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Voltammetric determination of bisoprolol fumarate in pharmaceutical formulations and urine using single-wall carbon nanotubes modified glassy carbon electrode

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Abstract

The electrochemistry of bisoprolol fumarate (BF) has been investigated by differential pulse voltammetry at a single-wall carbon nanotubes (SWNTs) modified glassy carbon electrode (GCE). The prepared electrode showed an excellent electrocatalytic activity towards the oxidation of BF leading to a marked improvement in sensitivity as compared to bare glassy carbon electrode where electrochemical activity for the analyte cannot be observed. The SWNTs-modified GCE exhibited a sharp anodic peak at a potential of ~950 mV for the oxidation of BF. Under optimum conditions linear calibration curve was obtained over the BF concentration range 0.01–0.1 mM in 0.5 M phosphate buffer solution (pH 7.2) with a correlation coefficient of 0.9789 and detection limit of 8.27×10^{-7} M. The modified electrode has been applied for the drug determination in human urine with no prior extraction and in commercial tablets. The proposed method has also been validated.

Keywords: Single-wall carbon nanotubes; Bisoprolol fumarate; Urine; Differential pulse voltammetry

1. Introduction

Carbon nanotubes (CNTs) play important role in nanotechnology greatly influencing many different fields including engineering, biology, chemistry, medicine, electronics and material science [1,2]. It is known that superior to the side walls of the CNTs which are very similar to basal-plane graphite and show slow electron transfer rates, the open ends of the CNTs have excellent electrochemical properties [3], which is similar to edge-plane graphite. Such an excellent electrochemical property of the open ends of the CNTs, e.g. fast electron transfer rate, is expected to be particularly attractive for electrochemical applications, especially for electrocatalysis and electrochemical determinations. Moreover, earlier reports have suggested that the shortened nanotubes containing functional groups at the open ends may block the adsorption of species on the CNTs [4]. Such intrinsic properties of the CNTs are believed to be favorable for the oxidation of electroactive species towards cathodic direction with the simultaneous enhancement of the peak current. Recently, Compton and co-workers reported that the electrocatalytic activity of CNT-modified electrodes is due to the presence of either edge-plane sides/defects or metal impurities in the carbon nanotubes [5].

There are several reports in literature concerning the development of stable CNT-based electrodes [6,7]. However, simple but effective method for the development of homogeneously and stably assembled CNT-based electrode is particularly desired for electroanalytical determinations. SWNTs-based electrodes generally are prepared by casting SWNTs suspension on conventional electrode surface [8,9] mixing SWNTs with bonds to form SWNTs paste electrode [10], or mixing SWNTs with other materials to prepare composite film modified electrode [11]. The resulting electrodes have been successfully utilized in the sensitive detection of various biological molecules such as uric acid [7], folic acid [8] and cytochrome c [9]. Generally, SWNTs-based electrodes can enhance the detection sensitivity and improve reversibility as it can promote electron transfer [6,12].

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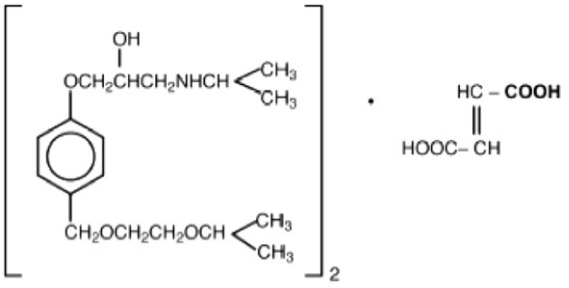
Bisoprolol fumarate (BF) is chemically described as (±)-1-(4-((2-(1-methylethoxy)ethoxy)methyl)phenoxy)-3-((1-methylethyl)amino)-2-propanol (*E*)-2-butenedioate (2:1) (salt). It is a highly selective β1 adrenoceptor antagonist. The *S* (−) enantiomer is responsible for most of the beta-blocking activity. It is effective in reducing blood pressure and has shown beneficial cardiac effects in patients with hypertension [13,14]. It has an elimination half-life of 10–12 h, which is about 50% renal and about 50% nonrenal. Pharmacokinetic profile of BF in patients with hyperthyroidism, hypertension, impaired liver function and mild renal function did not differ from healthy or younger hypertensives [15,16]. Studies reveal that bisoprolol is more effective than propanolol, atenolol and metoprolol [17].

A review of the literature revealed that few methods have been reported for the determination of bisoprolol fumarate in pharmaceutical preparations or biological samples with most of them relying on the use of chromatographic techniques. Ding et al. developed a sensitive liquid chromatography–electrospray ionization-mass spectrometry method for the determination of bisoprolol in human plasma [18]. Oniscu reported an HPLC method using liquid-phase extension and fluorescence detection to determine bisoprolol concentration in human plasma [19]. An HPLC [20] as well as RP-HPLC [21] method has been reported for bisoprolol fumarate determination and the related substances in tablets. Braza et al. described two HPLC methods with fluorimetric detection for the determination of bisoprolol in human plasma [22]. Simultaneous estimation of bisoprolol fumarate and hydrochlorothiazide in tablet dosage form was investigated using RP-HPLC method by Patel et al. [23]. However, using the above-mentioned methods, problems encountered include the need for derivatization, time-consuming extraction procedures, expensive instrumentation and running costs. Electrochemical methods have proved to be highly sensitive for the analysis of drugs in pharmaceutical formulations and human body fluids owing to the simplicity, low cost and relatively short analysis time as compared to the other routine analytical techniques including chromatography. Till date, no publications concerning the electroanalytical determination of bisoprolol fumarate in pharmaceutical formulations and biological fluids is available in the literatures. Therefore, the aim of the present investigation is to investigate the voltammetric behavior of bisoprolol in an attempt to develop a simple and reliable electrochemical method for its determination in pharmaceutical formulations and biological fluids such as human urine.



Structure of bisoprolol fumarate

2. Experimental

2.1. Reagents

Bisoprolol fumarate (BF) was obtained from Unichem Laboratories Ltd., Raigad, India, and was used as received. All solvents and chemicals were of analytical grade. The studies were carried out in the pH range 3.4–10.0 using 1.0 M phosphate buffer solution (PBS) prepared by mixing the stock solutions of Na_2HPO_4 and NaH_2PO_4, according to the method of Christian and Purdy [24]. All solutions were prepared in double distilled water.

2.2. Preparation of SWNTs-modified electrode

A 0.05 mg mL^{-1} suspension was prepared by dispersing 0.05 mg SWNTs in 1.0 mL *N*,*N*-dimethylformamide (DMF) by ultrasonic agitation. Prior to modification, the bare glassy carbon electrode (Φ = 3 mm) was first carefully polished to a mirror like surface with 50 nm alumina slurry on a polishing pad, rinsed and ultrasonicated in double distilled water for 3 min. Finally, the GCE surface was coated with 10.0 μL SWNTs suspension and allowed to evaporate DMF under an infrared lamp.

2.3. Apparatus and procedure

Differential pulse voltammetric experiments were performed using BAS (Bioanalytical systems, West Lafayette, IN, USA) CV-50W Voltammetric analyzer which was equipped with a three-electrode system incorporating a bare or modified glassy carbon electrode (GCE) (with an exposed geometry area of ca. 0.07065 cm^2) an Ag/AgCl (3 M NaCl) reference electrode (Model MF-2052 RB-5B) and a platinum wire as the counter electrode.

A stock solution of BF (1.0 mM) was prepared by dissolving the required amount of the compound in double distilled water. For recording voltammograms, aliquots of the stock solution of BF were diluted with appropriate amount of phosphate buffer of desired pH, so that the overall ionic strength of the solution became 0.50 M.

The three-electrode system was immersed in a 6 mL cell containing an appropriate amount of BF and phosphate buffer solution (pH 7.2). After accumulating for 180 s an open circuit under stirring, followed by rest for 5 s, the potential scan was initiated and cyclic voltammogram was recorded between 0.0 and +0.9 V at a scan rate of 100 mV s^{-1}. Then the modified electrode underwent successively potential scan in a blank solution for 10 cycles for reuse. After recording each voltammogram, the surface of the modified electrode was cleaned by applying a potential range from +0.9 to −0.5 V *vs.* Ag/AgCl for 40–50 s to remove any adsorbed material. This resurfacing procedure resulted in reproducible peak currents with deviation of ±4%. The optimized differential pulse voltammetry (DPV) parameters used were: sweep rate 50 mV s^{-1}, pulse amplitude 50 mV, sample width 20 ms, pulse width 50 ms, pulse period 200 ms, quiet time 2 s and sensitivity 1 mA V^{-1}.

The concentration of BF in two pure and one combination with Amlodipine besilate tablets were 2.61 mM (20 mg/20 mL) and 1.31 mM (10 mg/20 mL) in double distilled water, respectively. HPLC studies were performed on Agilent 1100 series system with C-18 reversed phase column (4.6 mm × 150 mm column). The mobile phase used for HPLC experiment was a mixture of phosphate buffer (pH 7.2): acetonitrile = 77.5:22.5 (v/v) at a flow rate of 0.6 mL min^{-1} [19] and detection wavelength 271 nm [21].

2.4. Sample preparation

Urine samples from patients undergoing treatment with BF were obtained from two volunteers. The samples were collected ~6–8 h after the administration of the 5 mg bisoprolol fumarate tablet from Zabesta. Urine samples were diluted two times with buffer of pH 7.2 prior to use for analysis.

3. Results and discussion

3.1. Voltammetric behavior of bisoprolol fumarate

The catalytic activity of the modified electrode is demonstrated in the differential pulse voltammograms (DPVs) observed for BF at the bare GCE and the SWNTs-modified GCE in 0.5 M phosphate buffer solution (pH 7.2) (Fig. 1). On scanning from 0.0 to 1.2 V, a well-defined oxidation peak at ~950 mV is obtained using the modified electrode, whereas, at the bare electrode an anodic peak cannot be observed for bisoprolol fumarate. This significant improvement of peak current together with the sharpness of anodic peak clearly demonstrate that single-walled carbon nanotubes act as an efficient electron

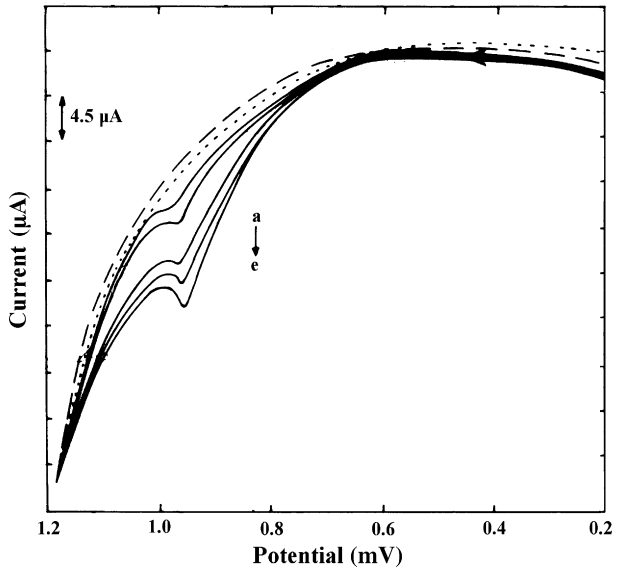


Fig. 1. Differential pulse voltammograms recorded for (i) 0.5 M phosphate buffer solution (background) at the modified electrode (–), (ii) 0.1 mM BF at pH 7.2 at bare. GCE (. . .) and (iii) increasing concentration of BF at the modified electrode (—) (curves were recorded at $a = 0.01$; $b = 0.025$; $c = 0.05$; $d = 0.075$; $e = 0.1$ mM concentration in 0.5 M phosphate buffer solution of pH 7.2).

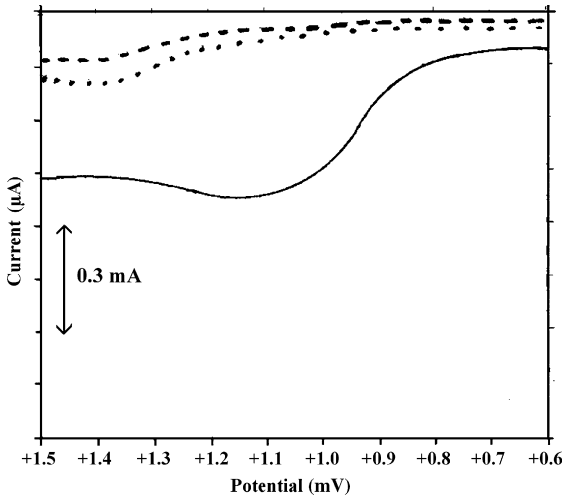


Fig. 2. A comparison of linear sweep voltammograms of 6.0 mM BF at pH 7.2 at (a) SWNTs-modified GCE (—) (b) basal plane graphite electrode (– –) and (c) edge plane graphite electrode (. . .).

mediator in the electrocatalytic oxidation of BF, leading to a considerable improvement in the analytical sensitivity.

As mentioned earlier [5], in order to check whether the electrochemical reactivity of single-walled nanotubes towards bisoprolol fumarate is due to edge-plane-like sites/defects or presence of metal impurities, linear sweep voltammogram of 6.0 mM BF at SWNTs-modified GCE is compared with that at edge-plane pyrolytic graphite (EPPG) and basal-plane pyrolytic graphite (BPPG) electrodes, as depicted in Fig. 2. Owing to fewer number of edge-plane sites, a very ill-defined anodic peak is observed at BPPG electrode. At EPPG electrode, the voltammetric response improves exhibiting an oxidation peak at ~1350 mV. However, the voltammetric response improves further when SWNTs-modified GCE is employed in BF solution under similar conditions. An oxidation peak at ~990 mV is observed with an improvement in the peak current as compared to the other two electrodes. This indicates that the observed electrocatalytic signal at the SWNTs-modified GCE is not due to edge-plane sites/defects on the SWNTs but due to the presence of significant amount of metal impurities within the nanotubes.

The quantitative determination is based on the dependence of the peak current on concentration of BF. The current values are obtained by taking the peak height at peak potential and are reported as an average of three replicate determinations. Fig. 1 depicts the differential pulse voltammograms with increasing concentration of BF in 0.5 M phosphate buffer solution (pH 7.2). From the data generated during DPV studies, it was observed that under the optimum conditions, the anodic peak current increases with increase in BF concentration (Fig. 3) and they show a linear relationship in the range from 0.01 to 0.1 mM (7.67–76.7 μg mL^{-1}). The linear regression equation is

$$i_p(\mu A) = 82.626\,C\,(mM)$$

with a correlation coefficient of 0.9789 and a sensitivity of 0.083 μA μM^{-1}. When BF concentration is increased further, the increase rate of peak current levels off and remains almost unchanged. The detection limit of BF at pH 7.2 was calculated

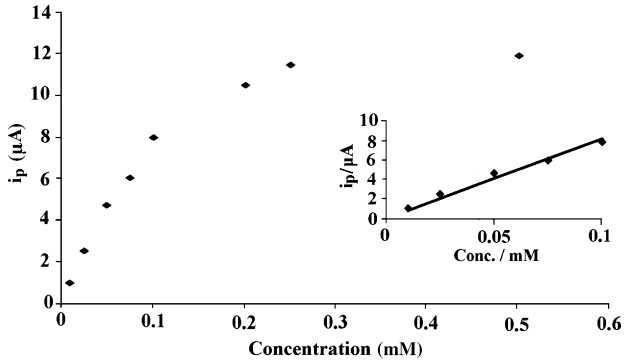


Fig. 3. Calibration curve observed for BF at SWNTs/GCE modified electrode at pH 7.2. Inset shows the plot of i_p *vs.* concentration of BF in the linear range 0.001–0.1 mM.

by using the formula $3\sigma/b$, where σ is the standard deviation of the blank and b is the slope of the calibration curve. The detection limit of the standard solution of BF is 8.27×10^{-7} M. The limit of quantification is found to be 2.75×10^{-6} M.

3.2. Effect of pH

The pH of the supporting electrolyte has a significant influence on the electrooxidation of BF at the modified electrode. The electrooxidation of BF was studied over pH range 3.4–10.0 in PBS. The potential of the oxidation peak shifted to less positive potential with increase in pH as depicted in Fig. 4. The peak potential (E_p) *vs.* pH plot was linear and the dependence of the peak potential on pH can be expressed by the following relation:

$$E_p = [1418.4 - 56.453\ \text{pH}]\ \text{mV}\ \textit{vs.}\ \text{Ag/AgCl}$$

having correlation coefficient ~0.9795. The observed slope of ~56 mV/pH clearly indicates that equal number of electrons and protons are involved in the electrode reaction.

3.3. Effect of sweep rate

The effect of sweep rate (υ) on peak potential (E_p) and peak current (i_p) of BF was studied in the sweep range 5–50 mV s^{-1} at pH 7.2 at SWNTs/GCE modified electrode. The plot of $i_p/\upsilon^{1/2}$ *vs.* log υ indicated an increase in peak current with an increase in sweep rate confirming that the electrode surface has some

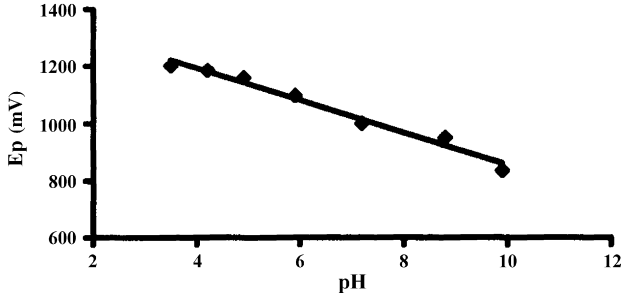


Fig. 4. Observed dependence of peak potential (E_p) on pH for BF at SWNTs/GCE modified electrode.

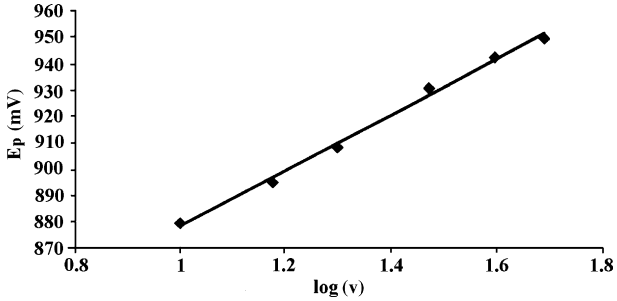


Fig. 5. Plot of E_p *vs.* logarithm of sweep rate of BF at pH 7.2.

adsorption complications. Also, the plot of peak potential (E_p) *vs.* logarithm of scan rate (Fig. 5) was linear and is expressed as

$$E_p\ (\text{mV}) = 774.03 + 105.12\ (\log\ \upsilon)$$

with a correlation coefficient of 0.9957 and this behavior was consistent with the EC nature of the reaction in which the electrode reaction is coupled with an irreversible follow-up chemical step [25]. Since the structure of bisoprolol is very much similar to atenolol, it is likely to assume that it follows a similar electrooxidation mechanism [26]. Thus, the most probable electrooxidation pathway for bisoprolol seems to be the subsequent oxidation of the secondary alcoholic group to give the corresponding ketone.

3.4. Validation of the method

Validation of the proposed method for the quantitative assay of the drug was examined via evaluation of the specificity, stability, recovery and precision of the method.

3.4.1. Specificity

The specificity of the optimized procedure for the assay of BF was investigated by observing any interference encountered from endogenous substances present in complex matrices such as biological fluids (e.g. urine and plasma), which may affect the specificity of the proposed method. The effect of the interferents (viz. uric acid, ascorbic acid, dopamine, serotonin and glucose) was examined by carrying out the determination of 0.01 mM BF in the presence of different concentrations of the interferents. The tolerance limit was defined as the concentrations of foreign substances, which gave an error less than ±5.0% in the detection of the drug. The study showed that none of the interferents caused a positive or a negative error greater than 5% indicating that the above method can be safely applied to assay BF in biological fluids and the method can be considered specific.

3.4.2. Recovery test

To study the accuracy of the proposed method, recovery experiments were carried out by standard addition method. The recovery test of BF was performed in the range 7.67–38.35 μg mL^{-1}. The results observed are listed in Table 1. The recoveries varied in the range from 97.0 to 103.0% and the relative standard deviation (R.S.D.) was 2.63%.

Table 1
Recovery test of BF at SWNTs-modified glassy carbon electrode

Added (mM)	Found (mM)	Recovery (%)
0.010	0.0098	98.0
0.020	0.0195	97.5
0.030	0.0309	103.0
0.040	0.0388	97.0
0.050	0.0513	102.6

3.4.3. Stability and reproducibility of the modified electrode

The long-term stability of SWNTs-modified GCE was investigated by measuring the current response at a fixed BF concentration of 0.01 mM over a period of 15 days. The modified electrode was used daily and stored in air. The experimental conditions show that the current response only deviates by 2.3%, suggesting that the SWNTs-modified glassy carbon electrode possess good stability for the determination of BF.

The intra-day precision of the method was evaluated by repeating six experiments on the same day and in the same solution of 0.01 mM BF. A R.S.D. value of 0.79% was obtained. To evaluate the inter-day precision, the response of the modified electrode was examined for six consecutive days for same concentration of BF solution. The relative standard deviation value was found to be 1.08%. The electrode-to-electrode reproducibility of the proposed method was examined on four SWNTs-modified glassy carbon electrodes constructed individually and the R.S.D. of the four average peak currents of 0.01 mM BF was calculated to be 1.92%, which demonstrates the good reproducibility of the method at the modified electrode.

The analytical characteristics observed during validation of the proposed method were then compared with those obtained in earlier reported methods in Table 2.

3.5. Analytical applications

3.5.1. In commercial samples

In order to evaluate the applicability of the proposed method, three commercial samples in combination or in pure form containing bisoprolol viz. Concor 5/10 (Merck Ltd.; pure), Zabesta (USV Ltd.; pure) and Concor AM 5 (Merck Ltd.; combination with Amlodipine Besilate) were studied. The tablets were dissolved in water and then further diluted so that the concentration of bisoprolol was in the working range. Following the proposed method the concentration of bisoprolol in the three pharmaceutical preparations was determined. Results summarized in Table 3 show that the content for all assayed tablets falls within the claimed amount indicating the good agreement with the proposed voltammetric method.

Table 3
Determination of BF in pharmaceutical preparations using SWNTs/GCE modified electrode

Sample	Stated content (mg/tablet)	Detected content (mg/tablet)	R.S.D. (%) ($n = 3$)
Concor (pure)	10.00	9.46	0.95
Concor (combination with Amlodipine besilate)	5.00	4.82	1.21
Zabesta	5.00	4.16	0.86

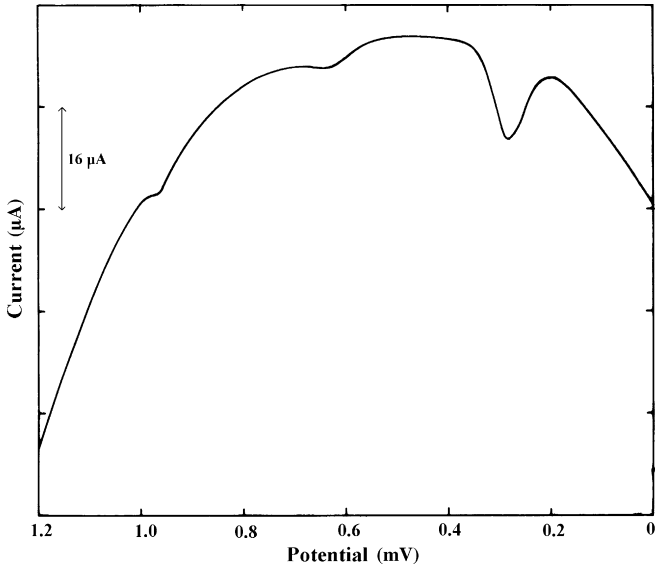


Fig. 6. Observed differential pulse voltammogram of human urine sample no. 1 at pH 7.2 at the modified electrode.

3.5.2. In human urine samples

The modified electrode was applied to the determination of bisoprolol in human urine samples of the patients undergoing treatment with BF, its concentration was determined in the samples after 6–8 h of administration of single dose of Zabesta tablet. Prior to their analysis, the samples were diluted two times with pH 7.2 PBS. A typical DPV of the urine sample at SWNTs/GCE is depicted in Fig. 6. A well-defined peak of BF at SWNTs/GCE

Table 2
Comparison of the SWNTs-modified glassy carbon electrode with the reported methods for the determination of BF

Sr. no.	Ref. no.	Working concentration range of BF (M)	Limit of quantitation (M)	Interference study	Precision (%)	Precision average recovery (%)
1	[18]	6.5×10^{-11}–1.6×10^{-7}	6.5×10^{-11}	Yes	>7.50	91.1
2	[19]	3.9×10^{-8}–2.6×10^{-7}	–	No	>8.00	72.0
3	[20]	3.3×10^{-5}–3.9×10^{-4}	3.3×10^{-5}	No	–	–
4	[21]	2.6×10^{-4}–1.30×10^{-3}	2.6×10^{-4}	No	–	99.9
5	[22]	8.2×10^{-9}–2.6×10^{-7}	–	No	>15.00	98.0
6	[23]	1.3×10^{-5}–1.9×10^{-4}	1.1×10^{-5}	Yes	>1.85	–
7	Proposed method	1.0×10^{-5}–1.0×10^{-4}	2.75×10^{-6}	Yes	>2.30	99.6

Table 4
A comparison of observed concentration of BF in human urine after 6–8 h of BF oral administration at SWNTs/GCE modified electrode and by using HPLC

Urine sample	Observed concentration (mM) as determined by	
	SWNTs-modified GCE	HPLC
1	0.021 (1.02%)	0.018 (2.31%)
2	0.028 (0.78%)	0.027 (2.94%)

The values in brackets represent the relative standard deviation for n determinations; $n = 3$.

was observed at ~975 mV. Although two other voltammetric peaks at ~290 and ~640 mV, estimated to be due to the presence of uric acid and serotonin, respectively, are also observed, they do not interfere in the determination of BF. Using the proposed method described above, the results obtained are tabulated in Table 4.

Since bisoprolol has not been determined using voltammetric method to the best of our knowledge, it was considered worthwhile to cross-validate the results of voltammetric determination with HPLC analysis. For this purpose various concentrations of BF were analyzed using HPLC and a well-defined peak was obtained at $R_t \sim 3.519$ min. The peak area under the peak was calculated. The calibration curve was obtained by plotting the peak area ratio of the analyte peaks relative to that of the internal standard (11.5 μg L^{-1}) against the analyte concentration.

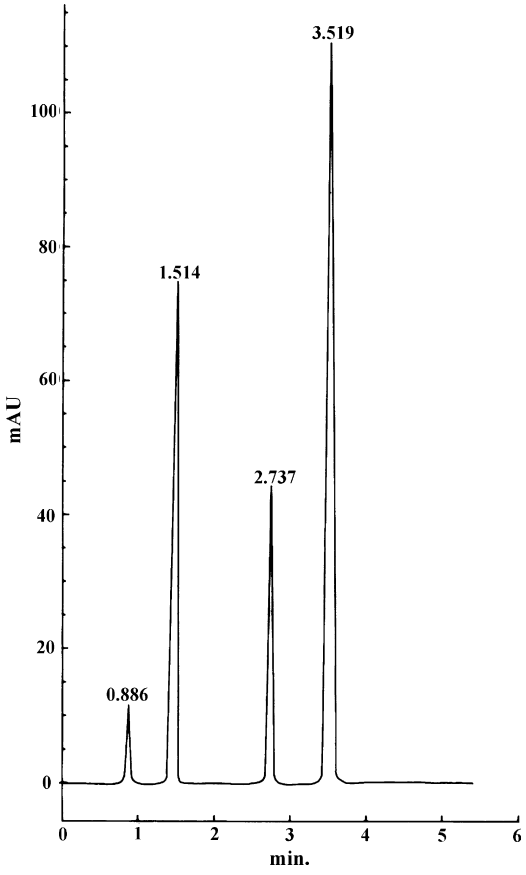


Fig. 7. A typical HPLC chromatogram observed for human urine sample of patient undergoing treatment with bisoprolol fumarate. The peak at $R_t \sim 3.519$ is due to BF.

The resulting calibration plot was linear. Finally, the concentration of BF in the urine samples was determined. Fig. 7 shows a typical HPLC chromatogram observed for human urine sample after 6 h of administration of bisoprolol fumarate tablet. Four peaks are obtained of which the peak at $R_t \sim 3.519$ min is of bisoprolol whereas the other three peaks are most probably due to the presence of bisoprolol metabolites in the urine sample. A comparison of BF values obtained by HPLC and proposed method (as listed in Table 4) clearly indicated that the results obtained by two methods are in good agreement.

4. Conclusion

The proposed methodology provides a very sensitive and selective method of BF analysis using SWNTs/GCE modified electrode. SWNTs-modified GCE allowed the successful determination of BF with a detection limit of 8.27×10^{-7} M. The anodic peak current varies linearly under optimized conditions in the concentration range from 0.01 to 0.1 mM. The results obtained are promising and demonstrate the utility of the developed method for the determination of BF content in biological fluids as well as pharmaceutical formulations. A comparison of the proposed method with some earlier reported ones is presented in Table 2. As can be seen, the limit of quantitation of the proposed method is higher to chromatographic methods [18,19,22]. However, in these methods BF has been determined in human plasma, whereas, in the present work BF has been determined in biological fluid (human urine), where nearly 60% of unchanged bisoprolol is excreted as well as in BF tablet dosage forms. The specificity of the voltammetric method was also investigated in the presence of substances present in complex matrices. The precision and recovery of the proposed method is far superior to those given in earlier methods [18,19,22]. Thus, present investigation revealed that the proposed method is simple, specific, sensitive and effective for the determination of bisoprolol fumarate at SWNTs-modified glassy carbon electrode in pharmaceutical formulations as well as biological fluids such as human urine.

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