Full Paper

Application of Single-Walled Carbon Nanotube and Poly (3-Methylthiophene) Modified Sensors for Electrochemical Determination of Levodopa and Benserazide

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Abstract- Sixteen electrochemical electrodes were prepared by modifying the electro-polymerized 3-methylthiophene to the below and above of the single-walled carbon nanotubes (SWCNTs) dispersion that dripped onto glassy carbon electrode. Determination of benserazide (BS) and levodopa (LD) in the presence of ascorbic acid (AA) was performed by differential pulse voltammetry (DPV) technique to find out which of these electrodes gave the best and fastest simultaneous response. The highest resolution and current densities were achieved with the electrode that 20 μL 1.0% SWCNT was dribbled onto the bare electrode. The morphology and structure of modified electrode were characterized by scanning electron microscopy. Under optimum conditions AA, BS and LD gave sensitive oxidation peaks at nearly 90, 210 and 320 mV, respectively. The oxidation currents increased linearly with concentration of BS (50-100 μM) and LD (5.0–9.5 μM) in phosphate buffer solution (pH 7.0). The detection limits obtained by DPV were 3.0 μM for BS and 1.1 μM for LD. Additionally, the proposed modified sensor was applied successfully to biological fluids and tablet samples. The results proved that the modified sensor showed excellent selectivity, repeatability and reproducibility with high stability and accuracy.

Keywords- Benserazide, Levodopa, Single-walled carbon nanotube, Electrochemical sensor

1. INTRODUCTION

Levodopa (L-dopa, 3,4-dihydroxyphenyl-l-alanine) [1] and Benserazide (2-amino-3-hydroxy-N'-[(2,3,4-trihydroxyphenyl) methyl] propane hydrazide) (Scheme 1) [2] are drugs used for the treatment of Parkinson's disease (PD) which is associated with dopamine depletion in the brain [3-5]. Parkinson's disease (PD) is a progressive neurodegenerative disorder consisting of resting tremors, loss of balance and slowness, which is believed to be due to large degeneration of nigrostriatal dopaminergic neurons [6-8]. Dopamine (DA) cannot be used as a pure form in treatment because it cannot cross the blood brain barrier itself [7,9,10]. Levodopa is converted to DA by aromatic l-amino acid decarboxylase in the brain. Furthermore, most of the LD is converted to DA in the peripheral tissue and a small amount of LD passes into the brain. Therefore, it is used in combination with BS to increase the ratio of LD to the brain [1, 9-15]. Benserazide allows levodopa to be used in smaller doses as it decreases the peripheral metabolism of LD. Benserazide does not pass the blood brain barrier, so DA is formed only in the brain [10,15,16]. Benserazide inhibits the carboxylation of LD outside of the brain and reduces the side effects by providing a low dose of LD [17-20]. Benserazide and L-Dopa are neurotransmitters that play an important role in the functioning of renal, cardiovascular and central nervous system. Therefore, selective determination of low amounts of BS and LD Have been important by a sensitive and reliable method. [1,9,21,22].

In the field of pharmaceutical analysis, various electrochemical techniques such as voltammetry, potentiometry have been used for the determination of biological compounds and drug compounds. [23,24]. The advantages such as simplicity, precision, high accuracy and precision, high dynamic range, less sensitivity to matrix effects, low cost and speed are available for selection of these methods [25,26]. Furthermore, the selectivity and sensitivity of the electrochemical methods further improves the diagnosis of drugs in complex matrixes such as pharmaceutical and biological samples by modification of the electrode surface [27,28]. The application of these modified sensors can be useful for trace analysis of electroactive species and can eliminate the overlap of signals in simultaneous analysis [29]. Many surface modification materials are being prepared, and this technique is more preferred [30].

Poly (3-methylthiophene) (P3MT) is an electronically conductive polymer that reduces surface contamination and electrocatalytic effects of oxidized compounds on the surface of the modified sensor [31]. The P3MT exhibits excellent electrocatalytic effect, which can be easily electro-precipitated to the electrode surface by electro-oxidation of the monomer [32]. Polymer-coupled nano-materials can provide an excellent system and these materials are effectively used in sensor applications [33]. It is possible to form polymers with nanoparticle materials and to perform nano-electronic sensor platforms with excellent electrocatalytic effect [33,34]. Electroanalytical studies such as catalysis, mass transport, high-impact surface area and control of the electrode microenvironment can be performed with a nanoparticle-modified electrode [33,35]. Especially, sensors formed by carbon nanotubes, electrochemical coating of

P3MT onto CNTs, or composite films produced by simultaneous electrochemical growth of CNTs and P3MT, are useful [31]. The electrochemical sensors generated with SWCNTs have very good responses due to their fine electronic properties, strong electrocatalytic effect, rapid electron transfer rate, high tensile strength and chemical stability, and ultra-small size effect [33,36].

The aim of this study is to develop a rapid sensor for selective, sensitive and repeatable detection of AA, LD and BS in very trace amounts using voltammetric techniques. For this purpose, sixteen modified sensors were produced by electrodeposition of 3-methylthiophene onto and under the single walled carbon nanotube (SWCNT) with the cyclic voltammetry (CV) technique. All experimental parameters were optimized to separate the oxidation potentials of LD and BS from each other. The best results were obtained with a modified sensor produced by dropping 20 µL of 1% SWCNT/DMF dispersion to the GCE surface. Electron scanning microscope (SEM) results showed that the electrode surface had excellent electrocatalytic effect against LD and BS with large surface area. To demonstrate the accuracy and precision of the proposed sensor, differential pulse voltammetry (DPV) technique was used to perform repeatability, reproducibility studies and recovery analyses in real samples such as tablets and urine samples.

Since LD, BS and AA have very close oxidation potential, the voltammetric responses of the naked electrode overlap and this makes it difficult to detect simultaneously with electroanalytical methods [9,37,38]. In our previous study [9], a multi walled carbon nanotube (MWCNT) based sensor was designed for determination of LD and BS. The higher detection limits were reached at the MWCNT modified sensor. In this study, the SWCNT / GCE sensor was used and the lower determination limits were successfully reached to determine BS and LD. However, thanks to the sensor obtained by modifying the SWCNT with 3-methylthiophene electro-polymerized film, the oxidation potentials of this triple mixture were easily separated by potential differences of more than 100 mV. The sensor with its excellent electrocatalytic effect, which was developed in accordance with the electrochemical data obtained as a result of the study, was enabled selective, stable and repeatable detection of AA, LD and BS at very low concentrations. This promises that this sensor can be used in practical applications of real samples.
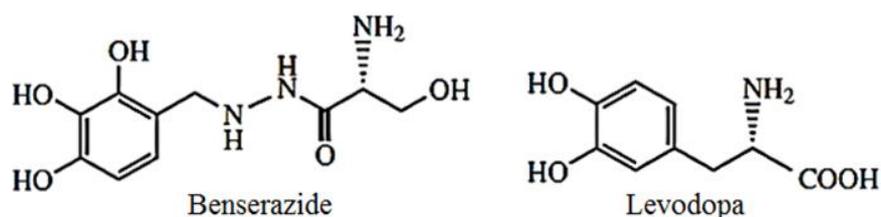
Scheme 1. Chemical structures of the drugs used in the treatment for Parkinson's disease [39]

2. EXPERIMENTAL

2.1. Reagents and Standard Solutions

Benserazide hydrochloride and Levodopa were purchased from Sigma and Alfa Aesar (A Johnson Matthey Company), respectively. Commercial tablet of Madopar® (100/50 mg, LD/BS) was obtained from Deva (Turkey). Single-walled Carbon Nanotube (SWCNT) (diameter:*<2 nm*, EC:>100 S/cm, length: 5-30 μm, purity >95%, surface area: 380 m^2g^{-1}) was provided from © Grafen Inc. which is headquartered in Ankara, Turkey. Tetrabutylammonium tetrafluoroborate (TBATFB, Merck) and $AgNO_3$ (Merck) were analytical purity. In addition, 3-methylthiophene and ascorbic acid were from Aldrich, N, N-dimethylformamide (DMF) was from Sigma, and acetonitrile was from Sigma-Aldrich. In the preparation of the aqueous solutions, Milli Q (Millipore, 18.2 MΩ.cm) ultra-pure water was used.

Stock standard solutions were freshly prepared at a concentration of 0.01 M in ultra-pure water for daily. Buffer solutions were prepared at different pH values. 0.10 M phospate buffer solution (PBS) was prepared by dissolving Na_2HPO_4 (Merck), KH_2PO_4 (Carlo Erba), KCl (Merck) and NaCl (Merck). H_3BO_3 (Merck), H_3PO_4 (Merck) and CH_3COOH (Merck) were used for Britton-Robinson (BR) buffer solution. 0.1 M CH_3COOH was used for acetate buffer solution.

2.2. Apparatus

The surface morphology of nanoparticle material on the surface of GCE was performed by scanning electron microscopy (SEM) (LEO EVO-40xVP) technique. The electroanalytical measurements with using CV and DPV techniques were performed by electrochemical analyser BAS *100 W* (Bioanalytical Systems, Inc., USA). Electroanalytical experimental studies were realized within three electrode system which consisted a GCE (geometric area: 6.85 mm^2, CHI) as a working electrode, platinum disc (handmade) as an auxiliary electrode and Ag/Ag$^+$ (CHI112) for nonaqueous media and Ag/AgCl for aqueous media as reference electrodes. The electrodes were cleaned mechanically and electrochemically as described in our previous works before they were modified [9,40]. During all experimental studies, nitrogen gas was passed through the solution for 5 *min* before the voltammetric measurements were performed.

2.3. Preparation of Modified Sensors

Conducting polymer coating on the GCE was achieved in a three-electrode single-compartment cell containing 0.15 mM 3MT and 0.1 M TBATFB (as electrolyte) dissolved in acetonitrile. The electrochemical polymerization was acquired at the potential range of (-200) to (+2000) mV for 14 cycles using CV technique. In order to vomit unreacted monomer, the obtained film was washed with acetonitrile. N,N-dimethylformamide (DMF) dispersions of SWCNT were prepared at different concentrations, 0.2%, 0.5%, 1.0% (mg/μL). SWCNT/DMF

dispersions were sonicated for 4 h before dripping onto the electrode surface. Modification of GCEs was carried out by electropolymerization of 3-MT on the surface of bare GCE or SWCNT modified sensor. Then SWCNT dispersions were dropped on the surface of bare GCE and electropolymerised GCE with 3MT. 3MT/SWCNT modified sensors were fabricated by first electropolymerising of 3MT on the GCE and then coating with the SWCNT/DMF dispersions. SWCNT/3MT modified sensors were fabricated by first dropping of the SWCNT/DMF dispersions to the surface of GCE and then electropolymerising of 3MT. Additionally, 10 µL, 20 µL of SWCNT dispersions were dropped and modified sensors were dried overnight.

3. RESULTS AND DISCUSSION

3.1. Electrodeposition of 3MT on the surface of GCE

3-Methylthiophene was electrodeposited on the surface of GCE and SWCNTs modified sensors by CV (*vs*. Ag/Ag⁺). During the polymerization period, a half-reversible redox couple emerged at about 620 mV corresponding to oxidation and 600 mV corresponding to reduction. Voltammetric responses of P3MT showed that the film was growing steadily on the surface of electrode. The best oxidation peak responses were obtained at fourteen-cycled films by elctropolymerized on GCE using CV technique *vs*. Ag/Ag⁺ [9]. Thereby, fourteen-cycled polymer films were used for modifying the sensors in subsequent works.
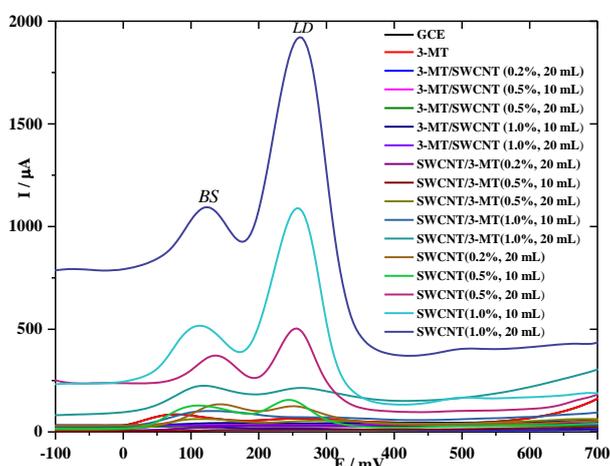

Fig. 1. DPV results of 1.0 mM BS and 1.0 mM LD at various sensors

Sixteen modified sensor were fabricated by combination of 3-MT with SWCNTs at different concentrations. Therefore, it was investigated which modified sensor best distinguish the peak potentials and increase peak current intensities of LD and BS. The best, sharp, high resolution and increased peak current densities were obtained at the modified sensor, which 20 µL from 1.0% SWCNT/DMF dispersion dripped onto the GCE surface, as shown in Fig. 1.

Benserazide was appeared at 120 mV and current density was 2.086×10^{-4} A, Levodopa was appeared at a distinct potential of 264 mV with a highly current density of 1.206×10^{-3} A.

The surface morphology of modified sensor was examined using SEM technique. The SEM surface images of the SWCNT modified sensor were compared at different magnifications in Fig. 2. In these images, the surface of the SWCNT modified sensor was found to be fractured and rough. SWCNT particles were clearly visible in the DMF structure. Surface area and surface roughness increased compared to bare electrode. This rough image confirms the increased surface area. As the roughness increased, the surface area grew and the sensitivity of the sensor increased.
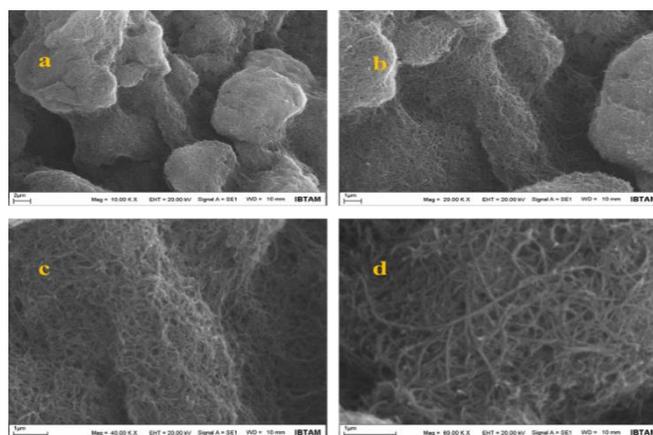
Fig. 2. SEM surface images of SWCNT/DMF on the surface of GCE at different magnifications: a) 10; b) 20; c) 40; d) 60

3.2. Electrochemical Determination of BS and LD

In addition to preparing a large number of modified sensors, the electrochemical test medium was also optimized. For this, the polymer film thicknesses, the supporting electrolytes and the pH of the medium were investigated in which the binary mixture of BS and LD could be well separated. In the electropolymerization step of 3-MT, various film thicknesses (8-22 cycles) were coated by electro-deposition on the GCE surface with CV method to determine the optimum film thickness. The maximum current response was obtained at the 14-cycles film thickness and the DPV responses of current densities for the active materials began to decrease at film thicknesses greater than 14-cycles. The stability of the film declined and spills were formed from the film surfaces more than 14-cycles.

In addition, the electrolyte effect was investigated by making determinations in different electrolyte mediums during the optimization procedures. For this purpose, individually and binary determinations of active compounds were carried out in different pH environments of phosphate, Britton-Robinson and acetate buffer solutions. The medium in which the highest peak currents and the active materials can be separated from each other by the best resolution

in the binary mixture was provided with PBS medium. In addition, more stable and selective separations were obtained in this electrolyte environment. At these optimum conditions, the DPV analysis of 1.0 mM binary mixture of BS and LD resulted with a peak potential difference of 144 mV, oxidation peaks were at nearly 120 and 264 mV, respectively. In addition, these conditions were used in ongoing studies.

Numerous sensors were designed to determine the sensor that will best distinguish to LD and BS signals and enhance the peaks resolution. The best responses were obtained at the modified sensor, which 20 µL from 1.0% SWCNT/DMF dispersion dripped onto the GCE surface (Fig. 1). The pH of the buffer solution, in which the best discrimination can be achieved for LD and BS, was investigated with this sensor. For this, DPV analyses of 1.0 mM binary mixture of BS and LD at various pH (3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 and 11.0) of PBS were performed at SWCNT / GCE modified sensor. High-resolution separation and increased peak current densities for BS and LD were achieved in PBS at pH 7.0.
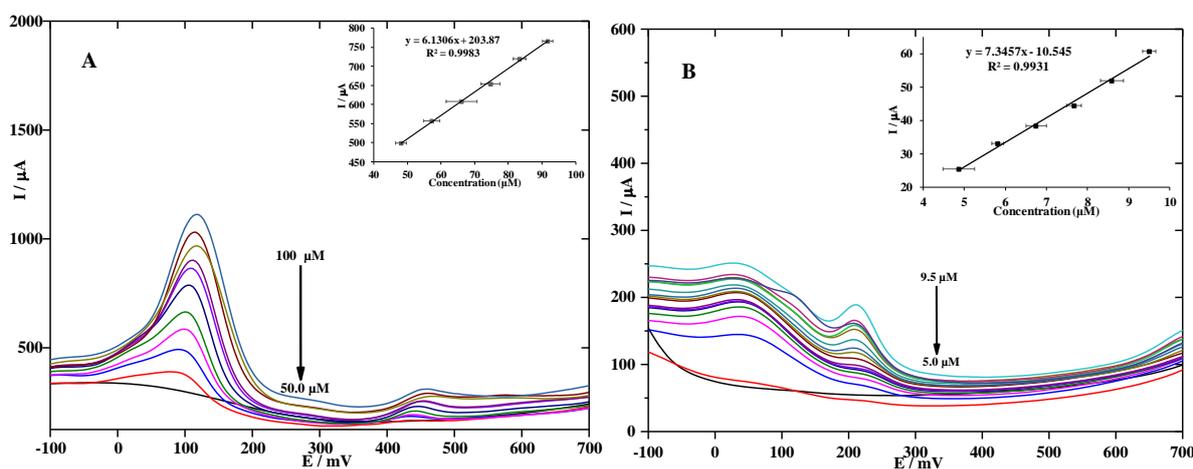
Fig. 3. DPVs of (A) 50.00 -91.74 µM BS and (B) 5.0-9.5 µM LD at SWCNT/GCE modified sensor

Electrochemical analyses of BS and LD were performed at SWCNT / GCE modified sensor (20 µL, 1.0%) in 0.1 M PBS (pH 7.0) using DPV technique. The voltammetric responses of the modified sensor at the wide range of concentrations of BS and LD were shown in Fig. 3. The oxidation peak currents of BS and LD increased in direct proportion to their increasing concentrations. A linear increase was observed between 50 and 100 µM for BS, and the corresponding calibration graph was shown in Fig. 3A. The regression equation was I (µA)=0.613C (µM)+203.87 (R=0.9983) and the detection limit (S/N=3) was calculated as 3.0 µM for BS (Table 1). For LD, a linear increase was observed at the range of 5.0–9.5 µM and the corresponding calibration graph was shown in Fig. 3B. The regression equation was I (µA)=0.7346C (µM)-10.545 (R=0.9931) and the detection limit (S/N=3) was calculated as 1.1 µM for LD (Table 1). The detection limits were calculated as 32.5 µM for BS and 10.3 µM for

LD at MWCNT/GCE in our previous study [9]. These results showed that response of (20 µL, 1.0%) SWCNT/GCE modified sensor was considerable good for BS and LD. Compared to the sensor in our previous study, this sensor has lower detection limits for BS and LD. Moreover, the SWCNT / GCE modified sensor was expected to be applicable in biological fluids at the neutral pH due to its low detection limit at wide concentration range.

Table 1. Analytical parameters of Benserazide and Levodopa in PBS (pH 7.0) by DPV technique at SWCNT/GCE modified sensor

Parameters	Benserazide	Levodopa
Potential (mV)	116	216
Linear concetration range (µM)	50 - 100	5.0 – 9.5
Slope (µA. µM^{-1})	6.1306	7.346
Intercept (µA)	203.87	-10.54
Correlation coefficient (r)	0.99831	0.99312
SD[a] of slope	0.0126	0.0306
SD of intercept	9.06	2.25
LOD (µM)	0.30	0.11
LOQ (µM)	1.01	0.36
Repeatability of peak current (RSD %)	5.31	2.56
Reproducibility of peak current (RSD %)	21.83	15.34
Repeatability of peak potential (RSD %)	0.00	0.00
Reproducibility of peak potential (RSD[b] %)	9.71	5.12

[a] Standard Deviation
[b] Relative Standard Deviation

Table 2. Voltammetric response characteristics of different modified electrodes for BS and LD determination

Modified electrode	Techniques	Linear range, µM BS	LD	Condition	LOD (µM) BS	LD	Ref.
CAMCPE	DPV	1.0–500	3–500	KCl	0.95	0.65	[1]
PAR/GCE	DPV	10–200	25–400	PBS (pH 5.2)	2.00	6.00	[2]
MWCNT/GCE	DPV	400–100	50–95	PBS (pH 7.7)	32.5	10.3	[9]
GCE	DPV	25–2500	25–2500	HClO$_4$	2.77	5.12	[39]
n-H-3MIHF	SWV	0.1–600	0.1–700	PBS (pH 7.0)	0.05	0.05	[44]
MWCNTs/GCE	DPV	–	–	PBS (pH 3.0)	–	4.50	[45]
Present work	DPV	50–100	5.0–9.5	PBS (pH 7.0)	0.30	0.11	–

The electrochemical investigation of BS and LD on the surface of GCE modified with SWCNT has shown linear ranges and very sensitive detection limits. However, the voltammetric response properties obtained in this work (including linear range and detection limit) are better than similar studies from literature. A comparison between voltammetric

response properties of various modified electrode and proposed modified sensor in this study for determination of BS and LD was shown in Table 2. As far as it can be found in the literature, there is no sensor other than the one used in this study which can reach the lower limit of determination.

3.3. Validation of the SWCNT/GCE Modified Sensor

Validation of used sensor was evaluated considering precision and accuracy by the analysis of five different solutions of active substances. Moreover, the stability and reproducibility of the sensor were studied. The intra-assay of five replicate samples for three repeated analyses both of 1.0 mM BS and LD in the same day that were responsible of repeatability of peak current and potential (Table 1). The inter-assay of three replicate samples for three repeated analyses of 1.0 mM BS and LD for five day that were responsible of reproducibility of peak current and potential (Table 1). In addition, the stability of the sensor was 95.8% after one week. From these results, we can say that the modified sensor has excellent repeatability, reproducibility and the stability. Recovery studies were carried out in tablet preparations and urine samples to prove the applicability of the modified sensor to real samples. In addition, interference effect was tested with ascorbic acid.

3.4. Application of the Modified Sensor in SWCNT/GCE Real Samples

Ten Madopar® tablets (Deva) (50 mg BS and 100 mg LD) were weighed and dusted into a mortar. The amounts of active ingredients representing the amount to be worked were calculated, weighed, the volume was adjusted to 100 mL with ultrapure water, and the solution sonicated for 2 h. The solution was then filtered by micro membrane filter. Five replicate samples from this solution were prepared with PBS [9].

Table 3. Quantitative performance of modified sensor in Madopar solutions

Sample	Included (mg)		Measured (mg)		Recovery (%)	
	LD	BS	LD	BS	LD	BS
1	1.97	0.986	1.76	0.975	89.32	98.89
2	1.97	0.986	1.94	0.945	98.64	95.87
3	1.97	0.986	1.84	0.981	93.58	99.53
4	1.97	0.986	1.95	0.996	98.87	101.0
5	1.97	0.986	1.94	1.001	98.57	101.5
			Mean		95.80	99.37
			SD		3.80	1.993
			% RSD		3.96	2.006
			% RE[*]		4.20	0.632

* Relative Error

Urine samples were prepared by diluting 10 times with PBS without pretreatment. LD and BS spiked in these urine samples by applying the standard addition method, and recovery values were calculated and shown in Table 3 and Table 4. With very satisfactory recovery values, the modified sensor showed excellent responses in both Madopar and urine samples.

Table 4. Analytical results by spiking the BS and LD to the tablet sample and urine sample at SWCNT/GCE modified sensor

	Spiked (mg)		Measurement (mg)				Recovery, %			
			Tablet		Urine		Tablet		Urine	
Sample	LD	BS	LD	BS	LD	BS	LD	BS	LD	BS
1	2.000	1.500	1.976	1.418	1.898	1.427	98.78	94.56	94.88	95.13
2	2.000	1.500	1.978	1.525	2.011	1.405	98.91	101.64	100.57	93.65
3	2.000	1.500	2.072	1.356	2.069	1.505	103.60	90.40	103.46	100.35
4	2.000	1.500	2.007	1.519	1.976	1.381	100.33	101.27	98.82	92.06
5	2.000	1.500	1.923	1.458	1.888	1.473	96.14	97.23	94.38	98.23
						Mean	99.55	97.02	98.42	95.88
						SD	2.436	4.229	3.437	3.020
						% RSD	2.447	4.359	3.492	3.150
						% RE	0.448	2.978	1.58	4.119

3.5. Electrochemical Separation of BS and LD in the Presence of AA

Neurotransmitters such as BS and LD are found together with AA in the body fluid. Therefore, it is important to develop a selective and sensitive method for the simultaneous determination of neurotransmitters and interfering AA [41]. Furthermore, the oxidation peak potentials of neurotransmitters and AA overlapped at the naked electrode and simultaneous determination by electroanalytical methods is a major problem [41-43].

In our study, simultaneous determination of BS, LD and AA as an interference was carried out at (20 µL, 1.0%) SWCNT/GCE modified sensor with stable and sharp distinct peaks. Therefore, DPV responses of binary mixtures in the presence of AA were examined and showed in Fig. 4. The concentrations of AA and BS were kept constant and LD concentration (1.0, 2.0, 3.0, 4.0 mM) was increased. As shown in Fig. 4A, the AA and BS peaks remained while the levodopa peaks increased in a direct proportion. Furthermore, LD and BS concentrations were kept constant and AA concentration (5.0, 6.0, 7.0, 8.0, 9.0 mM) was increased (Fig. 4B).

As shown in Fig. 4, at the study of the AA interference effect in the urine samples, the binary mixture was well separated individually. Sharp, distinct and stable oxidation peaks of AA and active substances at physiological pH were obtained at the modified sensor.
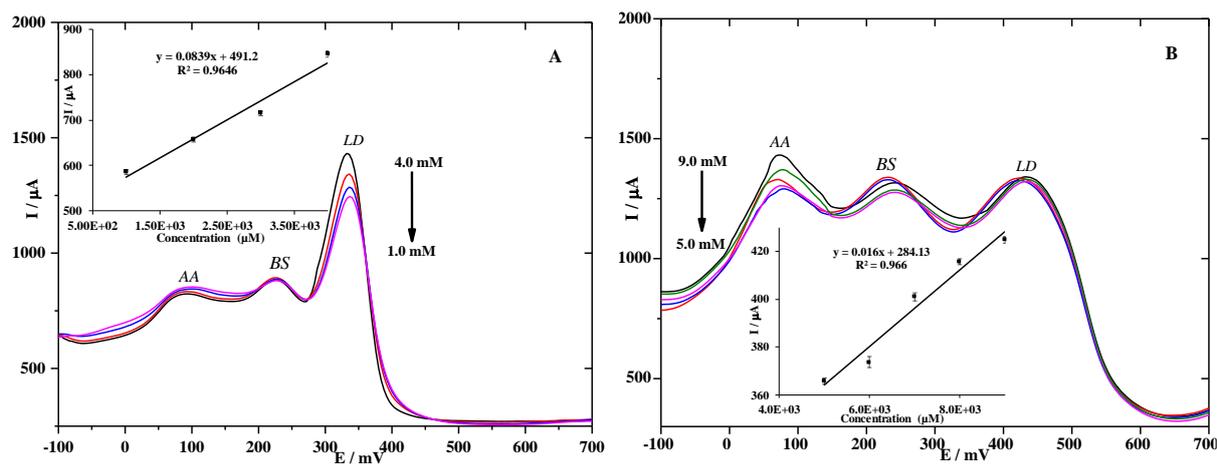
Fig. 4. DPVs of (A) LD (1.0-4.0 mM) in the presence of 5 mM AA and 0.1 mM BS; (B) AA (5.0-9.0 mM) in the presence of 0.1 mM LD and BS in urine samples at SWCNT/GCE modified sensor

4. CONCLUSION

Sixteen modified sensors were prepared for simultaneous determination of Benserazide, Levodopa and ascorbic acid. The best responses were belong to the modified sensor that 20 µL from 1.0% SWCNT/DMF dispersion dropped on the surface of GCE. The modified sensor showed excellent specificity, reproducibility, repeatability and high stability for the electrocatalytic oxidation of BS and LD in the presence of AA in PBS with low detection limit and wide linear range. In addition, the modified sensor was applied successfully to detection of BS and LD in real samples with high recovery values. Therefore, it is promising to be used in routine analyses.

Acknowledgements

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