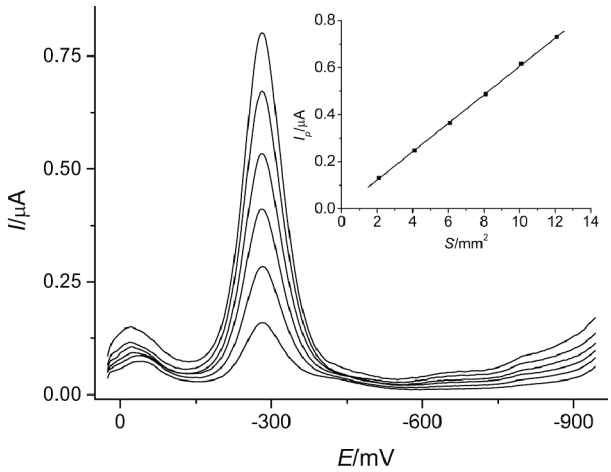

Fig. 2. DP voltammograms measured for Hg(Ag)FE electrode surface area (S): 2.1, 4.1, 6.1, 8.1, 10.1 and 12.1 mm^2 for 5 μM MNZ in 0.1 M acetate buffer (pH 4.4). All other conditions as in Fig. 1.

The parameters of the linear dependence of the peak current on the surface of the working electrode for 5 μM of metronidazole are: slope, 0.0603±0.0005 μA mm^{-2}, intercept, 0.0014±0.0039 μA, and correlation coefficient r = 0.9998. For the further study, the 10.1 mm^2 surface area was used.

Influence of the scan rate on MNZ peak current and peak potential

The influence of the scan rate (v) on the peak current and the peak potential of MNZ at Hg(Ag)FE was investigated using cyclic voltammetry in the range from 10 to 500 mV s^{-1} (Figs. 3 and 4, respectively). The electrochemical reduction of MNZ is an irreversible process due to the absence of oxidation peak.

The peak current *vs.* square root of the scan rate gave a straight line. The found linear regression equation is:

$$I_p / \mu A = -0.108v^{0.5} + 0.054, r = 0.999 \quad (1)$$

This suggests a diffusion-controlled reduction process at the Hg(Ag)FE.

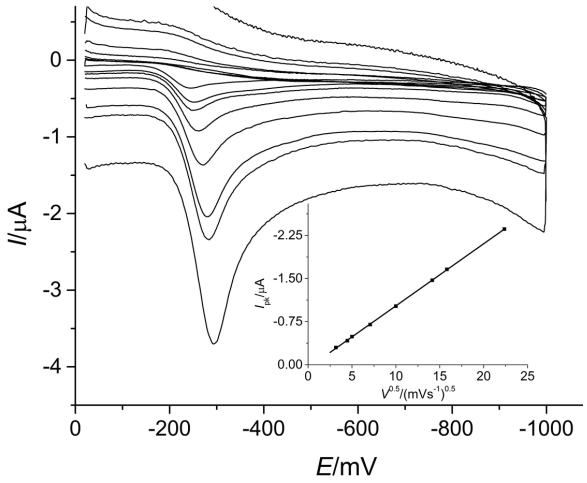

Fig. 3. Cyclic voltammograms measured for 10 μM MNZ on the Hg(Ag)FE electrode in 0.1 M acetate buffer (pH 4.4). Scan rate in the range from 10 to 500 mV s^{-1} (inset – dependence of the MNZ peak current on square root of the scan rate).

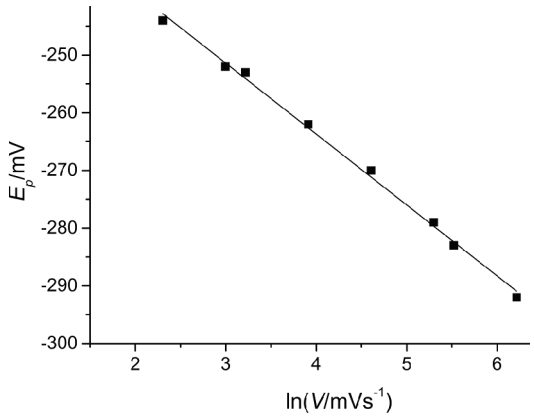

Fig. 4. Dependence of the MNZ CV peak potential on natural logarithm of the scan rate measured in the range from 10 to 500 mV s^{-1} for 10 μM MNZ in 0.1 M acetate buffer (pH 4.4).

The cathodic peak potential was shifted in the negative direction with the increasing scan rate. The peak potential *vs.* ln scan rate gives a straight line. The obtained linear regression equation is:

$$E_k \text{ / mV} = -12.3 \ln v - 214, r = 0.998 \quad (2)$$

Based on the theory, for an irreversible electrode reaction from the slope of E_k *vs.* ln v, $\alpha n = 1.04$, could be obtained.

The reduction peak of MNZ requires a total of four electrons and four protons reduction of the nitro group to the corresponding hydroxylamine, according to the known and described mechanism.[58,59]

Influence of pH on MNZ peak

In order to improve the MNZ peak current signal, the effect of pH of the supporting electrolyte was investigated. DP voltammograms of the MNZ depends on pH (Fig. 5).

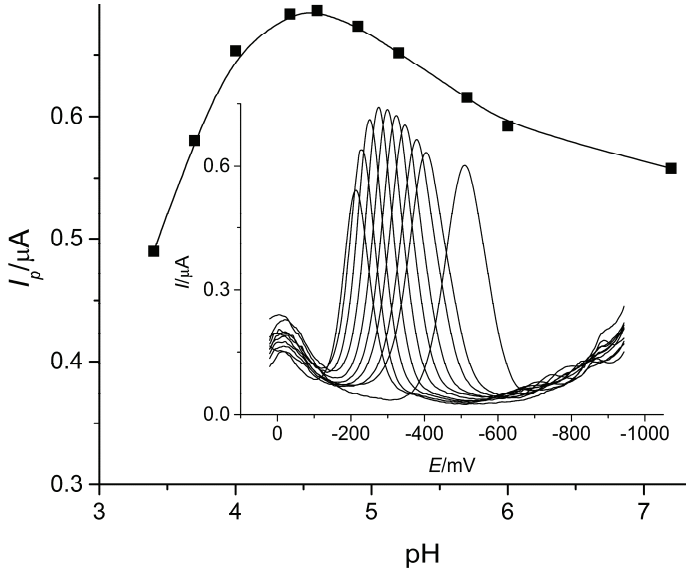

Fig. 5. Dependence of the DPV peak current at Hg(Ag)FE on pH in the range from 3.4 to 7.2 for 5 μM MNZ in 0.1 M acetate buffer and obtained DP voltammograms. All other conditions are as in Fig. 1.

The optimal pH was in the range from 4 to 5.2 (with the peak current reaching values about 0.65 μA). Higher pH than 5.2 caused a decrease in the peak current. The pH has also an influence on the peak potential, which changed to the positive values with decreasing pH. The found linear regression equation is:

$$E_p = -77.9\text{pH} + 59 \text{ mV}, r = 0.996 \quad (3)$$

and it indicates that protons are involved in the electrode process and that the protonation takes place before first electron uptake.[60,61]

For further study, the pH of 4.4 was applied.

Influence of DPV parameters on DPV peak of metronidazole

The significant factors of the *DPV* technique are pulse height (dE), potential step amplitude (E_s), pulse width, waiting time (t_w) and sampling time (t_s). Thus, these parameters were studied. To optimize the conditions for MNZ measurements, the following instrumental parameters were methodically varied: dE in the range 5–100 mV (both positive and negative mode), E_s in the range 1–6 mV, t_w and t_p in the range 10–100 ms, respectively.

The best results were obtained for an amplitude of 50 mV (the peak current was approx. 0.65 μA for 5 μM MNZ). Higher pulse amplitude (>50 mV) caused the minor growth of the peak current. In further studies, the pulse height of 50 mV was applied.

Changes of the step potential influence the peak current. For a step potential equal to 1 mV the peak current was 0.23 μA, and for a step potential of 6 mV the peak current was 0.7 μA. The step potential of 5 mV was applied in further studies.

The waiting time and probing time were varied in the range from 10 ms to 100 ms. The best results were obtained for t_w and t_p of 10 ms, respectively, and these values were used for further work.

Interferences

The DPV signals are strongly affected by the type and concentration of all the components of the measured electrolyte. The examined ions such as: Ca(II), Mg(II) in a 1000-fold excess, Fe(III), Mn(II), Zn(II) in a 10-fold excess, and Cu(II), Pb(II), Cd(II) in the same concentrations as MNZ did not interfere. Organic compounds such as: citric acid, ascorbic acid in a 10-fold excess and glucose 25 mg L^{-1} did not interfere.

The surface-active compounds are generally a source of high interferences in the voltammetric methods. A non-ionic surface-active compound (triton X-100) was studied bearing this in mind. For 0.5 mg L^{-1} of triton X-100 concentration, no suppression of the signal was observed. Higher concentration of triton X-100 suppressed the signal, *e.g.*, for 1 mg L^{-1} of triton X-100 by approx. 5 %, for 10 mg L^{-1} of triton X-100 by 60 %, and for 20 mg L^{-1} of triton X-100 by 75 %.

Analytical performance

The DPV calibration curves and voltammograms for MNZ are presented in Fig. 6.

For the electrode surface area of 10.1 mm^2 the obtained detection limit (calculated as 3σ) in acetate buffer (pH 4.4), is 20 nM and the linearity is up to 2 μM. The slope for the regression line is (0.192±0.001) μA μM^{-1}, the intercept is (–0.007±0.002) μA: and the correlation coefficient is 0.999. Nonlinearity for the concentration of MNZ above 2 μM may be due to the saturation of the electrode surface with the MNZ. Precision and recovery were determined using three different synthetic samples (which contained: K, Ca, Mg and Cl ions) spiked by 0.1; 0.25 and 0.55 μM of MNZ (Table I).

To validate the method, the urine, tablets and metronidazole injection were investigated.

The samples, spiked with MNZ were analysed according to the presented procedure using the renewable mercury film electrode. Determinations of MNZ were performed using the standard addition method (three additions of MNZ). Results from MNZ determination are presented in Table II.

The linear range and the detection limit obtained at various electrodes are presented in Table III.

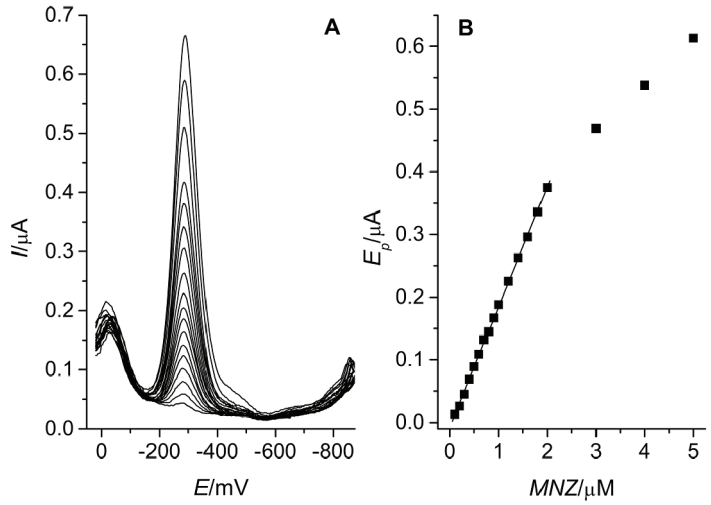

Fig. 6. A) DP voltammograms of MNZ at Hg(Ag)FE and B) calibration curve in the range of 0.1 to 5 μM in 0.1 M acetate buffer (pH 4.4). All other conditions are as in Fig. 1.

TABLE I. Recovery and precision of the determination of trace MNZ

Added amount, μM	Amount found, μM	Recovery, %	*RSD* / %
0.10	0.096	96	3.6
0.25	0.255	102	3.4
0.55	0.555	101	2.9

TABLE II. Results of MNZ determination in the urine, tablet and MNZ for injection

MNZ amount	MNZ determined $\bar{x} \pm s$ (recovery, %)		
	Concentration in urine, μM	Amount in tablet,[a] mg	MNZ for injection,[b] mg
0	0	245±9 mg	492±14
0.5 μM	0.46±0.05 (93)	–	–
1.5 μM	1.44±0.11 (96)	–	–
250 mg	–	510 ± 13 (103) mg	749±23 (101)

[a]Product declared, 250 mg per tablet; [b]product declared, 500 mg per 100 ml

TABLE III. Voltammetric determination of MNZ at various electrodes

Electrode	Method	*LOD*	Ref.
Silver solid amalgam composite electrode	DCV	2 μM (*LoQ*)	57
b-Cyclodextrin-functionalized gold nanoparticles/ /poly(L-cysteine) modified glassy carbon electrode	LSSV	14 nM	60
Glassy carbon electrode modified with single-walled carbon nanotubes	Amperometry	63 nM	61
Glassy carbon electrode immobilised with DNA	DPSV	1 μM	62

TABLE III. Continued

Electrode	Method	*LOD*	Ref.
Mercury film electrode	DPV	4.76	3
Carbon paste electrode modified α-cyclodextrin	DPV	0.28 μM	64
Hg(Ag)FE	DPV	20 nM	This work

The recovery of MNZ ranged from 93–103 %. The analytical usefulness of the studied method for the determination of MNZ in urine and drug samples was confirmed.

CONCLUSIONS

The work demonstrates the Hg(Ag)FE as a suitable electrode for the DP voltammetric determination of metronidazole. The studied DPV method is very rapid and allows the determination of MNZ at low concentrations, with the detection limit of 20 nM (3.42 $\mu g \cdot L^{-1}$) for a surface area of 10.1 mm^2. The reproducibility of the studied method is very good, giving *RSD* 2.1 % (with each measurement performed at a renewed surface of the working electrode). The satisfactory recovery (93–103 %) shows that the proposed method can be used for the routine determination of MNZ in real samples (urine, tablets and drugs for injection).

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ИЗВОД

БРЗА И ПРЕЦИЗНА МЕТОДА ЗА ОДРЕЂИВАЊЕ МЕТРОНИДАЗОЛА НА ОБНОВЉИВОЈ ЕЛЕКТРОДИ ОД АМАЛГАМА СРЕБРА БЕЗ ПРЕКОНЦЕНТРАЦИЈЕ

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Описана је примена циклично обновљиве електроде од амалгама сребра (Hg(Ag)FE) за прецизну детекцију метронидазола, помоћу диференцијално-пулсне волтаметрије (DPV). Јединствена својства електроде Hg(Ag)FE, као што су релативно велика површина и брза и веома једноставна обновљивост су искоришћене за прецизно мерење. У поређењу са класичном HMDE, на обновљивој Hg(Ag)FE региструју се знатно веће струје редукције метронидазола због велике површине. Оптимизовани су различити фактори за одређивање метронидазола као што су: висина и ширина пулса, потенцијал, површина радне електроде и састав основног електролита. Добијена калибрациона крива је линеарна у области концентрације од 0,1 (17 μg L^{-1}) до 2 μM (342 μg L^{-1}) са корелационим коефицијентом од 0,999. За Hg(Ag)FE површине 10,1 mm^2, *LOD* износи 20 nM (3,4 μg L^{-1}). Поузданост методе, са концентрацијом аналита од 0,5 μM (5,6 μg L^{-1}), је изражена као *RSD* и износи 2,1 % (n = 7). Предложена метода је успешно примењена и потврђена одређивањем процентуалног приноса метронидазола у концентрисаним узорцима.

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