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An Electrochemical Sensor for Fentanyl Detection Based on Multi-Walled Carbon Nanotubes as Electrocatalyst and the Electrooxidation Mechanism

Mostafa Najafi[a], *, Esmail Sohouli[a], and Farimah Mousavi[b]

[a]Department of Chemistry, Imam Hossein University, Tehran, Iran
[b]Faculty of Chemistry, Razi University, Kermanshah, Iran
e-mail: mnajafi@ihu.ac.ir

Abstract—The electrochemical behavior and determination of fentanyl as a strong analgesic drug was studied at the surface of glassy carbon electrode (**GCE**) modified by multi-walled carbon nanotubes (**MWCNTs**). The electrochemical determination of fentanyl was accomplished by differential pulse adsorptive stripping voltammetry after preconcentration under open circuit potential. The distribution of adsorbed MWCNTs on the surface of GCE was studied by scanning electron microscopy. Experimental parameters such as pH and accumulation conditions were optimized by monitoring the cyclic voltammetry responses toward fentanyl oxidation. Under the optimized conditions, the modified electrode showed a wide linear dynamic range from 5×10^{-7} to 1×10^{-4} M with a detection limit of 1×10^{-7} M for the voltammetric determination of fentanyl. Also, a probable mechanism for the electrooxidation of fentanyl was proposed. The prepared electrode was successfully applied to the determination of fentanyl in presence of interferents and also in real samples such as pharmaceutical preparation, human serum and urine.

Electrochemical methods are very useful for drug determination because of their high sensitivity and selectivity as well as their cheap and easy to use setup [1, 2]. Carbon-based electrodes are extensively used as working electrodes due to their cost-effective price and amplitude range. However, these electrodes have some disadvantages such as slow transition of electrons that can be solved by modifying the electrode surface.

Adsorptive stripping voltammetry method is a powerful tool for trace determination of analytes with high sensitivity. Adsorptive stripping voltammetry is similar to anodic stripping voltammetry and cathodic stripping voltammetry except that the preconcentration step is not controlled by electrolysis but rather is accomplished by adsorption of analyte on the working electrode surface.

Fentanyl is a potent synthetic narcotic. Its chemical name is 1-(2-phenethyl)-4-N-(N-propionylanilino)piperidine (Scheme 1) and trade name is sublimates [3]. It was introduced as an intravenous anesthetic in 1960 [4]. Fentanyl has almost the same respiratory effect as morphine or meperidine, however, by the use of fentanyl, the respiration of healthy individual sooner returns to normal. On the other hand, fen-

tanyl has such effects as hypotension, flushed skin, blurred vision and nausea [5, 6].
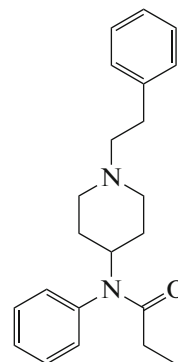
Scheme 1. Chemical structure of fentanyl.

Various techniques have been reported for the analytical determination of fentanyl in biological and urine samples in the literature including radioimmunoassay [7, 8], gas chromatography [9–12], HPLC [13–17] and liquid chromatography–mass spectrometry [18–20]. All these methods are very sensitive, but they have disadvantages including high cost, long analysis time and lengthy process of sample preparation. In contrast, electrochemical methods are fast,

cheap and easy to perform and offer a good alternative for them.

After discovery of multi-walled carbon nanotubes (**MWCNTs**), this material has been used by many scientists in various fields including electrochemical sensors and biosensors due to their unique properties such as electrical conductivity, good stability and high surface area [21, 22]. Also, recent studies have shown that carbon nanotubes can increase the electrochemical activity and electron transfer rate of organic molecules [23], biomolecules [24] and drugs [25, 26].

Reviewing the literatures revealed that there are only a few studies concerning polarographic [27, 28] and potentiometric determination [29] of fentanyl. For example, Hu et al. [28] studied adsorptive properties of fentanyl at a hanging mercury electrode and developed the sensitive cathodic adsorptive-stripping-voltammetric method for trace measurement of fentanyl. However, this method suffers from some problems associated with the mercury electrode.

In this work, the surface of glassy carbon electrode (**GCE**) was modified by abrasion immobilization of MWCNTs. The bare and modified GCEs were used to investigate the electrochemical behavior of fentanyl. In addition, the modified GCE was applied to the sensitive determination of fentanyl in aqueous solution using adsorptive stripping voltammetry after accumulation of fentanyl on the electrode surface during an open circuit preconcentration step.

EXPERIMENTAL

Regents and materials. Fentanyl citrate (>99.5%) was purchased from Aburaihan Pharmaceutical Company (Tehran, Iran). Multi-walled carbon nanotubes (95% purity, 1−5 μm length, 30 ± 15 nm OD) were obtained from Nanolab Inc. All aqueous solutions were prepared with double distilled water. Stock solutions of fentanyl were freshly prepared in double distilled water and diluted with buffer solutions for the preparation of working solutions. 0.1 M sodium acetate, sodium phosphate and sodium carbonate solutions were employed to obtain the required pH values from 2 to 10. Injection samples of fentanyl were purchased from local pharmacies. Human blood serum and urine samples were obtained from the Clinic of Taleghani Hospital (Tehran, Iran).

Apparatus. Voltammetric experiments were performed with a μAutolab Type II/FRA2 (Eco Chemie B. V.) potentiostat/galvanostat. A conventional three-electrode system was used with a bare or modified glassy carbon electrode (Metrohm, geometrical area of 0.0314 cm^2) as the working electrode, an Ag/AgCl (3 M KCl) and a Pt wire as the reference and counter electrodes, respectively. A Metrohm-691 pH-meter (Switzerland) was used for pH adjustments. The images of scanning electron microscopy (**SEM**) were obtained using a Vega©Tescan SEM operated at 30 kV.

Preparation of the multi-walled carbon nanotube-glassy carbon electrode. First, the GCE was polished with 0.05 μm-sized alumina slurry on a polishing cloth and rinsed thoroughly with double distilled water with further sonication in ethanol and double distilled water. The GCE was modified with MWCNTs (MWCNTs-GCE) using the reported procedure in literature [30]. Briefly, the electrode was placed for 5 min at 50°C in an oven and then MWCNTs were immobilized on the preheated electrode by gently rubbing the electrode surface for 1 min on fine qualitative filter paper containing dry amount of purified MWCNTs. The modified electrode was rinsed with ethanol before usage.

RESULTS AND DISCUSSION

Morphological study of the electrode surfaces. Figures 1a, 1b shows the SEM images of the bare GCE and MWCNTs-GC modified electrode, respectively. As it is shown in Fig. 1b, many adsorbed MWCNTs are observed on the surface of the GCE.

The microscopic area of the MWCNTs-GCE was evaluated by cyclic voltammetry using 1 mM $K_3[Fe(CN)_6]$ solution containing 0.1 M KCl as a redox probe. For a reversible process, the Randlse-Sevcik formula (Eq. (1)) is used [31].

$$I_{pa} = 2.69 \times 10^5 n^{3/2} A c_0 D^{1/2} v^{1/2}, \qquad (1)$$

where I_{pa} is the anodic peak current, n is the number of electrons transferred, A is the surface area of the electrode, D is the diffusion coefficient of $K_3[Fe(CN)_6]$, v is the scan rate and c_0 is the concentration of $K_3[Fe(CN)_6]$. For $K_3[Fe(CN)_6]$, $n = 1$ and $D = 7.6 \times 10^{-5}$ cm/s and the microscopic areas of electrode were calculated from the slope of I_{pa} vs. $v^{1/2}$ [31]. Finally, the effective surface area of MWCNTs-GC modified electrode was found to be 0.093 cm^2, which was about 3 times larger than the geometrical surface area of the bare GCE (0.0314 cm^2).

Electrochemical behavior of fentanyl at the multi-walled carbon nanotube-glassy carbon modified electrode. Figure 2 shows cyclic voltammograms of fentanyl on the bare GCE and MWCNTs-GC modified electrode in 0.1 M phosphate buffer solution (**PBS**, pH 7.4) at the scan rate of 50 mV/s. In this figure, the scans *2* and *4* show the cyclic voltammograms of fentanyl (0.1 mM) on the bare electrode and MWCNTs-GC modified electrode. On the other hand, the scans *1* and *3* are the corresponding voltammograms in 0.1 M PBS. It can be seen that over a potential range from −0.2 to 1.2 V, the cyclic voltammograms of both electrodes show a single irreversible oxidation peak. The MWCNTs-GC modified electrode shows significant oxidation current starting at ca. 0.25 V vs. Ag/AgCl reference electrode and a reduction signal was observed at ca. 0 V in the reversed scan. This result
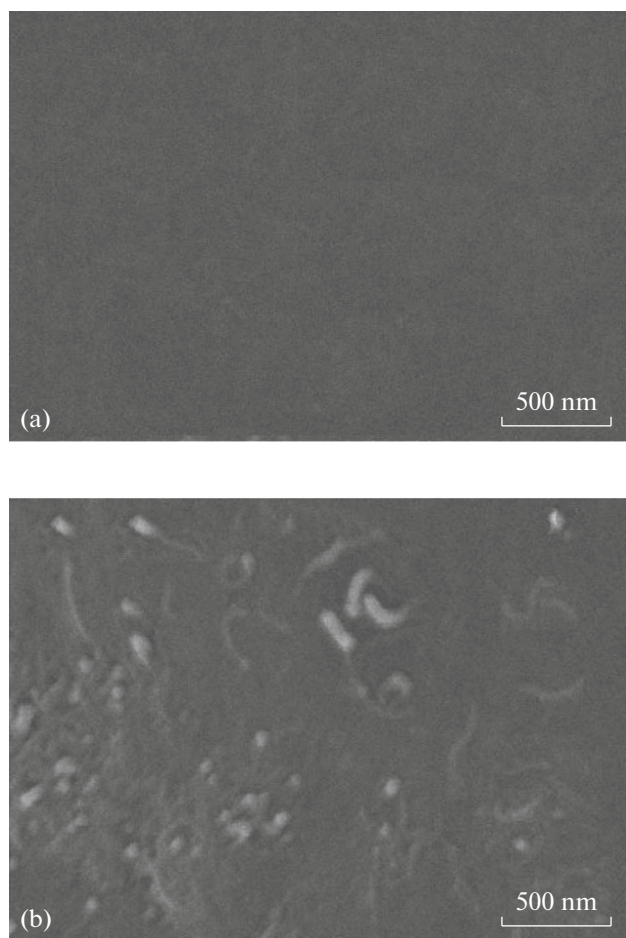
Fig. 1. The SEM images of GCE (a) and MWCNTs-GC modified electrode (b).

Fig. 2. Cyclic voltammograms of the bare GCE (*1*, *2*) and MWCNTs-GC modified electrode (*3*, *4*) in phosphate buffer solution (pH 7.4) at the scan rate of 50 mV/s and accumulation time of 500 s without (*1*, *3*) and with (*2*, *4*) 0.1 mM fentanyl.

shows low redox activity at the bare GCE over the same potential range and fentanyl oxidation current was started at ca. 0.7 V. A considerable negative shift of the onset potential for electrooxidation of fentanyl and a large enhancement of fentanyl peak current indicate the significant catalytic ability of MWCNTs toward fentanyl oxidation.

The scan rate effect in the range of 5–400 mV/s on the cyclic voltammograms of the MWCNTs-GC modified electrode in 0.1 M PBS containing 0.1 mM fentanyl was investigated and presented in Fig. 3a. Also, Figs. 3b, 3c show the plots of peak currents for electrooxidation of fentanyl vs. $v^{1/2}$ and v, respectively. Linear correlations between the anodic currents with both the square root of the scan rate and the scan rate are observed. This indicates that the kinetic of the overall process is controlled by a mixed adsorption−diffusion on the surface of the modified electrode [32, 33].

Influence of pH. In order to effectively determine fentanyl, the influence of pH was studied and opti-
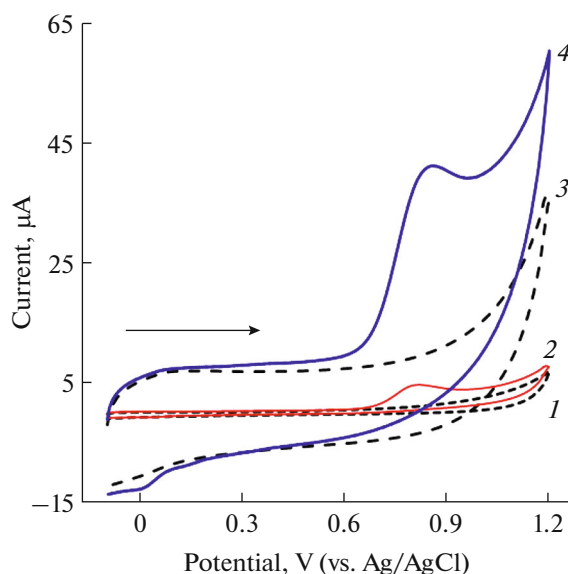
mized by varying the type (i.e., phosphate, acetate and carbonate) and value of buffer solutions. The results show that the highest oxidation peak current for fentanyl can be obtained in phosphate buffer solution. The voltammetric investigations of fentanyl were performed in the pH range of 5−9 using 0.1 M PBS (Fig. 4). Based on the results of pH investigation, phosphate buffer solution with pH 7.4 was chosen as optimum pH for achieving the best sensitivity (maximum peak current) in the voltammetric experiments.

On the other hand, it was found that the peak potential was negatively shifted with increasing the pH value and a good linear relationship was observed between the E_p and pH values with the following equation: E_{pa} (V) $= -0.054$ pH $+ 1.226$ ($R^2 = 0.9914$). The linear relationship revealed a slope of -0.054 V/pH which was close to the Nernstian value of 59 mV clearly indicating that equal number of electrons and protons processed in the electrooxidation of fentanyl on the surface of MWCNTs-GC modified electrode.

The Tafel plot and its corresponding slope can be used for the elucidation of the mechanism of electrode reaction. A Tafel plot ($\log I$ vs. E) derived from data of the rising part of the current−voltage curve of 1×10^{-4} M fentanyl at the surface of MWCNTs-GCE in 0.1 M PBS (pH 7.4) was drawn. Figure 3d depicts a Tafel diagram obtained at a low scan rate (5 mV/s) and the equation was $\log I$ (μA) $= 8.1211E$ (V) $+ 4.9346$ ($R^2 = 0.9989$). For an irreversible anodic reaction, the Tafel slope is calculated accord-
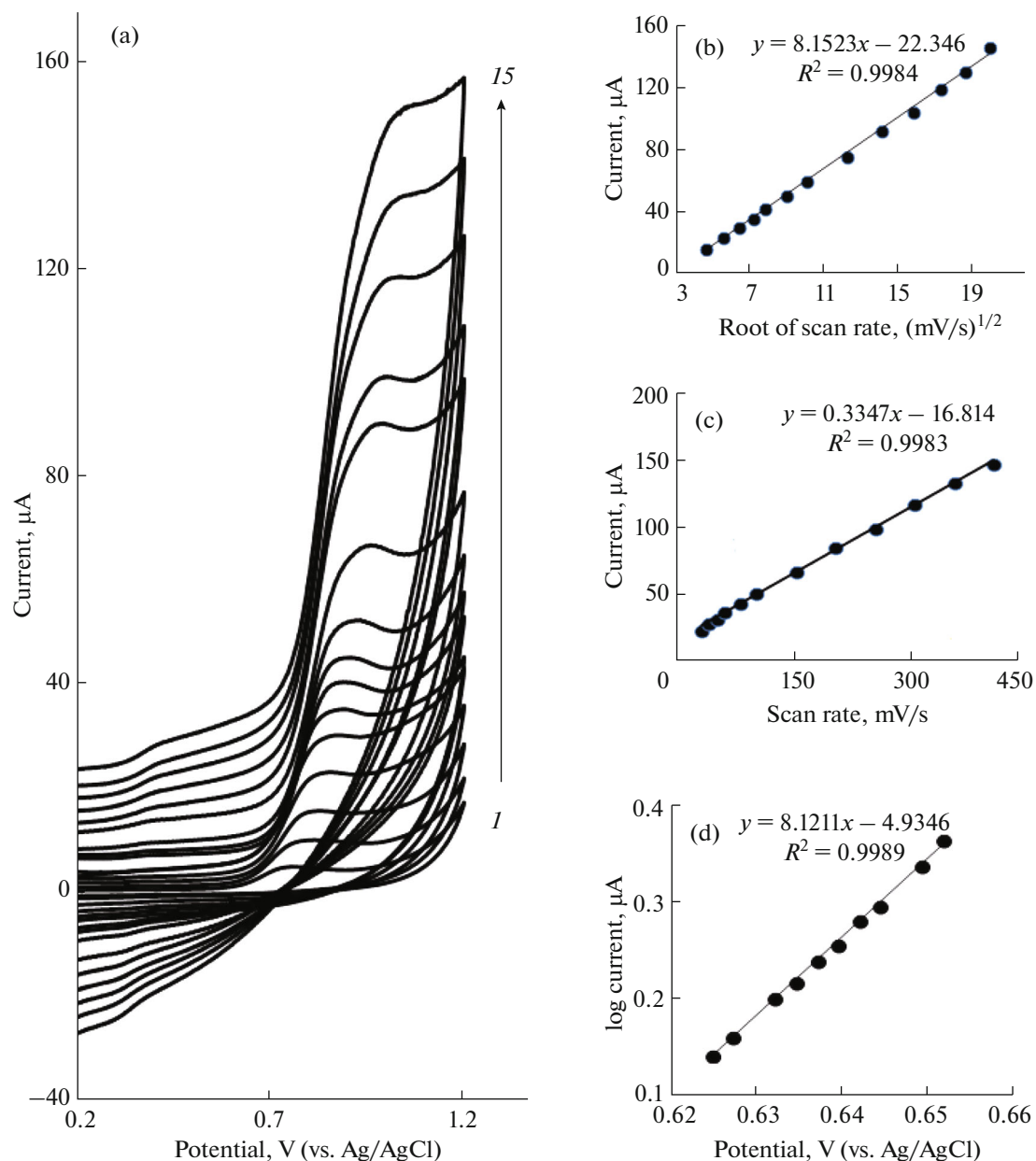
Fig. 3. (a) The effect of scan rate on cyclic voltammograms response of 0.1 mM fentanyl (pH 7.4) at MWCNTs-GCE with different scan rates (*1–15*: 5–400 mV/s). Dependence of the peak currents on the root of scan rate (b) and scan rate (c). (d) The Tafel plot of 0.1 mM fentanyl at the surface of MWCNTs-GCE in 0.1 M phosphate buffer solution (pH 7.4) at the scan rate of 5 mV/s.

ing to the Eq. (2) [31]. The slope of 8.1211 V^{-1} was obtained from Tafel plot indicating the involvement of one electron in the rate determination step. Therefore, a transfer coefficient (α) of 0.52 was obtained. If two electrons are assumed to be in the rate determination step, an α-value of 0.91 should be accepted which is not a common value, since α is in the range of 0.2 to 0.7 for most electrodes [31]:

$$\text{Slope} = n\alpha(1-\alpha)F/2.3RT. \qquad (2)$$

Based on the obtained results, the process is probably involved in an EirCEir mechanism in which a chemical reaction prevents the second oxidation process at low scan rates. However, by increasing the scan rate, the second peak is observed, and the mechanism turns to EirEir. The proposed mechanism is shown in Scheme 2.
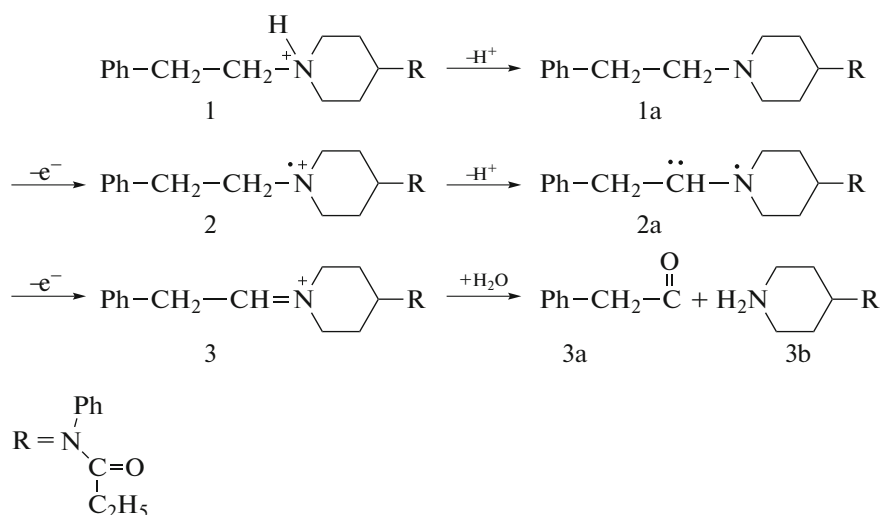
Scheme 2. The proposed mechanism of electrochemical oxidation of fentanyl at MWCNTs-GC modified electrode.

There are aliphatic tertiary amines in fentanyl structure and their non-pair electrons may act as donors. Fentanyl loses an electron from nitrogen on the piperidine ring (1−1a) to form a cation radical (2) which on losing a proton and an electron in subsequent (2−2a) steps forms a quaternary Schiff base (3). Then, the quaternary Schiff base is rapidly hydrolyzed to the secondary amine (3a−3b). This prediction was in accordance with earlier reports for the oxidation of similar structures [34, 35].

Time and potential of accumulation. The effect of accumulation time on the voltammetric response of 0.1 mM fentanyl at MWCNTs-GCE in PBS (pH 7.4) was investigated. In the first scan, a well-defined oxidation peak appeared which gradually disappeared in subsequent cycles resulting from the fact that the electrode surface was blocked by the strong adsorption of fentanyl or its oxidation products. By increasing the accumulation time, the peak current significantly increased. The results indicated that after the accumulation time of 500 s, the adsorptive equilibrium was achieved. Thus, the accumulation time was set at 500 s. Also, the influence of the accumulation potential was investigated which revealed that the accumulation potential had no effect on the anodic peak current. Therefore, the accumulation of fentanyl was carried out under open circuit conditions.

Chronoamperometry. Figure 5 shows the chronoamperograms that were obtained for a series of fentanyl solutions with various concentrations (1×10^{-5} to 1×10^{-4} M). The results indicated that oxidation current increased with an increase in fentanyl concentration. The diffusion coefficient (D) of fentanyl can be evaluated from Cottrell Eq. (3) [31]:

$$I = nFAcD^{1/2}/\pi^{1/2}t^{1/2}. \quad (3)$$

The linear experimental plots of I vs. $t^{-1/2}$ are illustrated in Fig. 5b. The plot of the slopes of these lines in Fig. 5c vs. the concentration of fentanyl can be used to obtain the value of D. The diffusion coefficient was calculated to be 2.7×10^{-6} cm^2/s for fentanyl.

Chronoamperometry technique was also used to evaluate the catalytic rate constant for the chemical reaction between fentanyl and the surface of MWCNTs-GC modified electrode according to the method described in the literature (Eqs. (4) and (5)) [31]:

$$\frac{I_{cat}/I_L}{} = \lambda^{1/2}\left[\pi^{1/2}\mathrm{erf}\left(\lambda^{1/2}\right) + \exp(-\lambda)/\lambda^{1/2}\right]\lambda = k_{cat}c_0 t, \quad (4)$$

$$I_{cat}/I_L = \pi^{1/2}\left(k_{cat}c_0 t\right)^{1/2}, \quad (5)$$

where I_{cat} and I_L are the currents of MWCNTs-GC modified electrode in the presence and absence of fentanyl,
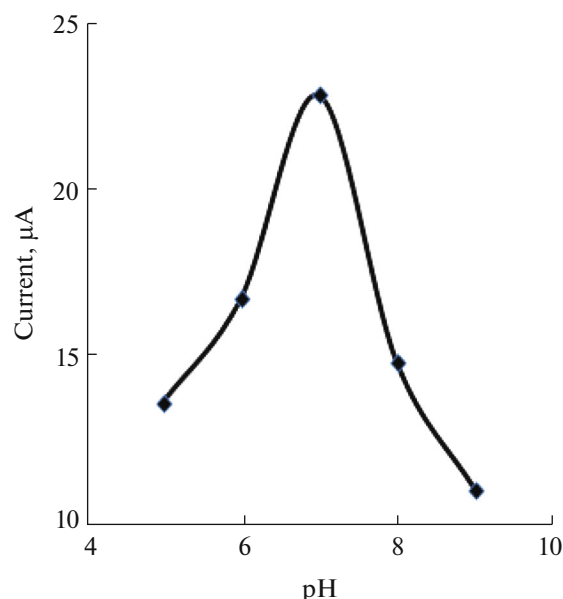
Fig. 4. Dependence of fentanyl oxidation peak current (I_{pa}) on the pH value of the solution.
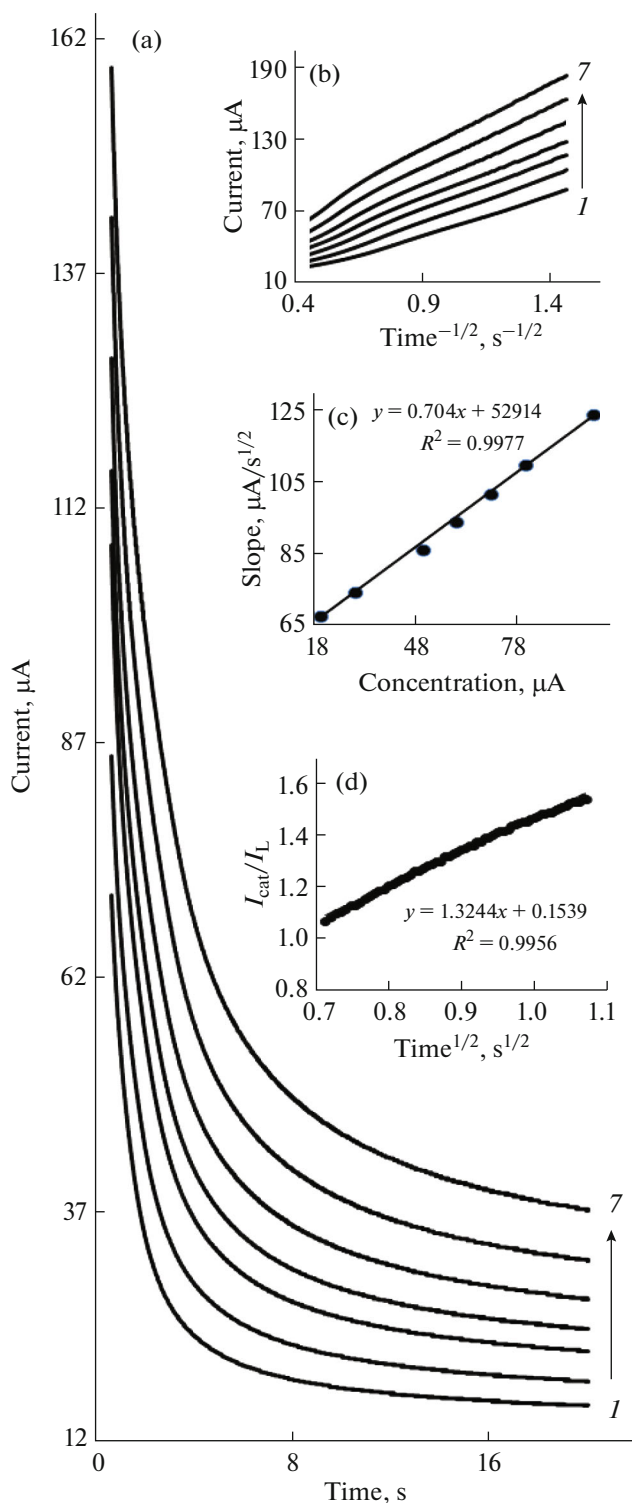
Fig. 5. (a) Chronoamperograms obtained at MWCNTs-GC modified electrode for diferent concentrations of fentanyl at the potential step of 1100 mV vs. Ag/AgCl in the buffer solution (pH 7.4). The numbers (*1–7*) correspond to 20, 30, 50, 60, 70, 80, and 100 μM of fentanyl. (b) Plots of I vs. $t^{-1/2}$ obtained from chronoamperograms, (c) the relationship between the slopes of the lines in Fig. 5b and fentanyl concentrations, (d) the plot of I_{cat}/I_L vs. $t^{1/2}$ from chronoamperometry for 5×10^{-5} M fentanyl at the optimum conditions for catalytic rate constant (k_{cat}) evaluation.

respectively. The plot of I_{cat}/I_L vs. $t^{1/2}$ (Fig. 5d) is linear and k_{cat} could be obtained from the slope for a given fentanyl concentration. The slops were found to be 1.32 for 5×10^{-5} M fentanyl solution and, therefore, k_{cat} was calculated to be $1.12 \times 10^4 \ M^{-1} \ s^{-1}$.

Differential pulse voltammetry (DPV) is more sensitive than cyclic voltammetry. In addition, the charging current contribution to the background current which is a limiting factor in the analytical determination is negligible in DPV mode. Therefore, this method was used to determine the linear range and detection limit of fentanyl. The dependence of adsorptive stripping peak current on fentanyl concentration was investigated by differential pulse voltammetry after 500 s accumulation (Fig. 6). The calibration equation obtained by the least-squares method is $I_p \ (\mu A) = 0.20 c_{fentanyl} - 10.22$ with regression coefficient (R^2) of 0.9979. The oxidation peak currents of fentanyl were linear with their concentrations in the range of 5×10^{-7} to 1×10^{-4} M. The detection limit of fentanyl was estimated to be 1×10^{-7} M according to the $3s_b/m$ criterion, where m is the slope of the corresponding calibration graph of fentanyl and s_b is the standard deviation of the blank solution ($n = 6$).

The reproducibility of the electrode was investigated by 6 independently prepared MWCNTs-GC modified electrodes. Then, their cyclic voltammograms were recorded in 1×10^{-4} M fentanyl solution and the relative standard deviation (**RSD**) was estimated to be 3.1%. Also, the RSD was calculated to evaluate the repeatability of MWCNTs-GC modified electrode which was 2.3% by measuring the peak currents of 1×10^{-4} M fentanyl in 6 replicates.

Table 1 compares the characteristic responses of MWCNTs-GC electrode with the potentiometric and polarographic methods for the determination of fentanyl. As can be seen in this table, the proposed electrode exhibits more appropriate analytical properties, for example low detection limit and wide linear dynamic ranges, for the electrochemical determination of fentanyl.

Analytical application. In order to evaluate possible application of the proposed method, DPV technique was employed to determine fentanyl in urine and protein-free spiked human serum samples at the surface of MWCNTs-GCE. Acetonitrile was applied as a serum precipitating agent. No extraction steps other than the centrifugal protein separation were required prior to the determination of the drug. The standard addition method was used to prepare the samples and the results are shown in Table 2. In these experiments, no amount of fentanyl was detected in healthy human urine and serum samples. The accuracy of the analysis was calculated by achieving the recovery of known amounts of fentanyl spiked in urine and serum solutions at 3 different concentrations. The results showed an average recovery of 101 and 103% for fentanyl added to the urine and serum samples, respectively.
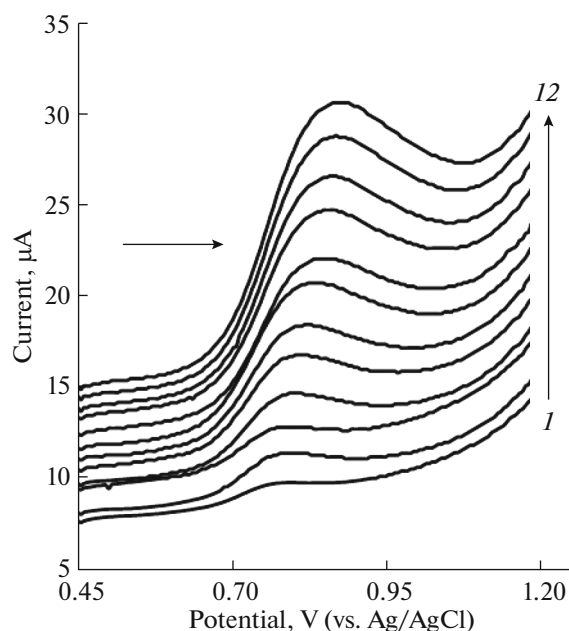
Fig. 6. Adsorptive stripping differential pulse voltammograms of fentanyl in 0.1 M PBS (pH 7.4) containing different concentrations of fentanyl from (*1*) to (*12*) of 0.5, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 µM. Voltammograms were obtained by accumulation under open circuit potential after 500 s.

The obtained recovery of the method reveals its capability for the determination of fentanyl in clinical samples. The proposed method was successfully applied to the determination of fentanyl in the 0.05 mg injection sample. The results showed that the injection matrix did not have any interference effect on the electrochemical measurement of fentanyl. The determined fentanyl content was 0.049 mg per injection with the RSD of 2.5% indicating the reliable accuracy of the method.

Interferences. Uric (**UA**) and ascorbic (**AA**) acids as electroactive coexistent compounds in biological systems such as blood plasma were chosen as potential interferents. The interference effects of 1×10^{-4} M AA and UA were examined under the optimum conditions on the voltammetric response of 1×10^{-5} M fentanyl

(Fig. 7). As seen, no detectable change was observed in the response current of fentanyl in the mixture with the presence of these compounds. Furthermore, the influence of various ions such as Cl^-, NO_3^-, CO_3^{2-}, PO_4^{3-}, Na^+ and Mg^{2+} (30-fold concentrations) as foreign substances on the determination of 1×10^{-5} M fentanyl was studied. These ions barely influenced the current response of 1×10^{-5} M fentanyl (signal change below $\pm 4\%$) revealing that modified electrode had excellent selectivity to fentanyl determination.

CONCLUSIONS

The MWCNTs-GC modified electrode provides electroactive sites for the accumulation of fentanyl at

Table 1. Analytical characteristics for fentanyl determination at several reported methods

Method	Electrolyte	LOD*, M	Linear range, M	Real sample	Reference
Potentiometry	–	5.43×10^{-6}	1×10^{-2}–1×10^{-5}	Injection	[29]
Polarography	NaOH	5×10^{-8}	1×10^{-6}–1×10^{-7}	Injection	[27]
DPASV**	Phosphate buffer	1×10^{-7}	1×10^{-4}–5×10^{-7}	Injection, serum, urine	This work***

  * Limit of detection;
 ** differential pulse adsorptive stripping voltammetry;
*** in this work, determination was performed after 500 s accumulation time under open circuit potential.

Table 2. Determination of fentanyl in various samples by differential pulse voltammetry using MWCNTs-GC modified electrode

Sample	Amount added, μM	Amount found, μM ($n = 6$)	Recovery, %	RSD, %
Urine	0	—	—	—
	0.7	0.7	104	3.23
	1.5	1.6	103	2.83
	3.0	2.0	96	2.66
Serum	0	—	—	—
	0.7	0.7	97	2.90
	1.5	1.6	106	3.16
	3.0	3.2	106	3.42

All determinations were performed after 500 s accumulation under open circuit potential.

open circuit potential. This electrode was used for the determination of fentanyl with a low detection limit using differential pulse adsorptive stripping voltammetric method. This electrode is simple to prepare, and the SEM images showed the presence of MWCNTs on the surface of the modified electrode. The overpotential for oxidation of fentanyl is decreased on the surface of this modified electrode compared to an unmodified electrode. Furthermore, the modified electrode indicates remarkable enhancement in the electrooxidation peak current of fentanyl in comparison to the bare GCE. This modified electrode was successfully utilized for the determination of fentanyl in real samples.
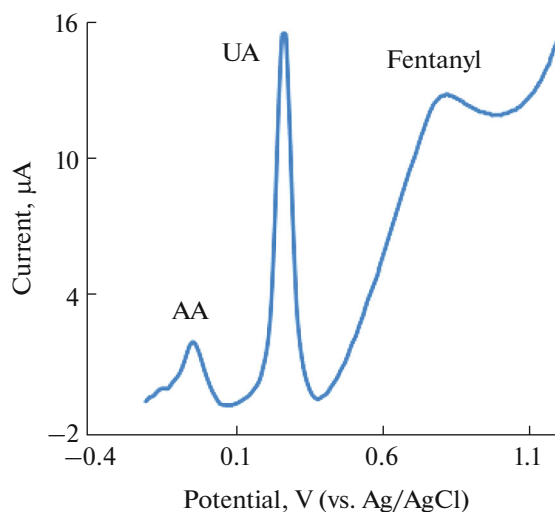
Fig. 7. Adsorptive stripping differential pulse voltammograms of fentanyl (1×10^{-5} M) in the presence of 1×10^{-4} M ascorbic and uric acids in phosphate buffer solution (0.1 M, pH 7.4).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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