Int. J. Electrochem. Sci., 10 **(2015)** 4571 - 4584

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Voltammetric Determination of Nifedipine at a Hanging Mercury Drop Electrode and a Mercury Meniscus Modified Silver Amalgam Electrode

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Received: 22 February 2015 / *Accepted:* 19 March 2015 / *Published:* 28 April 2015

The voltammetric behavior of nifedipine (NFD) has been studied with two different types of working electrodes (hanging mercury drop mini-electrode (HMDmE) and mercury meniscus silver solid amalgam electrode (m-AgSAE)) using differential pulse voltammetry (DPV). The optimal conditions for DPV determination are: a mixture of Britton-Robinson (BR) buffer pH 8 with methanol in three different ratios (1:1, 9:1, 99:1), respectively, in the concentration range of 0.2 to 20 µmol/L. The limit of quantification (L_Q) was found to be 0.12 µmol/L (HMDmE) and 1.2 µmol/L (m-AgSAE). Attempts to increase the sensitivity using adsorptive stripping DPV at both HMDmE and m-AgSAE were not successful. Using the optimum conditions, the practical application of the newly developed method has been verified on the determination of NFD in spiked samples of drinking and river water.

Keywords: Nifedipine, hanging mercury drop mini-electrode, mercury meniscus silver solid amalgam electrode, differential pulse voltammetry

1. INTRODUCTION

3,5-Dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate also known as nifedipine (NFD, see Fig.1) is a calcium channel blocker that belongs to dihydropyridine family mainly used as an antianginal (especially in Prinzmetal's angina) and antihypertensive [1-3] agent. NFD is also a photosentitive and thermally unstable compound. The nitro-pyridine derivative is

formed when the compound is exposed to visible light (in a solution) and to UV light [4-6]. During pharmaceutical application, nifedipine can undergo photodegradation processes and can lose its pharmacological activity due to the reduction of aromatic nitro group to nitroso group and/or due to the oxidation of the dihydropyridine ring to pyridine ring [7].

In sensitive individuals, even the therapeutical doses can cause toxic effects like vomiting, dizziness and pounding heartbeats [8, 9]. A number of sensitive analytical methods have been developed for the determination of the trace amounts of NFD. High performance liquid chromatography (HPLC) [10,11,12,13], gas chromatography (GC) [14,15,16], and HPLC-MS [17,18,19] are the most frequently used methods for the determination of NFD in various samples including food, plasma and other body fluids. These methods are relatively expensive, time consuming, and they require complicated preconcentration and preseparation techniques.

Using voltammetry, NFD was successfully determined using several types of working electrodes such as glassy carbon electrode [20,21], carbon paste electrode [22], and mercury electrodes [23, 24, 25]. These studies proved that the determinations of NFD could be based on the reduction of its nitro group. Mercury electrodes are unique electrodes with extremely wide cathodic potential window. Hanging mercury drop electrode (HMDE) was successfully used for differential pulse voltammetry (DPV) of NFD [23]. However, due to the toxicity of metallic mercury, alternative electrodes are searched possibly with performance similar to mercury electrodes but less toxic and more environmentally friendly.

Solid amalgam electrodes (SAE) represent an intermediate step between mercury and solid working electrode [26, 27]. They were firstly introduced by Novotny and Yosypchuk in 2000 [28] and up to now they seems to be the best alternative for mercury which is compatible with the concept of "green analytical chemistry" [29]. The research in this field further led to polished silver solid amalgam electrode (p-AgSAE) and especially to mercury meniscus silver amalgam electrode (m-AgSAE) [30,31,32,33,34,35]. This electrode has electrochemical properties comparable with mercury electrodes [36,37,38,39]. Besides, this electrode also has a good mechanical stability, it is easy to handle and practically non-toxic.

According to our knowledge, the determination of NFD using m-AgSAE had not yet been described. The aim of this paper was to compare voltammetric determination of NFD using two types of electrodes, namely HMDE and m-AgSAE and to apply both electrodes for model drinking and river water samples.

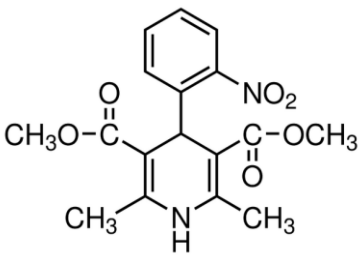

Figure 1. Structure of 3,5-dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nifedipine, NFD)

2. EXPERIMENTAL

2.1. Chemicals and Reagents

Nifedipine (NFD, 3,5-dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, TCI, Japan, 99%) was reagent grade purity. A stock solution of 0.01 mol/L NFD was prepared by dissolving 0.0346 g of the pure substance in 100 mL of methanol (MeOH, 99.9%, Merck, Darmstadt, Germany). The Britton-Robinson (BR) buffers (0.04 mol/L phosphoric acid, acetic acid, and boric acid adjusted to appropriate pH by 0.2 mol/L NaOH (all p.a., Lachema, Brno, Czech Republic)) were prepared in a usual way. Deionized water (DW) was obtained from a Water Purification System (Millipore, Billerica, MA, USA).

2.2. Apparatus

Voltammetric experiments were carried out using an Eco-Tribo Polarograph driven by PolarPro 2.0 software (both Polaro-Sensors, Prague, Czech Republic). The software worked under the operational system Microsoft Window 98 (Microsoft Corporation, Redmond, WA, USA). The measurements were carried out using three electrode system - a platinum wire auxiliary electrode (Monokrystaly, Turnov, Czech Republic), a silver–silver chloride (3 mol/L KCl, Monokrystaly, Turnov, Czech Republic) reference electrode and laboratory-made m-AgSAE (the disc diameter 0.50 mm) or hanging mercury drop mini-electrode HMDmE (working surface: 0.73 mm^2, Polaro-Sensors, Prague, Czech Republic) as a working electrode. For DPV scan rate of 20 mVs^{-1}, pulse amplitude of -50 mV and pulse width of 100 ms were used. pH was measured by pH meter 3510 (Jenway, Chemsford, UK) with a combined glass electrode.

2.3. Procedures

2.3.1. Preparation and pretreatment of the working electrode

For the preparation of m-AgSAE [30], the p-AgSAE was polished on the alumina with particle size of 1.1 μm before dipping it into the mercury for 15 s. The electrochemical activation of m-AgSAE was carried out in 0.2 mol/L KCl at -2200 mV under stirring for 300 s and the electrode was the rinsed with distilled water. This activation had to be performed before starting the measurement as well as after every longer pause (more than 1 hour).

The regeneration procedure included the application of 300 polarizing cycles (switching the electrode potential from $E_{1.reg}$ to $E_{2.reg}$ for 50 ms). E_1 was selected about 100 mV more negative than the potential of the anodic dissolution of the electrode material and E_2 was selected about 100 mV more positive than the potential of the hydrogen evolution in the given supporting electrode. Under these conditions, eventual oxides of mercury are reduced and absorbed molecules are desorbed.

2.3.2. Measurement procedures

In voltammetric measurements, the stock solution of NFD in methanol (0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL or 1.0 mL) was added into 10.0 mL voltammetric flask. Methanol was added to a certain volume and the flask filled up to 10.0 mL with BR buffer of appropriate pH. Three ratios of BR buffer : methanol (1:1, 9:1 and 99:1) supporting electrolyte were prepared in order to find the optimum conditions for the determination of NFD. Oxygen was removed by bubbling nitrogen gas (purity class 4.0, Linde, Prague, Czech Republic) through the solution whilst stirring for 5 minutes with 30 s quiet period before each measurement. Each measurement was repeated three times to estimate the repeatability of the results.

The peak heights recorded using DPV and DPAdSV were evaluated from the straight lines connecting the minima before and after the peak. The calibration curves were treated by linear regression.

2.4. Preparation of model samples of drinking and river water

The drinking water sample was taken from the public water pipeline in the building of Faculty of Science, Charles University in Prague, while river water sample was taken from Vltava River in Prague. These samples were spiked with appropriate amounts of stock solutions of NFD. For DPV determination of NFD, 9.0 mL of a spiked model sample were filled to 10.0 mL with BR buffer of appropriate pH

3. RESULTS AND DISCUSSION

3.1 Voltammetric behavior of nifedipine at HMDE and m-AgSAE

The effect of pH on DP voltammetric behavior of 1.10^{-4} mol/L NFD at HMDmE and m-AgSAE (see Fig. 2A for HMDE and Fig. 2B for m-AgSAE) was investigated in BR buffer-methanol (1:1) media at from pH 2.0 to 12.0. It can be seen that NFD gives one peak at cathodic potential over the whole pH range studied which shifts to more negative potentials with increasing pH. This can be explained by the participation of protons in the electrochemical reduction of NFD. This reduction peak is due to the four-electron reduction of the nitro group to a hydroxylamino derivative and corresponding process is electrochemically irreversible [40] (see Eq. 1). NFD reduction peak was higher at HMDmE compared to m-AgSAE, clearly in accordance with the respective areas of the electrode surfaces. Nevertheless, m-AgSAE can give good results as well.

$$ArNO_2 + 4e^- + 4H^+ \longrightarrow ArNHOH + H_2O \qquad \text{(Eq. 1)}$$

Fig. 3A and Fig. 3B show the dependence of DPV peak potential on pH of BR buffer for HMmDE and m-AgSAE. The highest, best developed and most easily evaluable peak was obtained at

pH 8 ofBR buffer for both electrodes (See Fig. 4A for HMDE and Fig. 4B for m-AgSAE) and these optimum conditions were used for all subsequent measurements.

The NFD peak potential ($E_{p)}$ for DPV at HMDmE varied with pH according to the relationship: E_p vs (Ag/AgCl) [mV] = -56.136 pH – 283.95 (correlation coefficient (R) = 0.9842, in the pH range from 2.0 to 12.0. Similarly, the NFD peak potential ($E_{p)}$ for DPV at m-AgSAE varied with pH according to the relationship: E_p vs (Ag/AgCl) [mV] = -32.517 pH – 552.9 (correlation coefficient (R) = 0.9826 in the pH range from 2.0 to 12.0.

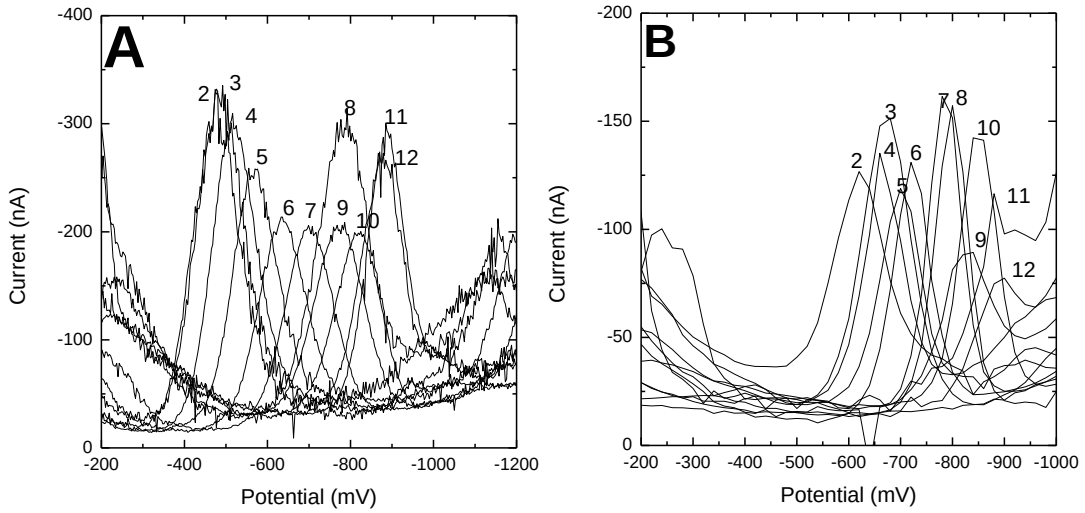

Figure 2. DP voltammograms of 1.10^{-4} mol/L NFD at (A) HMDmE and (B) m-AgSAE in BR buffer–MeOH (1:1) medium. The numbers indicate pH of BR-buffer.

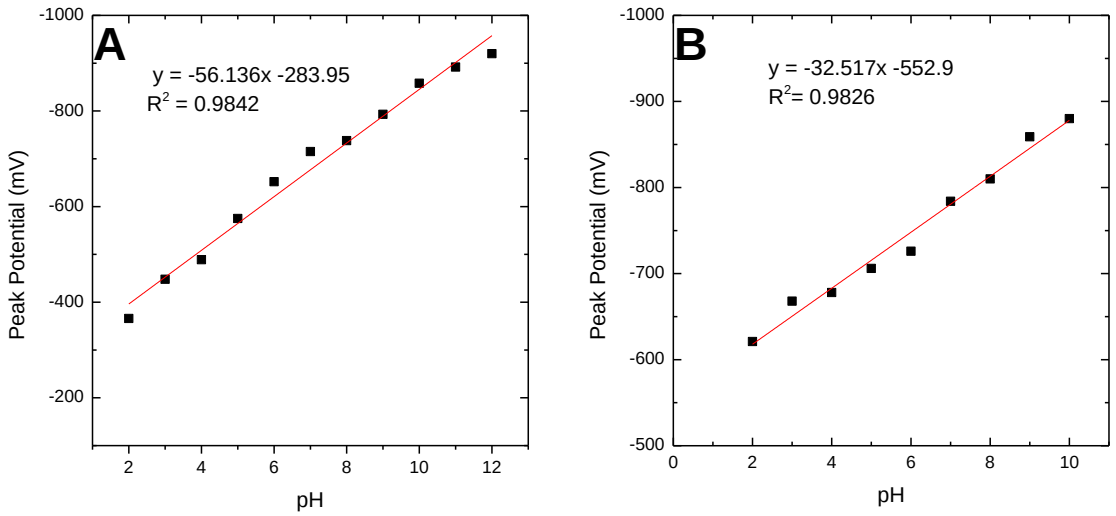

Figure 3. The dependence of DPV peak potential of NFD (c_{NFD} = 1.10^{-4} mol/L) at (A) HMDmE and (B) m-AgSAE on pH of BR-buffer in a mixture of BR buffer and MeOH (1:1).

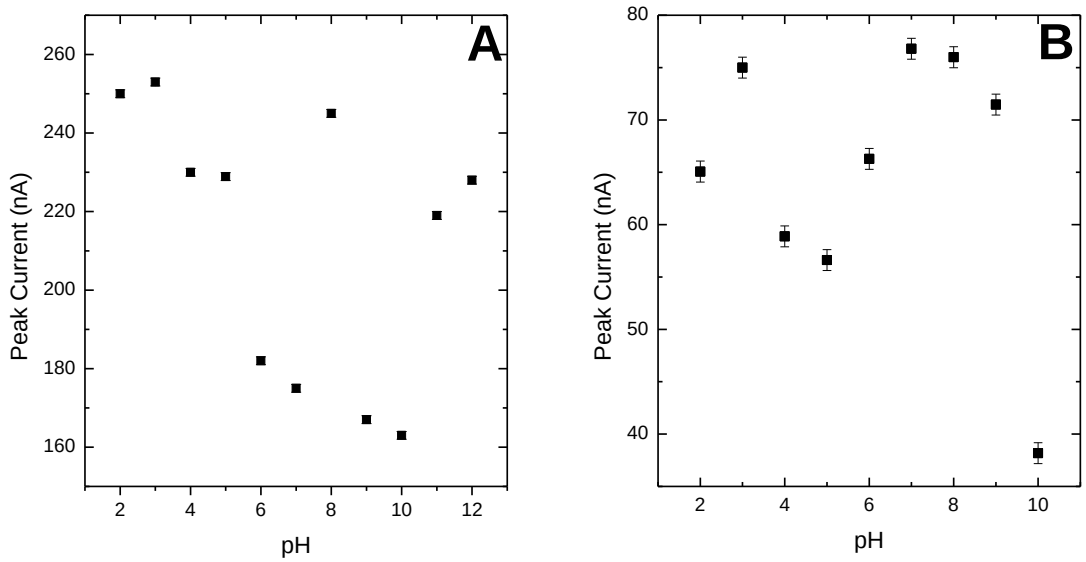

Figure 4. The dependence of DPV peak current of NFD (c_{NFD} = 1.10^{-4} mol/L) at (A) HMDmE and (B) m-AgSAE on pH of BR-buffer in a mixture of BR buffer and MeOH (1:1).

3.2 Effect of Methanol Concentration

Due to a low solubility of NFD in aqueous media, a mixture of BR buffer of different pH with methanol in different volume ratios were used as the supporting electrolyte for these measurements. Afterwards, the conditions at which the best developed and highest peak was obtained were further used for measuring at both electrodes of lower concentrations of NFD.

Two concentration ranges from 2 to 10 μmol/L and 0.2 to 1.0 μmol/L of NFD were measured at different BR buffer to methanol ratios to see the effect of methanol and to choose the optimum volume of methanol in the supporting electrolyte. Three BR buffer pH 8 to methanol ratios were studied, namely 1:1, 9:1 and 99:1.

For both studied ranges the calibration lines were constructed for tested electrodes, (see Fig. 5A, 6A and 8A for HMDmE and Fig. 5B, 6B and 8B for m-AgSAE). Table 1 shows the calculated parameters of the calibration curves.

Using HMDmE, well developed analytical peak was obtained and the method had slightly higher sensitivity, however, no significant differences were observed between the tested electrodes. It was shown that the supporting electrolyte containing BR buffer: methanol ratio 9:1 and 99:1 gave the best evaluable NFD peaks. Using 9:1 ratio, NFD can be determined with a lower limit of quantitation at HMDE (See Fig 7). Using the equation of the calibration straight lines and according to the 3 *s/m* definition [41] (where s is the standard deviation of the signal and m is the slope of calibration graph), the limit of detection (LOD) for NFD in both electrodes was calculated from 5 replicate measurements in concentration range of 0.2 to 1.0 μmol/L for HMDmE and in the range of 2 to 10 μmol/L for m-AgSAE. It was found that the LOD for NFD is 0.08 μmol/L for HMDE and 0.9 μmol/L for m-AgSAE.

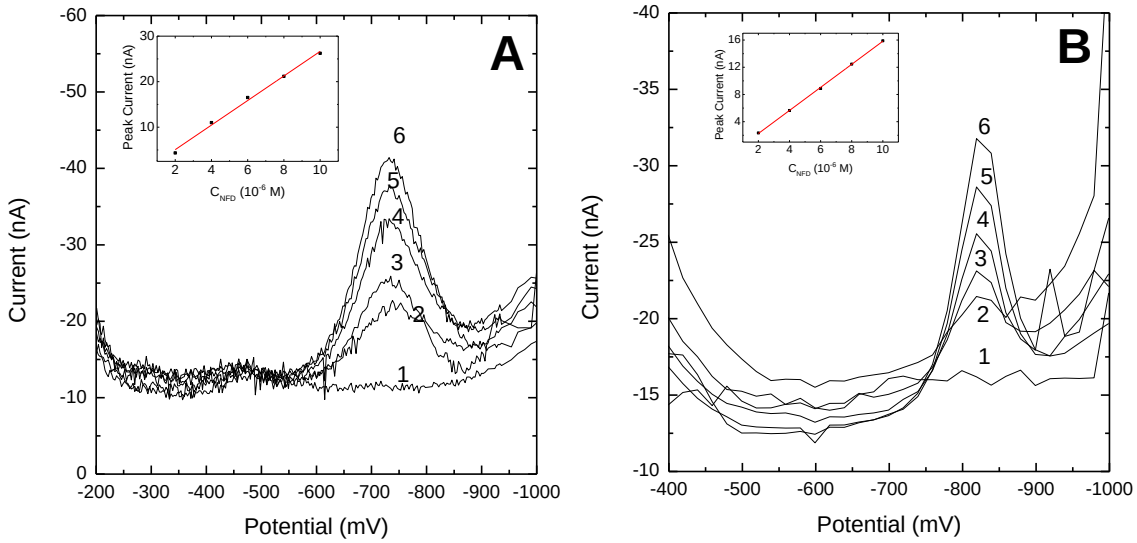

Figure 5. DP voltammograms of NFD at (A) HMDmE and (B) m-AgSAE in BR-buffer pH 8-MeOH (1:1), (c_{NFD} (1) 0 (supporting electrolyte), (2) 2, (3) 4, (4) 6, (5) 8, (6) 10 µmol/L. Inset: Corresponding calibration straight lines.

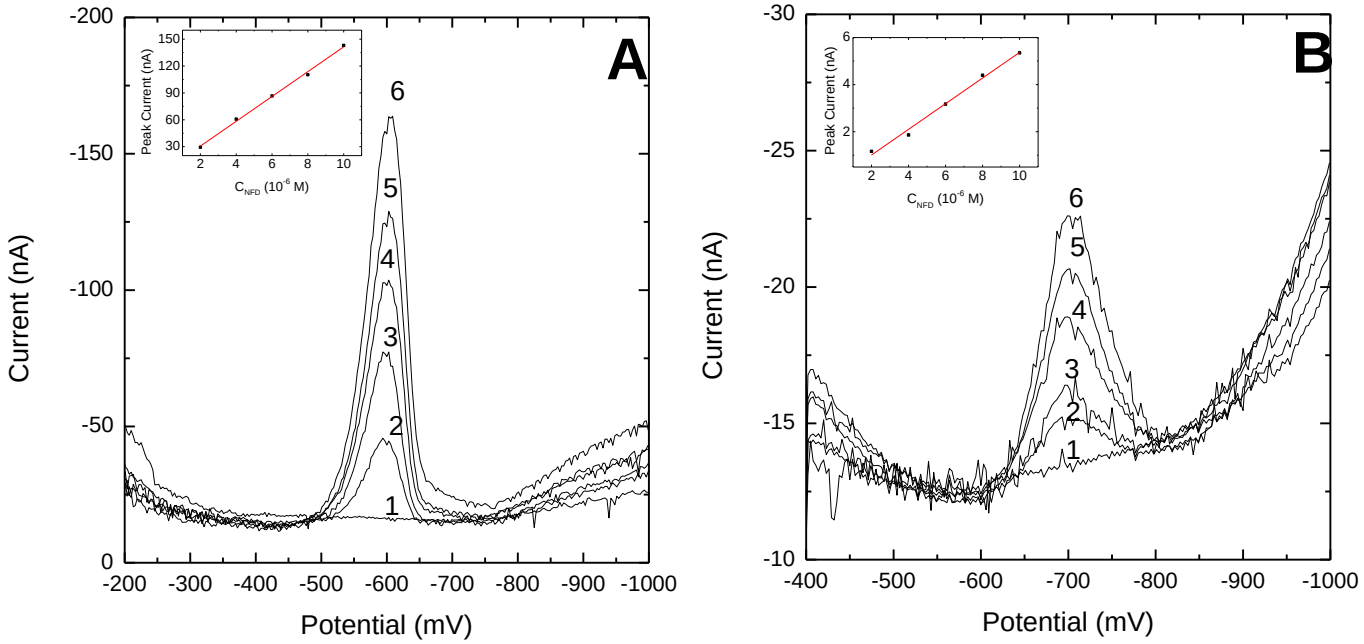

Figure 6. DP voltammograms of NFD at (A) HMDmE and (B) m-AgSAE in BR-buffer pH 8-MeOH (9:1), (c_{NFD} (1) 0 (supporting electrolyte), (2) 2, (3) 4, (4) 6, (5) 8, (6) 10 µmol/L. Inset: Corresponding calibration straight lines.

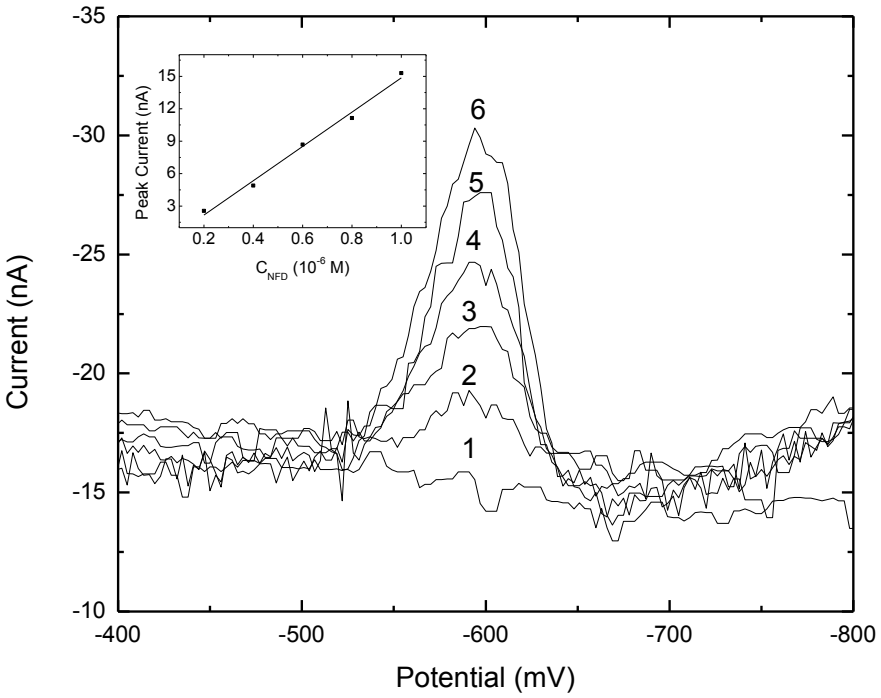

Figure 7. DP voltammograms of NFD at HMDmE in BR-buffer pH 8-MeOH (9:1), (c_{NFD} (1) 0 (supporting electrolyte), (2) 0.2, (3) 0.4, (4) 0.6, (5) 0.8, (6) 1.0 µmol/L. Inset: Corresponding calibration straight line.

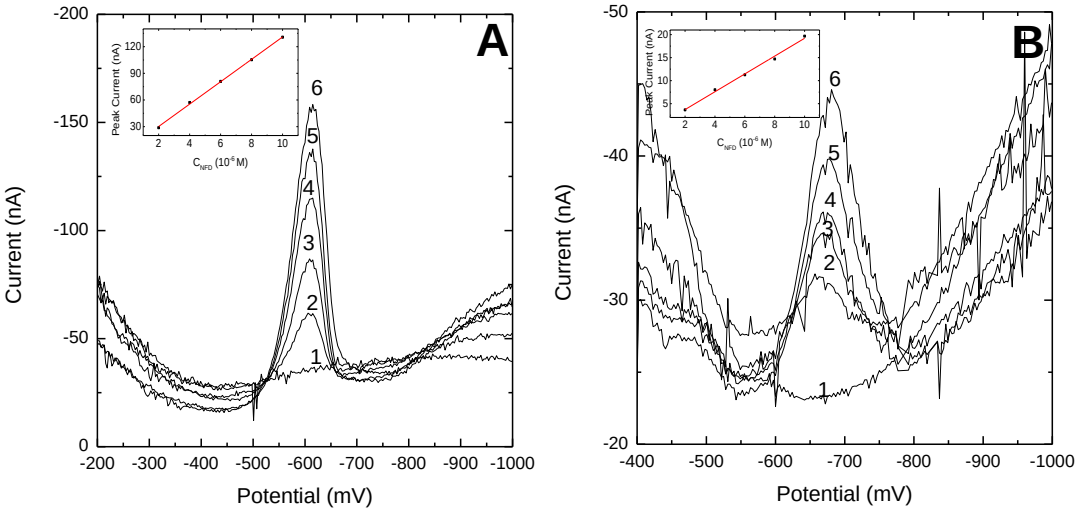

Figure 8. DP voltammograms of NFD at (A) HMDmE and (B) m-AgSAE in BR-buffer pH 8-MeOH (99:1), (c_{NFD} (1) 0 (supporting electrolyte), (2) 2, (3) 4, (4) 6, (5) 8, and (6) 10 µmol/L. Inset: Corresponding calibration straight line.

Table 1. Parameters of calibration lines for NFD determination using DPV at HMDE and m-AgSAE

Electrode	Medium	Concentration (µmol/L)	Slope (nA µmol/L)	Intercept (nA)	R^2
HMDmE	50% MeOH	2 to 10	2.67	-0.32	0.9951
	10% MeOH	2 to 10	13.9	2.94	0.9971
		0.2 to 1	15.9	-1.00	0.9915
	1% MeOH	2 to 10	12.6	4.94	0.9992
m-AgSAE	50% MeOH	2 to 10	1.70	-1.13	0.9971
	10% MeOH	2 to 10	0.55	-0.08	0.9920
	1% MeOH	2 to 10	1.94	-0.16	0.9945

3.3 Adsorptive Stripping Voltammetry

The attempts to increase the determination sensitivity by adsorptive accumulation of the analyte on the surface of the working electrode were not successful. Accumulation times from 0 to 90 sec were tested. The peak was slightly increased with 30 s accumulation time then slowly decreased (see Fig. 9). However, the increase was not too pronounced.

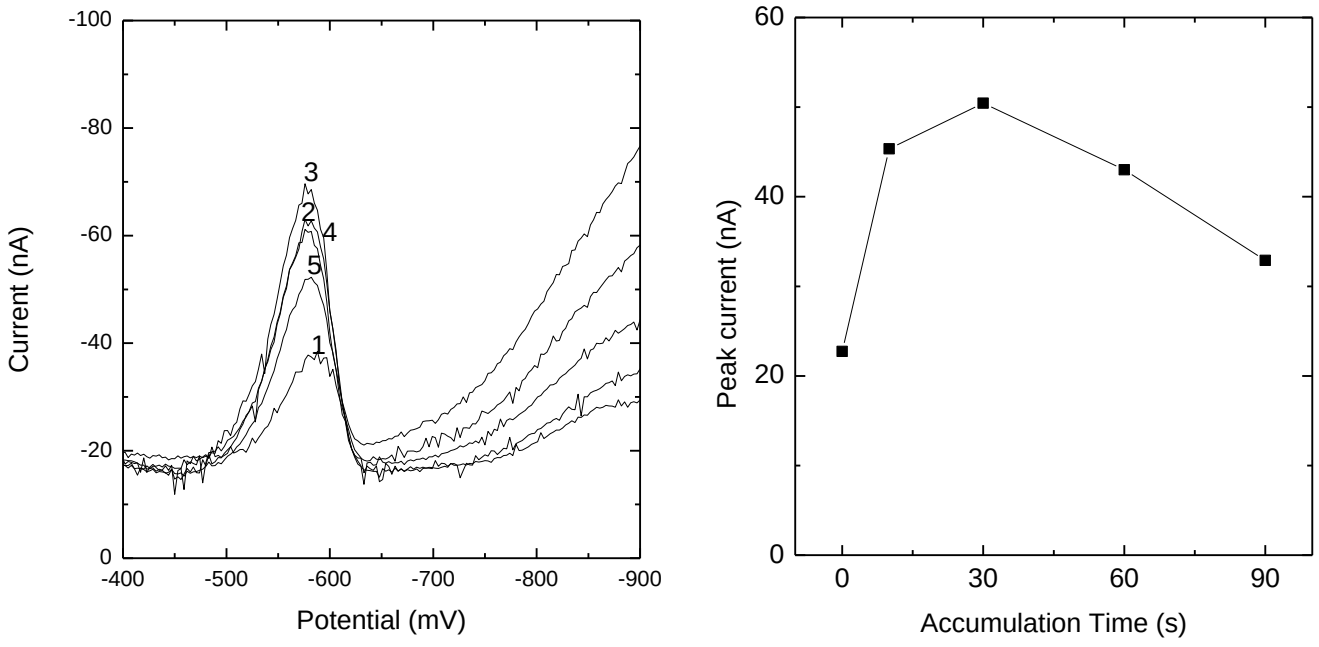

Figure 9. DP adsorptive stripping voltammograms of NFD with accumulation time (1) 0 sec (2) 10 sec, (3) 30 sec, (4) 60 sec, (5) 90 sec at HMDmE in BR buffer pH 8-MeOH (9:1). Concentration of NFD = 1 µmol/L

3.4 Voltammetric determination of nifedipine in Model Samples of Drinking and River Water

In order to verify the applicability of the method, the determination of NFD was carried out in model samples of river and drinking water. Both samples were spiked by known amount of NFD in the concentration range from 2 to 10 μmol/L. Calibration curves were measured using the mixture of 9.00 mL of model sample (river and drinking water) and 1.00 mL of BR buffer pH 8: methanol (9:1).

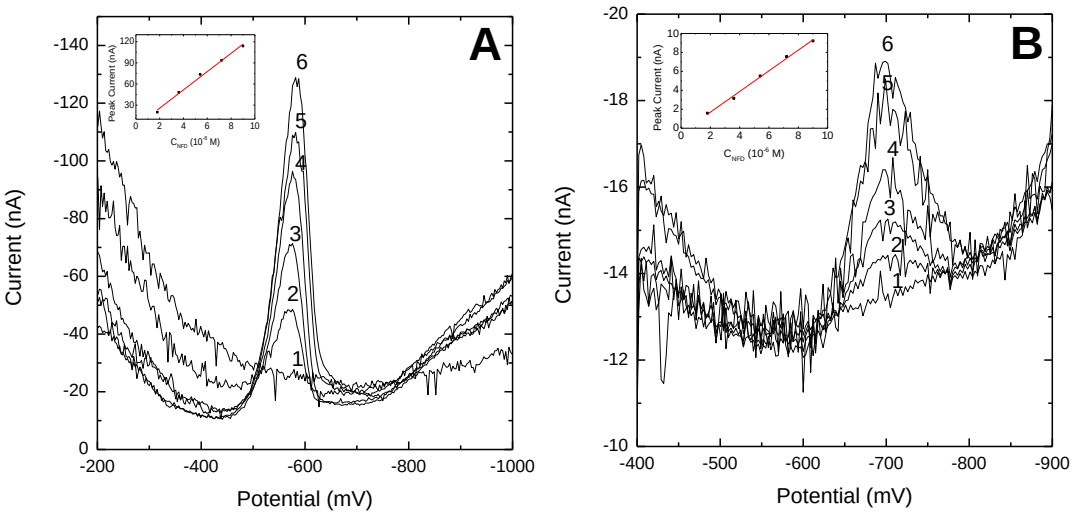

Figure 10. DP voltammograms of NFD (c_{NFD} (1) 0 (supporting electrolyte) (2) 1.8, (3) 3.6, (4) 5.4, (5) 7.2, (6) 9.0 μmol/L at (A) HMDmE and (B) m-AgSAE in drinking water sample - BR buffer pH 8 (9:1) mixture. Inset: Corresponding calibration straight lines.

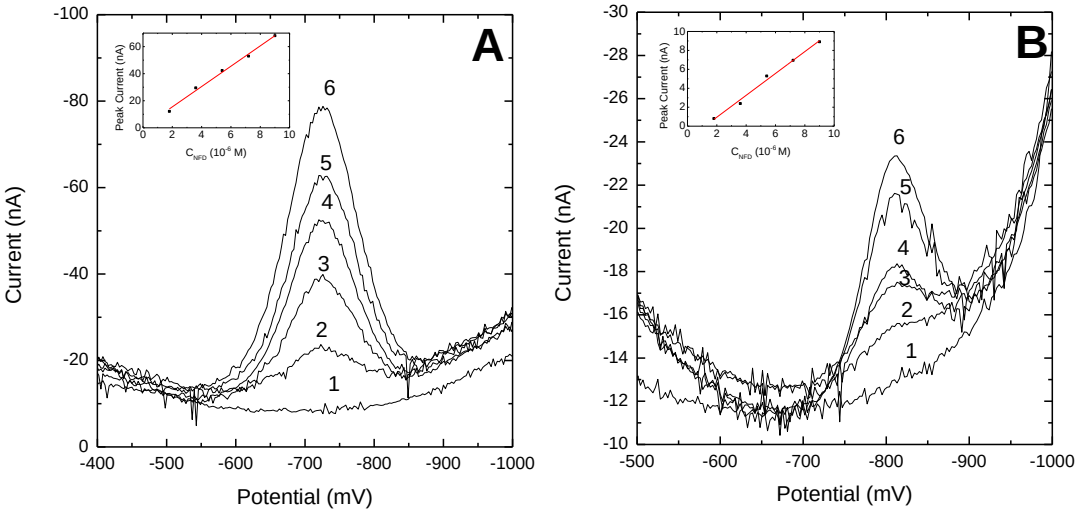

Figure 11. DP voltammograms of NFD (c_{NFD} (1) 0 (supporting electrolyte) (2) 1.8, (3) 3.6, (4) 5.4, (5) 7.2, (6) 9.0 μmol/L at (A) HMDmE and (B) m-AgSAE in river water sample - BR buffer pH 8 (9:1) mixture. Inset: Corresponding calibration straight lines.

DP voltammograms of NFD at HMDmE are depicted in Fig.10A (drinking water) and Fig. 11A (river water), and at m-AgSAE in Fig.10B (drinking water) and Fig.11B (river water). The peak potential shifted somewhat to more negative value in the river water sample (pH of river water was 8.17). The results are summarized in table 2 (HMDmE) and table 3 (m-AgSAE). These data prove that NFD can be reliably determined in the environmental samples using both tested electrodes.

Table 2. Results of determination of NFD using DPV at HMDE of mixtures of sample (river and drinking water): BR buffer pH 8 (9:1)

Matrix	Taken C (µmol/L)	Found C (µmol/L)	Recoveries (%)	RSD (%)
River water	1.8	1.76	98	2.55
	3.6	3.77	105	0.76
	5.4	5.57	103	0.86
	7.2	7.00	97	1.78
	9.0	9.00	100	0.15
Drinking water	1.8	1.79	99	2.12
	3.6	3.71	103	0.61
	5.4	5.51	102	0.55
	7.2	7.22	100	0.25
	9.0	8.81	98	0.29

Table 3. Results of determination of NFD using DPV at m-AgSAE of mixtures of sample (river or drinking water): BR buffer pH 8 (9:1)

Matrix	Taken C (µmol/L)	Found C (µmol/L)	Recoveries (%)	RSD (%)
River water	1.8	1.88	104	3.53
	3.6	3.45	96	1.4
	5.4	5.70	105	2.00
	7.2	7.2	100	1.17
	9.0	8.9	99	1.09
Drinking water	1.8	1.90	105	1.76
	3.6	3.46	96	2.60
	5.4	5.5	102	1.95
	7.2	7.18	99	1.75
	9.0	8.88	98	0.76

3.6 Comparison of the Proposed Method with Previously Published Methods

Only three studies were reported in the literature for the determination of nifedipine using voltammetric techniques. The comparison of the newly developed method and the previous voltammetric studies is presented in Table 4. The lowest limit of detection for nifedipine was achieved by using square wave adsorptive stripping voltammetry with HMDE as the working electrode at pH 9 but in completely different matrix with different sample pretreatment. Moreover, mercury meniscus modified silver amalgam electrode (m-AgSAE) is more compatible with the concept of "green analytical chemistry" because the silver amalgam used is non-toxic.

Table 4. Comparison of Nifedipine Determination of Proposed Method with other Voltammetric Methods

Working Electrode	Techniques	Linear range (μmol/L)	Limit of of detection (μmol/L)	Matrix	Ref.
Activated Glassy carbon	CV, LSV	80 to 100	11	Tablets and capsules	[21]
β-Cyclodextrin modified multi-walled carbon nanotube	CV, DPV	0.047 to 20	0.02	Urine and serum	[22]
Hanging Mercury Drop Electrode (HMDE)	SWAdSV	0.003 to 0.4	0.001	Human plasma	[23]
HMmDE and m-AgSAE	DPV	2 to 20	0.12 (HMDmE) 1.2 (m-AgSAE)	River water and drinking water	This work

4. CONCLUSIONS

It has been proved that m-AgSAE can be used for DPV determination of trace amounts of nifedipine with figures of merits comparable with HMDmE. Using BR buffer pH 8: methanol (9:1) mixture, nifedipine could be successfully determined in the concentration range from 0.2 to 100 μmol/L at both electrodes. The attempt to increase the sensitivity using adsorptive accumulation of the analyte was not successful. The practical applicability of these methods was confirmed by the determination of nifedipine in spiked samples of drinking and river water. For drinking water, the limit of quantification (L_Q) was 1.2 μmol/L (HMDmE) and 1.6 μmol/L (m-AgSAE) while for river water it was 1.2 μmol/L (HMDE) and 1.5 μmol/L (m-AgSAE). Thus, it can be concluded that nifedipine can be successfully determined using m-AgSAE as an environmentally friendly and mechanically more robust alternative

ACKNOWLEDGEMENTS
MDHW, ARMY and JZ would like to acknowledge the Ministry of Education Malaysia for providing LRGS grant on Water Security entitled Protection of Drinking Water Source Abstraction and Treatment (203/PKT/6720006). JB thanks for financial support to the Grant Agency of the Czech Republic (Project P206/12/G151).

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