Electroanalysis of cardioselective beta-adrenoreceptor blocking agent acebutolol by disposable graphite pencil electrodes with detailed redox mechanism

Atmanand M. Bagoji, Shreekant M. Patil and Sharanappa T. Nandibewoor

Cogent Chemistry (2016), 2: 1172393
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Abstract: A simple economic graphite pencil electrode (GPE) was used for analysis of cardioselective, hydrophilic-adrenoreceptor blocking agent, acebutolol (ACBT) using the cyclic voltammetric, linear sweep voltammetric, differential pulse voltammetric (DPV), and square-wave voltammetric (SWV) techniques. The dependence of the current on pH, concentration, and scan rate was investigated to optimize the experimental condition for determination of ACBT. The electrochemical behavior of the ACBT at GPE was a diffusion-controlled process. A probable electro-redox mechanism was proposed. Under the optimal conditions, the anodic peak current was linearly proportional to the concentration of ACBT in the range from 1.00 to 15.0 μM with a limit of detection 1.26 × 10⁻⁸ M for DPV and 1.28 × 10⁻⁸ M for the SWV. This method was applied for quantitative determination of the ACBT levels in urine as real samples. The obtained recovery ranges for ACBT in urine were from 95.4 to 101% as found by the standard addition technique. Further interference study was also carried with some common interfering substances.

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PUBLIC INTEREST STATEMENT

This work demonstrates electroanalysis of acebutolol by disposable graphite pencil electrodes with detailed redox mechanism where green chemistry involved. Acebutolol drug is analyzed by highly sensitive voltammetric techniques. The proposed method is simple, sensitive, and accurate. The method has the advantage that no prior extraction or clean-up procedure is required. The obtained detection limits using proposed method were comparable and improved to that reported by earlier methods. This allows the determination of acebutolol in biological fluids at levels found after drug administration at normal doses. The present method could possibly be adopted for the pharmacokinetic studies as well as for quality control laboratories.
1. Introduction

Graphite pencil electrodes (GPEs) have been successfully applied to the advanced voltammetry by virtue of its high electrochemical reactivity once they attain suitable potential, good mechanical rigidity, low cost, and low technology (Demetriades, Economou, & Voulgaropoulos, 2004; Gao, Song, & Wu, 2005; Karadeniz et al., 2003). Low-tech disposable GPE is extremely inexpensive and provides attractive electrochemical features compared to high-tech carbon electrodes (Saleh, Askal, Refaat, Naggar, & Abdel-aal, 2016). GPEs offer a renewable and selective surface, which is simpler and faster than polishing procedures that were common with conventional solid electrodes such as glassy carbon and gold electrode. Hence, GPEs produce good reproducibility for the individual surfaces (Wang, Kawde, & Sahlin, 2000).

β-adrenoceptor blocking agents namely acebutolol, atenolol, betaxolol, bisoprolol, epanolol, propranolol, etc., are greatly used for the treatment of cardiovascular diseases such as arterial hypertension, coronary heart disease, supraventricular and ventricular tachyarrhythmias (Baker, 2005). They also find applications in hypotensive circulatory disorders, the hyper kinetic heart syndrome, tremor, migraine, portal hypertension, hyperthyroidism, anxiety, and psychosomatic disorders or glaucoma (Borchard, 1998). Acebutolol shown in Scheme 1 is a cardioselective, lipophilic β-adrenoreceptor blocking agent with mild intrinsic sympathomimetic activity (Manjunatha et al., 2008). It is therefore more suitable than non-cardioselective β-blockers. It is marketed in tablet form for oral administration (Al-Ghamdi, Hefnawy, Al-Majed, & Belal, 2012).

Various analytical methods have been reported in the literature concerning with the determination of acebutolol both in pharmaceutical formulations and biological fluids. These techniques comprise liquid chromatography (LC) (Szymura-Oleksiak, Walczak, Bojarski, & Aboul-Enein, 1999), mass spectrometry (MS) (Bussy, Ferchoud-Roucher, Tea, Krempf, & Silvestre, 2012), capillary electrophoresis (Li, Zhu, & You, 2011), spectrophotometry (Abdellatef, El-Henawee, El-Sayed, & Ayad, 2006), spectrofluorimetry (El Dawya, Mabrouk, & El Barbary, 2006), and thin layer chromatography (El-Gindy, Ashour, Abdel-Fattah, & Shabana, 2001). A high-throughput LC–MS/MS bioanalytical method was developed and validated for the simultaneous determination of acebutolol and its active metabolites in human plasma (Jiang, Randlett, Junga, Jiang, & Ji, 2008). Electrochemical technique such as square-wave adsorptive stripping voltammetry (SW-AdSV) (Al-Ghamdi et al., 2012) has been employed for determination of acebutolol. Since most of these methods required expensive equipment and special treatment, it is necessary to develop a new technique that is easy to use, saves time, has low cost, low detection limit, high accuracy, and wide concentration range. This study deals with the electrochemical behavior of acebutolol and the demonstration of the usefulness of a low-cost GPE for the electroanalysis of ACBT using cyclic voltammetric (CV), linear sweep voltammetric (LSV), differential pulse voltammetric (DPV), and square wave voltammetric (SWV) techniques. To the best of our knowledge, this work is the first report describing a voltammetric method using a GPE for the determination of ACBT considerably at low-level concentrations. The proposed method is a highly sensitive, simple, fast, economic, and accurate with lower detection limit for the determination of ACBT in urine samples.

Scheme 1. Chemical structure of acebutolol.

O
H
N
O
200x111
200x104
O
240x81
O
270x64
N
270x57
H
250x52
OH
240x116
O
2. Experimental

2.1. Instrumentation
With the aid of a CHI630D Electrochemical Analyser (CH Instruments Inc., USA), cyclic, linear sweep, differential pulse, and square-wave voltammetric curves at GPE were recorded. The voltammetric measurements were carried out in a 10-ml single compartment of three electrode cell with the Ag/AgCl (3 M KCl) as reference electrode, a platinum wire as the auxiliary electrode and GPE as a working electrode. The pH values of solutions were measured using an Elico L1120 pH meter (Elico Ltd., India).

2.2. Reagents and chemicals
Acebutolol was purchased from Sigma Aldrich, India. The phosphate buffers from pH 3.0–10.4 were prepared in Millipore water (Christian & Purdy, 1962). All reagents were of analytical grade and prepared using deionized water from a Milli-Q (Millipore, Bedford, USA) device. The GPEs were (HB 0.5 mm in diameter and 6 cm length) from a local book store.

2.3. Voltammetric measurements
The GPE in the three-electrode system was immersed in 0.2 M phosphate buffer (pH 7.0) containing a known amount of ACBT. Then, CV, LSV, DPV, and SWV were performed. The common parameter for CV was at scan rate of 100 mV s\(^{-1}\). The parameters for DPV and SWV were initial potential \(E_0\): 0.70 V; final potential \(E_f\): 1.0 V; sample interval: 0.001 V; frequency: 15 Hz; quiet time: 2 s; sensitivity: \(1.0 \times 10^{-5}\) A V\(^{-1}\); differential pulse and square-wave with amplitude of 50 mV and 25 mV, respectively; \(E_{step}\) 4 mV and 6 mV for SWV and DPV, respectively; voltammograms were recorded with the phosphate buffer in the absence of ACBT also.

2.4. Preparation of CPE and calibration of the GPE
The conventional carbon paste electrode (CPE) was prepared by hand mixing of graphite powder with paraffin at a ratio 70/30(w/w) in a mortar. The homogeneous paste was packed into a cavity of Teflon tube, the electrical contact was made with a copper wire connected to the paste in the tube.

The actual surface area of an electrode where electron exchange takes place is obtained by the CV method using 1.0 mM K\(_3\)Fe(CN)\(_6\) as a probe at different scan rates. For a reversible process, the following Randles–Sevcik formula was used (Rezaei & Damiri, 2008)

\[
I_{pa} = (2.69 \times 10^5)n^{3/2}A_0D_0^{1/2}C_0^{1/2}ν^{1/2}
\]

(1)

where \(I_{pa}\) refers to the anodic peak current, \(n\) is the number of electrons transferred, \(A_0\) is the surface area of the electrode, \(D_0\) is diffusion coefficient, \(ν\) is the scan rate, and \(C_0\) is the concentration of K\(_3\)Fe(CN)\(_6\). For 1.0 mM K\(_3\)Fe(CN)\(_6\) in 0.1 M KCl electrolyte, \(n = 1, D_0 = 7.6 \times 10^{-6}\) cm\(^2\) s\(^{-1}\). The pencil electrodes have configuration of 0.05 cm diameter and 6 cm length. About 0.25 cm length was inserted into the sample by coating remaining surface with Teflon. The geometrical area was found to be 0.353 cm\(^2\) which is nearly coincided with active surface area 0.299 cm\(^2\) calculated from the slope of the plot of \(I_{pa}\) vs. \(ν^{1/2}\) (Equation 1). The surface area of the CPE was found to be 0.0412 cm\(^2\). Electroactive area of GPE was higher than the CPE. Hence, greater response of peak current was observed for GPE toward ACBT.

3. Results and discussion

3.1. Voltammetric behavior of ACBT at GPE
The ability of the GPE to oxidize ACBT was investigated in phosphate buffer of pH 7. It can be seen that ACBT showed reproducible cyclic voltammograms bearing two anodic peaks and one cathodic peak (Figure 1, curve II). For quasi-reversible redox pair, anodic peak \(A (E_{pa1})\) was at 542 mV and cathodic peak \(A (E_{pc})\) was at 321 mV, the peak-to-peak separation (Δ\(E = E_{pc} - E_{pa}\)) was 221 mV which was greater than 59 mV expected for reversible process. Further, from the variation of ΔE values with the potential scan rate, shown in SI Table 1 and from the behavior of the ratio \(|I_{pc}/I_{pa}|\) for the redox pair,
0.856 ≈ 1, one may conclude that the ACBT electrochemical oxidation at GPE is a quasi-reversible mass transfer-controlled process (Chandra, Kumar Swamy, Gilbert, & Sherigara, 2010). Hence, peak A was quasi-reversible, whereas second peak B was completely irreversible. Thus, there might be a coupled chemical reaction (Corona-Avendaño et al., 2007). Since, second peak B was more intense than first peak A, peak B was considered for further experiments. GPE had no electrochemical activity in phosphate buffer solution (Figure 1, curve I) suggesting the redox peaks in curve II (Figure 1) were undoubtedly assigned to ACBT. The voltammogram corresponding to first scan was generally recorded. The electrochemical behavior of ACBT at mercury drop electrode yielded one oxidation peak (Al-Ghamdi et al., 2012). But, GPE produced well-defined voltammogram with two oxidation peaks and one cathodic peak. GPE can be a good electrode for the ACBT determination compared to mercury drop electrode.

### 3.2. Influence of pH

In order to systematically study how the pH affects electrochemical redox behavior of ACBT at GPE, phosphate buffer with varying pH has been employed. The influence of pH on the redox peak currents of ACBT was studied in the pH range from 3.0 to 10.4 (SI Figure 1a). The formal standard potential \( E^0 \) of ACBT was pH-dependent, SI Figure 1b shows the effect of pH on the formal standard potential \( E^0 = (E_{pa} + E_{pc})/2 \) of the electrode which gave two linear segments with slope of −63 mV/pH and −37 mV/pH in the pH range of 3.0–7.0 and 7–10.4, respectively, for quasi-reversible couple. It is known that the slope values of the linear fragments are determined using the equation of

\[
dE_{pa}/dpH = (-2.303mRT)/nF
\]

(2)

here \( m \) and \( n \) are the number of protons and electrons involved in the redox reactions, respectively (Zare & Nasirizadeh, 2011). Therefore, the slope value in the pH ranges of 3.0–7.0 (−63 mV) showed that the theoretical value of −59 mV/pH was in good agreement with \( n = m \). Further, with increase in the pH of the solution, the second anodic peak potential linearly shifted to less positive values and the linear relation between \( E_{pa2} \) and pH (SI Figure 1c) can be expressed as

\[
E_{pa2}(V) = 0.050pH + 1.258 \quad (r = 0.997)
\]

(3)

The ratio of \( m/n \) at this electrode was 0.902 ≈ 1, suggesting that the equal number of electrons and protons was involved in the reaction corresponding to second anodic peak. Variation in peak current with pH of the solution is shown in SI Figure 1d, which indicates that pH 7 gives a well-defined and more intense voltammogram. Hence, phosphate buffer of pH 7, which is a biological pH, was selected for further experiments.

### 3.3. Influence of scan rate

Valuable information involving an electrochemical mechanism generally can be acquired from the relationship between peak current and scan rate. Therefore, voltammetric behavior of ACBT at
different scan rates was studied using LSV. This study was carried to assess whether the process on GPE was under diffusion controlled or adsorption controlled. These experiments were conducted in phosphate buffer of pH 7. SI Figure 2a shows a series of linear sweep voltammograms for ACBT in 0.2 M phosphate buffer over a range of scan rates from 50 to 500 mV s\(^{-1}\).

The plot of logarithm (scan rate) on the logarithm (peak current) showed a linear relationship in the range from 50 to 500 mV s\(^{-1}\) (SI Figure 2b) for the second anodic peak with slope 0.438 \(\approx\) 0.5 which is a typical of diffusion-controlled process (Gowda & Nandibewoor, 2014) and linear equation is as follows:

\[
\log I_{pa}(A) = 0.438 \log v(Vs^{-1}) + 0.395 \quad (r = 0.986)
\]  

(4)

With increase in the scan rate, peak potential shifted toward more positive values, a linear relationship between peak potential and logarithm of scan rate was observed in the range 50–500 mV s\(^{-1}\) as shown in SI Figure 2c. The linear equation can be expressed as:

\[
E_p(V) = 0.050 \log v(Vs^{-1}) + 0.885 \quad (r = 0.993)
\]  

(5)

\[E_p\] of peak B can be defined using Laviron (1979) Equation (6),

\[
E_p = E^0 + \left[ \frac{2.303RT}{nF} \right] \log \left[ \frac{RTk^0}{nF} \right] + \left[ \frac{2.303RT}{anF} \right] \log v
\]  

(6)

where \(\alpha\) is the transfer coefficient, \(k^0\) is the standard heterogeneous rate constant of the reaction, \(n\) is the number of electrons transferred, \(v\) is the scan rate, and \(E^0\) is the formal standard redox potential. Other symbols have their usual meaning. Thus, value of \(\alpha n\) can be easily calculated from the slope of \(E_p\) vs. \(\log v\) plot. In this system, the slope was 0.050, taking \(T = 298\) K, \(R = 8.314\) J K\(^{-1}\) mol\(^{-1}\), and \(F = 96480\) C mol\(^{-1}\), the \(\alpha n\) value was calculated to be 1.182. According to Bard and Faulkner (2006)

\[
\alpha = \frac{47.7}{(E_p - E_{p/2})} \quad \text{mV}
\]  

(7)

where \(E_{p/2}\) is the potential value when the current is at half the peak value. So, from this value, the value of \(\alpha\) was found to be 0.6344. Therefore, the number of electrons (\(n\)) transferred in electro-oxidation of ACBT was calculated to be 1.883 \(\approx\) 2. Further, the value of \(k^0\) can be determined from the intercept of the plot of \(E_p\) vs. \(\log v\) (Equation 5) if the value of \(E^0\) is known. The value of \(E^0\) in equation can be obtained (Wu, Ji, & Hu, 2004) from the intercept of \(E_p\) vs. \(v\) curve (SI Figure 2d) by extrapolating to the
vertical axis at \( v = 0 \) and \( E^0 \) obtained was 0.895 V. The heterogeneous rate constant \( k^0 \) for irreversible process was calculated to be \( 4.6 \times 10^{-1} \) s\(^{-1} \). Further, the number of electrons transferred in quasi-reversible electrode process was found to be 1.0 using the formula,

\[
E_p - E_{p/2} = \frac{59}{n} \text{ mV}
\]

(8)

3.4. Proposed mechanism

In order to depict the reaction pathway and to identify the oxidized product, the electrolysis was carried out for two and a half hour for complete oxidation using \( 1.0 \times 10^{-3} \) M ACBT in phosphate buffer as supporting electrolyte at GPE. The redox mechanism of ACBT was involved a coupled chemical reaction. As for quasi-reversible redox pair (peak A), ACBT (I) undergoes oxidation with loss of a hydrogen molecule to form (II) and in reverse reaction, addition of a hydrogen molecule to form starting compound (I) (Scheme 2 (i)). But for peak B, the irreversible process involves transfer of two electrons. Thus, the electrochemical mechanism was proposed for this irreversible process as shown in Scheme 2 (ii). The literature survey reveals that aromatic ether cleavage reactions were already been observed for other compounds (Lohmann & Karst, 2009; Madsen, Olsen, Skonberg, Hansen, & Jurva, 2007). With this basic hypothesis, the electrochemical cleavage of aromatic ether of ACBT (I) would be initiated by the loss of one electron to form the radical molecule as intermediate which upon addition of water molecule leads to the formation of two species (III) and 3-(isopropylamino)propane-1,2-diol (IV) on O-dealkoxylation which is in accordance with a similar mechanism already proposed to explain the aromatic ether alkyl cleavage of butylated hydroxyanisole (3-tert-butyl-4-hydroxyanisole) (Bussy et al., 2012). The second oxidation step takes place by loss of one electron to form the radical compound (V). Further, the final product N-(3-acetyl-4-oxocyclohexa-2,5-dienylidene)butyramide (VI) was formed by the loss of a
hydrogen molecule. The final products were confirmed by ESI-Mass spectrum (Figure 2) which shows the m/z value 219 assigned to the product (VI) and the 133 m/z value of the product (IV).

3.5. Analytical applications

The differential pulse and SWV modes were selected in order to develop a voltammetric method for determining the ACBT, since the peaks are sharp and better defined at lower concentrations of ACBT than those obtained by cyclic voltammetry, with a lower background current, resulting in improved resolution. The proposed method on GPE offered well-defined concentration dependence. Figure 3 presents DPV voltammograms obtained by successive addition of ACBT over the 1–17 μM concentration range. The peak current at a potential of +0.855 V increased proportionally with the ACBT concentration (Figure 3 inset) to yield a highly linear calibration plot,

\[ I_{pa} = 0.478[ACBT] + 4.611 \quad (r = 0.994) \]  

(9)

The sensitivity of the proposed method was evaluated by both the limit of detection (LOD) and limit of quantification (LOQ) values. The LOD and LOQ were calculated using the following equations (Patil, Sataraddi, Bagoji, Pathan, & Nandibewoor, 2014):

\[ \text{LOD} = 3 \, s/m \quad \text{LOQ} = 10 \, s/m \]  

(10)

where \( s \) is the standard deviation of the peak current of (five runs) of the lowest concentration of the linearity range (1 μM) and \( m \) is the slope of the calibration equation. LOD and LOQ were
calculated as $1.26 \times 10^{-8}$ M and $4.18 \times 10^{-8}$ M, respectively. Similarly, for SWV (Figure 4), obtained LOD and LOQ were $1.28 \times 10^{-8}$ M and $4.27 \times 10^{-8}$ M, respectively. From the above data, it is cleared that DPV produced sensitive and advanced tool to determine the ACBT at a very low level with intercept 4.61 of calibration plot smaller than that of SWV (7.24). Thus, DPV was employed for further experiments. The LOD and linearity range values of some reported methods (Al-Ghamdi et al., 2012; Pospíšilová, Kavalírová, & Polášek, 2005) and present method are given in Table 1. The LOD and linearity range values found by the present method are better compared to the reported work, which indicates the superiority of the proposed method.

### 3.6. Reproducibility and selectivity

In order to study repeatability of the electrode for ACBT oxidative determination, a 1.0 mM ACBT solution and the same electrode (renewed every time) were used for every several hours within a day and the R.S.D. of the peak currents of five successive measurements was 3.01%. The reproducibility between days was similar to that of within day repeatability.

### 3.7. Study of interferences

Excipients are formulated alongside active ingredients of medicines to grant therapeutic enhancement on the active part of the medicine. So, it is important to study the effect of excipients on the electrocatalytic oxidative determination of ACBT. In order to investigate the effect of co-formulated substances such as glucose, starch, sucrose, etc., on the voltammetric response of ACBT, DPV experiments were carried out for 1.0 μM ACBT in the presence of 1.0 mM of each of the interferents. The results are listed in Table 2. It was observed that 1,000-fold excess concentrations of glucose, starch, sucrose, citric acid, magnesium stearate, talc, and oxalic acid did not interfere, whereas glucose interfered. Thus, the method was able to assay ACBT in the presence of excipients except glucose; hence, it can be considered specific.

### Table 1. Comparison of linear range and detection limits for ACBT with different classical methods

| Method                        | Linearity range (μM) | LOD (μM) | Reference                          |
|-------------------------------|----------------------|----------|------------------------------------|
| Mercury drop electrode        | 0.500–6.00           | 0.500    | Al-Ghamdi et al. (2012)            |
| Analytical capillary isotachophoresis | 0.380–3.80       | 0.110    | Pospíšilová et al. (2005)         |
| Pencil graphite electrode     | 1.00–15.0            | 0.0126   | Present work                       |

### Table 2. Influence of potential interferents on the voltammetric response of 1.0 μM ACBT while each interferent kept at 1.0 mM

| Interferents    | Peak current (μA) | Signal changea (%) |
|-----------------|-------------------|--------------------|
| Acebutolol      | 5.27              | 0                  |
| Citric acid     | 5.36              | +1.76              |
| Dextrose        | 5.36              | +1.76              |
| D-Glucose       | 5.54              | +5.23              |
| Gum acacia      | 5.267             | −0.0580            |
| Oxalic acid     | 5.262             | −0.157             |
| Starch          | 5.34              | +1.30              |
| Sucrose         | 5.45              | +3.40              |

aAverage of five determinations with % error (signal change).
3.8. Determination of ACBT in urine samples

The proposed method was successfully applied for the determination of ACBT in urine samples as real sample using DPV. No tedious extraction or filtration procedures have been applied during sample preparation and only dilution of aliquot from the supernatant layer with the supporting electrolyte (0.2 M PBS pH 7.0) is required before measurement. The obtained recovery ranges for ACBT in urine were from 95.4 to 101% as found by the standard addition technique (Table 3). Good recovery values denote better selectivity and sensitivity of the method. The statistical calculations for the assay results indicated good precision for the DPV method.

4. Conclusions

The GPE was successfully applied to the electrochemical characterization and electroanalytical determination of ACBT at extremely low concentrations by CV, DPV, and SWV techniques. The proposed method is simple, sensitive, and accurate. As applied to real samples, the method has the advantage that no prior extraction or clean-up procedure is required. The detection limit for DPV and SWV were 1.26 × 10⁻⁸ M and 1.28 × 10⁻⁸ M, respectively. The proposed method gave better LOD compared to earlier reported methods. This allows the determination of ACBT in biological fluids at levels found after drug administration at normal doses. The present method could possibly be adopted for the pharmacokinetic studies as well as for quality control laboratories.

Table 3. Determination of ACBT in urine samples

| Sample | Spiked (μM) | Found* (μM) | Recovery (%) | SD ± RSD (%) |
|--------|-------------|-------------|--------------|--------------|
| Sample 1 | 1.00 | 0.985 | 98.5 | 0.0184 ± 2.56 |
| Sample 2 | 3.00 | 2.93 | 97.5 | 0.0589 ± 2.26 |
| Sample 3 | 5.00 | 4.77 | 95.4 | 0.0314 ± 6.77 |
| Sample 4 | 7.00 | 7.14 | 101 | 0.00420 ± 0.0586 |

*Average of five measurements.
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