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Voltammetric Determination of Isoniazid using Cyclic Renewable Mercury Film Silver Based Electrode

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Abstract

A new cathodic voltammetry method for the determination of isoniazid based on the cyclic renewable mercury film silver based electrode (Hg (Ag) FE) is presented. The effects of various factors such as: preconcentration potential and time, pulse height, step potential and supporting electrolyte composition are optimized. The calibration graph is linear from 5 nM up to 500 nM (68.55 μgL^{-1}). For Hg (Ag) FE with a surface area of 9.7 mm^2 without time consuming preconcentration the limits of detection LOD and quantification LOQ were 4.1 nM and 10.5 nM of isoniazid, respectively. The repeatability of the method at a concentration level of the analyte as low as 0.5 nM, expressed as RSD is 3.6% (n=6). The proposed method was successfully applied in analysis of isonizid in simple and composed pharmaceutical formulations.

Keywords: Isoniazid; Pharmaceutical analysis; Mercury film electrodes; Cathodic voltammetry

Introduction

Isoniazid - isonicotinyl acid hydrazide (INH) are being used as first-line agent continously from 50 years in *Mycobacterium tuberculosis* infection and prevention. *Mycobacterium tuberculosis* infects approximately one third of the world's population. Isoniazid is associated with hepatotoxicity and peripheral neuropathy, and slow acetylators may be at increased risk of toxicity [1]. Finally, INH cause many interactions with many popular drugs with a vue of its metabolism by cytochrome P450. Active ingredient analysis is necessary in drug quality control and as well as a useful tool in therapeutic drug monitoring during treatment of tuberculosis [2].

The analytical methods most often used to determine of isoniazid in pharmaceutical preparations and biological fluids are: separation methods - liquid chromatography [3-5], high performance liquid chromatography [6-14], capillary electrophoresis [15-18], gas chromatography [19], high-performance thin-layer chromatography [20]; optical methods - spectrophotometry [21-26], flow injection chemiluminescence [27-34], colorimetry [35-37] and electroanalytical methods. In case of electroanalysis used are stripping methods such as potentiometry [38,39], polarography [40,41], differential-pulse polarography [42,43] and stripping voltammetry [44-49]. The HMDE is the electrode of preference due to its high sensitivity, reproducibility and linearity. However, the toxicity of mercury limits the usage of the mercury electrodes in the analytical practice and excludes them from the out-of-laboratory applications. The problem of limiting the amount of mercury or its soluble salts needed for the analytical procedure can be solved with the help of a renewable silver amalgam film electrode. The principle of working and first proposal of a construction of the (Hg (Ag) FE) was described in [50]. The simple construction of the applied electrode allows the mercury film to be refreshed before each measurement. The (Hg (Ag FE) electrode was successfully applied for the determination of many elements [51-58]. In this work differential pulse cathodic voltammetry for the determination of isoniazid was used. The method based on the cyclic renewable mercury film silver based electrode (Hg (Ag) FE) without preconcentration time allows detection of isoniazid at trace level. The new procedure was examined and was successfully applied for determination of isoniazid contents in several simple and composed pharmaceutical formulations.

Material and Methods

Measuring apparatus and software

A multipurpose Electrochemical Analyzer M161 with the electrode stand M164 (both MTM-ANKO, Poland) were used for all voltammetric measurements. The classical three-electrode quartz cell, volume 10 mL, consisting of a homemade cylindrical silver based mercury film electrode (Hg (Ag) FE), refreshed before each measurement and with a surface area of 1 – 12 mm^2, as the working electrode, a double junction reference electrode Ag/AgCl/KCl (3 M) with replaceable outer junction (3 M KCl) and a platinum wire as an auxiliary electrode. pH measurements were performed with laboratory pH-meter. Stirring was performed using a magnetic bar rotating at approximately 500 rpm. All experiments were carried out at room temperature.

Chemicals and glassware

All reagents used were of analytical grade. CH_3COOH (Merck, Suprapur), mercury GR for polarography (Merck, Germany), Triton X-100 (Windsor Laboratories Ltd, UK). A standard stock solutions of isoniazid (0.1 M) were prepared by dissolving isoniazid (Sigma-Aldrich) in quadrouple distiled water (two last stages in quartz). Solutions with lower isoniazid concentrations were made weekly by appropriate dilution of the stock solution. The silver base for the film electrode was prepared from polycrystalline silver wire with a diameter of 0.5 mm, and of 99.99% purity (Goodfellow Science Park, England).

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Prior to use, glassware was cleaned by immersion in a 1:10 aqueous solution of HNO_3 (37%), followed by copious rinsing in distilled water.

Standard procedure of measurements

Quantitative measurements were performed using differential pulse cathodic voltammetry and the standard addition procedure. The procedure of refreshing the mercury film Hg (Ag) FE electrode was carried out before each measurement. A potential of -600 mV (3 s) was applied to condition the electrode after the refreshing step. The Hg (Ag) FE electrode conditioned in this way was used to determine isoniazid in the supporting electrolytes: acetic acid (pH 3.3) contained in a quartz voltammetric cell. The potential of the electrode was changed in the following sequence: conditioning and starting potential -600 mV for 3 s. Then, after a rest period of 5 s a differential pulse voltammogram was recorded in the cathodic direction from -600 mV to -975 mV. The other experimental parameters were as follows: step potential, 4 mV; pulse potential, 30 mV; time step potential, 20 ms (10 ms waiting +10 ms probing time). The measurements were carried out from deaerated solutions.

Analysis of isoniazid in pharmaceutical formulation

Five tablets of Isoniazid® Jelfa and ten Rifamiazid® capsules content was weighed and micronised separately in agate mortar. Next appropriate amount of the ground material was weighed and transferred to volumetric flask and filled with deionized water to achive desirable concentration. Then obtained solution in the flask was treated with ultrasonic bath for 15 minutes. The solution was directly analyzed, according to the proposed procedure, without the need for neither pretreatment nor extraction steps.

Results and Discussion

Influence of DPV parameters on technique on isoniazid peak

The important parameters of the DPV technique are pulse amplitude (dE), potential step amplitude (Es), waiting time (tw) and sampling time (tp). Measurements of isoniazid in acetic acid were characterized by the formation of two peaks. The peaks were observed at potentials -576 mV (peak 1) and -768 mV (peak 2), while the second was 2-3 times higher. After all, influence of instrumental and chemical factors have been investigated for two peaks. To optimize the instrumental conditions for INH measurements, the following parameters were investigated: dE in the range 10 – 75 mV (both positive and negative mode), Es in the range 1 – 5 mV, tw and tp from 5 to 40 ms. For a pulse amplitude of 30 mV the isoniazid peak 2 current was equal to 0.16 μA and increased with increasing pulse amplitude. Higher pulse amplitude (>40 mV) caused significant growth of the background current. The increase in pulse amplitude from 10 mV to 75 mV caused the peak potential to shift from -744 mV to -688 mV and from -556 mV to -524 mV for negative pulse amplitude respectively (Figure 1). The best results were obtained for amplitude of 30 mV for further work, the pulse amplitude of 30 mV was applied. The increase of the step potential caused increasing of peak current (Figure 2). The step potential of 4 mV was applied in further work. The waiting time and probing time were changed in the range from 10 ms to 60 ms. The best results were obtained for waiting time and probing time of 10 ms, and this was the value chosen for further study. Current value of peak 2 for Hg (Ag) FE electrode was over two times higher than for HMDE in the same condition.

Influence of supporting electrolyte type on Isoniazid Peak

Various supporting electrolyte in different concentration were investigated as ionic medium such as Britton – Robinson, phosphorate buffer, acetate buffer, KNO_3, KCl, NaOH, acetic and phosphoric acid. For further analysis acetic acid was chosen for the best peak shape and good signal/background ratio. The concentration of acetic acid was investigated from 0.025 M to 0.5 M and was shown in Figure 3. Along with increasing concentration, first peak potential was shifted from -776 mV to -736 mV whereas second peak potential was change from -584 mV to -576 mV. The best results were obtained for second peak analysis and for further analytical application the second peak occurring at -768 mV was chosen. The concentration of 0.1 M was chosen as optimal for height and ionic medium conductivity.

Influence of pH on isoniazid peak

The peak current and width depends on the pH in investigated range with increasing pH value peak became wider and greater. Furthermore, less acidic medium caused close up of potential peak. The optimal pH was in the range from 3.3 to 4.1. More acidic and more

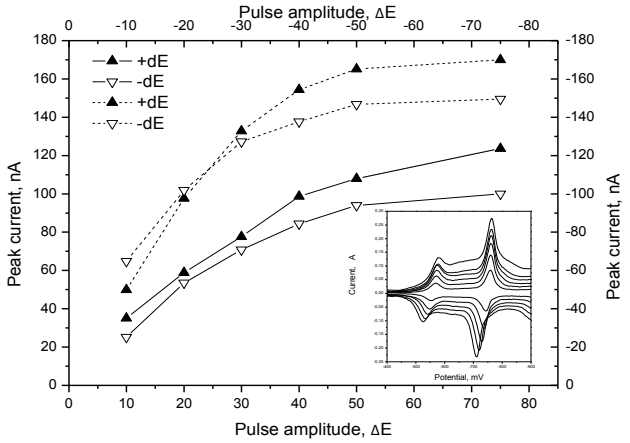

Figure 1: Pulse amplitude (from 10 mV to 75 mV) dependence on peak current. The electrode area was 9.7 mm². Instrumental parameters: E_s=4 mV, t_w, t_p=10 ms. Stirring rate, 500 rpm (– – dashed line for second peak, —solid line for first peak).

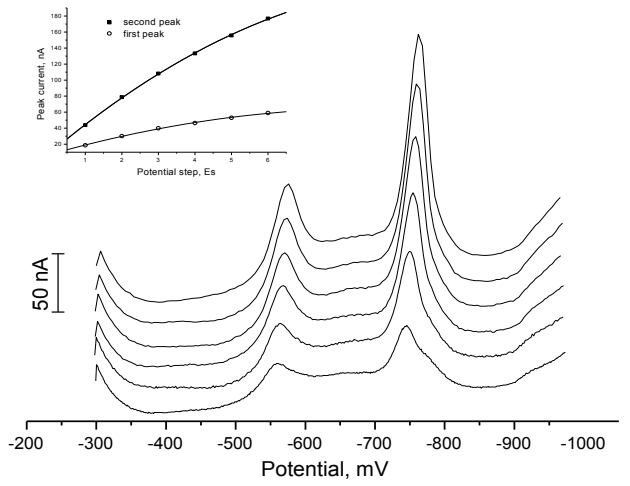

Figure 2: The dependence of potential pulse step (Es) on peak current for 1; 2; 3; 4; 5; 6 mV. Instrumental parameters: ΔE=30 mV, t_w, t_p=10 ms. Stirring rate, 500 rpm.

alkaline conditions caused a decrease in the peak current. The pH also had an influence on the peak potential, which changed to positive values for lower pH values. In investigated pH values the peak potential changed value from -576 mV to -820 mV and from -764 mV to -956 mV, for first and second peak respectively. For further measurements, a pH of 3.3 was applied.

Influence of the surface of the Hg (Ag) FE electrode on isoniazid peak

The surfaces of solid electrodes are usually much larger than those of mercury drop electrodes. When using the Hg (Ag) FE electrode the surface of the working electrode may easily be varied in a wide range. The isoniazid peaks grew linearly as the surface of the working electrode increased in size (Figure 4). The parameters of the linear growth of peak current *vs.* surface of working electrode are: (peak 1) slope, 6.84 ± 0.18 [nA mm^{-2}], intercept, -1.83 ± 1.23 [nA], and correlation coefficient r = 0.9993; (peak 2) slope, 17.83 ± 0.46 [nA mm^{-2}], intercept, -0.72 ± 3.22 [nA], and correlation coefficient r = 0.9994 For further study, a 9.7 mm^2 surface area was applied.

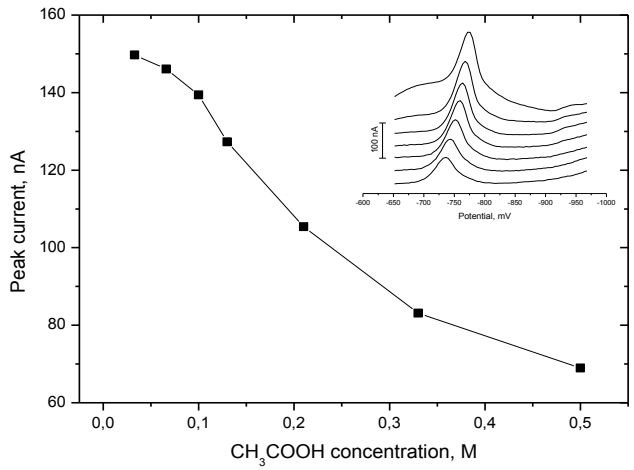

Figure 3: Effect of acetic acid concentration on peak current in short potential range, isoniazid concentration 5*10^{-7}M. Instrumental parameters: ΔE=30 mV, E_s=4 mV, t_w, t_p=10 ms. Stirring rate, 500 rpm.

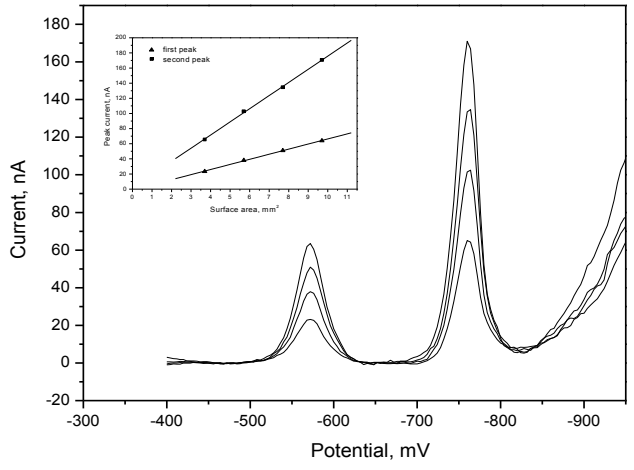

Figure 4: Voltammograms obtained for surface area of Hg (Ag) FE: 3.7, 5.7, 7.7 and 9.7 mm^2 for 5 10–7 M of isoniazid in 0.1 M CH_3COOH. Instrumental parameters: ΔE=30 mV, E_s=4 mV, t_w, t_p=10 ms. Stirring rate, 500 rpm.

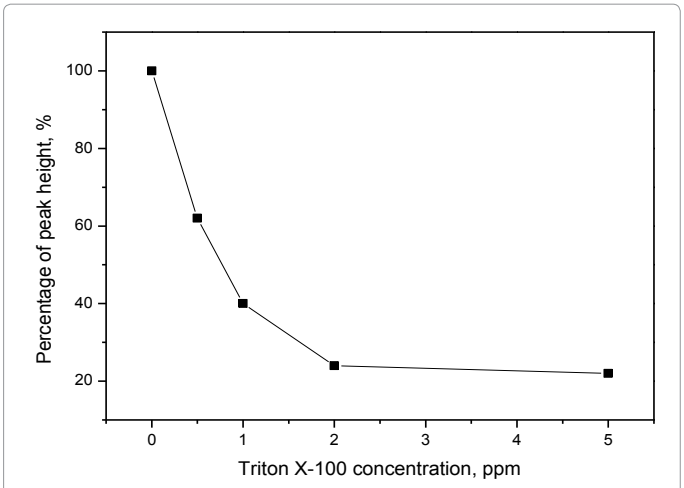

Figure 5: Influence of Triton X–100 addition in range 0.5 – 5 mgL^{-1}, isoniazid concentration 5 ·10^{-7} M. Instrumental parameters: ΔE=30 mV, E_s=4 mV, t_w, t_p=10 ms. Stirring rate, 500 rpm.

Interferences

The surface-active compounds are usually a source of strong interferences in voltammetric methods. A nonionic surface-active compound (Triton X-100), common excipients found in pharmaceutical preparations (e.g. starch, lactose, talc and magnesium stearate). The results showed that investigated excipients do not affect INH analysis. A concentration of 0.5 mgL^{-1} for Triton X-100, decreased signal of isoniazid (peak 2) by 38%, for 1 mgL^{-1} of Triton X-100 by 60%, for 2 mgL^{-1} of Triton X-100 by 76%, for 5 mgL^{-1} of Triton X-100 by 78% (Figure 5). Triton concentration >1 mgL^{-1} involve peak drift to more negative potential both for the first and the second peak and causing peaks approaching. The results showed that hundred times concentration of Triton does not affect isoniazid analysis. The presence of rifampicin, as one of the component of Rifamazid® was studied. Rifampicin in strong acidified electrolyte solution (0.1 M CH_3COOH) does not interfere.

Analytical performance

The linearity range is up to 500 nM but for further study smaller range was chosen. For a short time analysis without preconcentration step the obtained detection limit (surface of working electrode area = 9.7 mm^2) LOD and quantification LOQ were 4.1 nM and 10.5 nM of INH, respectively. The limits were estimated according to the following relationships: LOD = 3 S.D./b and LOQ =/10 S.D./b. The differential pulse cathodic voltammograms of isonizid for the 10 – 100 nM concentration range without preconcentration step are presented in figure 6. In this concentration range the slope for regression line is 2.77 ± 0.04 [nAnM^{-1}] with correlation coefficient r = 0.9993. Precision and recovery were determined using pharmaceutical samples spiked by 50, 100 and 150 mg of isoniazid. Samples were analyzed according to the described procedure using the Hg (Ag) FE electrode. Determinations of isoniazid were performed using the standard addition method. Results from isoniazid determination are presented in table 1. The recovery of isoniazid ranged from 99.8 – 104.1%.

Conclusions

The presented differential pulse cathodic voltammetry method

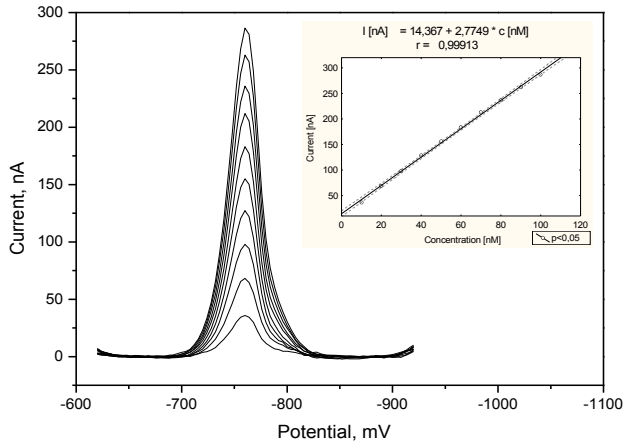

Figure 6: Linarity range of voltametric determination of isoniazid 10–100 nM, The electrode area was 9.7 mm^2. Instrumental parameters: ΔE=30 mV, E_s=4 mV, t_w, t_p=10 ms. Stirring rate, 500 rpm.

	Added [mg]	Found [mg]	Recovery [%]	RSD [%]
Isoniazid® (100 mg)	–	104.2	104.2	3.2
50%	50	151.2	100.8	2.9
100%	100	198.5	99.2	1.6
150%	150	246.0	98.6	2.7
Rifamazid® (150 mg)	–	151.8	101.2	2.1
50%	75	225.4	100.2	3.2
100%	150	298.8	99.6	4.3
150%	225	377.3	100.6	3.6

Table 1: Isoniazid determination in bulk pharmaceuticals formulation.

for the electrochemical determination of isoniazid using a cylindrical silver based mercury film electrode (Hg (Ag) FE), refreshed before each measurement, allows to determine isoniazid at trace level, without preconcentration time. The reproducibility of the method is very good, i.e. when measured as RSD is 3.6% (with each measurement performed at a fresh surface of the working electrode). The proposed method can be used for the determination of isoniazid in pharmaceuticals even in the presence of rifampicin. The method showed high sensitivity (LOD = 4.12 nM, LOQ = 10.48 nM), good precision (RSD = 3.6%), and a wide linearity range (5 – 500 nM). The obtained results confirm that method and Hg (Ag) FE may be in the future incorporated into out-of-laboratory sensor systems.

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