Electrochemical Study of Gliclazide and Its Complexation with β-Cyclodextrin

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Abstract
The electrochemical oxidation of gliclazide has been investigated at glassy carbon electrode in phosphate buffer solutions over the pH range 2.7–11.8 using cyclic and differential pulse voltammetry (DPV). Gliclazide exhibited one anodic peak in the pH range of 2.7–6.3 and a second peak was produced above pH 6.3. The oxidation processes have been shown to be irreversible and diffusion controlled. The formation of an inclusion complex of gliclazide with β-cyclodextrin (β-CD) has been investigated by cyclic and differential pulse voltammetry. A phase solubility study with spectrophotometric detection has been also applied. The stability constant of the complex was determined to be 839 and 360 M^{-1} using the differential pulse voltammetric method and the phase solubility method, respectively.

Keywords: Cyclodextrins, Gliclazide, Inclusion compounds, Phase solubility study, Voltammetry

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1 Introduction

Amongst the many analytical techniques available, electrochemical methods have received considerable attention in the field of host-guest interactions for the past few years and an increased number of papers have been dedicated to their applications especially in the development of chemical sensors. Fullerene C_{60} is one of the host molecules that have recently been widely used as an electrode modifier exhibited a strong catalytic function towards the reduction of dexamethasone [1], the oxidation of dopamine [2] and employed for the simultaneous voltammetric determination of adenosine and guanosine [3] as well as uric acid [4]. A pyrolytic graphite electrode (PGE) to study the electrochemical oxidation of 2,3-dideoxyadenosine [5], single-wall carbon nanotubes pyrolytic graphite electrode (PGE) for the simultaneous determination of adenosine and inosine using Osteryoung square wave voltammetry (OSWV) [6] and an edge plane pyrolytic graphite electrode (EPPGE) modified with single-wall carbon nanotubes (SWNTs) for the determination of triamcinolone have been also reported [7]. Macrocycle compounds are also class of host molecules that have been used in the preparation of electrochemical ion sensors such as tetrapyrazole macrocycles and calix[4]arene derivatives in the preparation of Pb^{2+} selective sensor [8], 4-*tert*-butylcalix[6]arene (I) used as an ion active material in poly(vinyl chloride) (PVC) based matrix for preparation of uranyl selective sensors [9], 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene diperchlorate, 3,5,7,7,10,12,14,14-octamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene diperchlorate and 5,10,15,20-tetraphenylporphyrin, as sensor materials for the determination of Cobalt(II) Ions [10]. Cyclodextrin is among such hosts that comprise a family of cyclic oligosaccharides known to form noncovalent inclusion complexes with many substances especially with hydrophobic drug molecules. Therefore, many papers have been devoted to the use of electrochemical methods to investigate the CD-drugs interactions as shown with several drugs such as barbitone sodium [11], phenylhydrazine hydrochloride [12], indomethacin (IMC) [13], nalidixic acid [14], irisquinone [15], catecholamines (dopamine, DA, and adrenaline, AD) [16], lumazine [17], rutin [18], β-lapachone [19], antitumor Morin [20], and 1,4-dihydropyridine calcium antagonists [21]. The inclusion of some pharmaceutically related molecules, such as 1,4-benzoquinone (BQ), 9,10-anthraquinone (AQ), anthracene (AN), acridine (AC), phenothiazine (PT) and thianthrene (TH) within β-cyclodextrin (β-CD) has been also investigated using an electrochemical method [22].

Gliclazide, (*N*-[[(hexahydrocyclopenta [c] pyrrol-1(1*H*)-yl) amino]carbonyl]-4-methyl-benzenesulfonamide) is a potent, second generation oral sulfonylurea antidiabetic agent widely-used to lower blood glucose levels in patients with type II noninsulin-dependent diabetes mellitus. The major drawback in the therapeutic application and efficacy of gliclazide as oral dosage forms is its very low aqueous solubility because of its hydrophobic nature. It is characterized by low dissolution rate and hence interindi-

vidual variability on its bioavailability [23]. The solubility and dissolution rate of gliclazide have shown to be enhanced by complexation with β-CD cyclodextrin. Thus, the inclusion mode between gliclazide and β-CD has been investigated in the solid state using several techniques including, X-ray diffractometry, infrared spectroscopy [24–26], cross polarizing/magic angle spinning ^{13}C-nuclear magnetic resonance spectroscopy [27], differential scanning calorimetry [28] and thermogravimetric analysis [26]. In the liquid medium only few reports have been appeared in the literature including, phase-solubility studies [24,25,28,29], ^{1}H and ^{13}C NMR studies [29]. The present study was carried out to investigate the voltammetric oxidation behaviour of gliclazide at glassy carbon electrode and to take the advantage of its electroactivity in order to study its inclusion complex with β-CD by cyclic and differential pulse voltammetry.

2 Experimental

2.1 Materials and Reagents

Gliclazide powder was obtained from Amoun Pharmaceutical Co., Cairo, Egypt. β-CD was purchased from Sigma Chemical Company (St. Louis, USA). Phosphate buffer solutions (*o*-phosphoric acid 85 %, potassium dihydrogen phosphate KH2PO4, disodium hydrogen phosphate Na_2HPO_4, and sodium phosphate Na_3PO_4, mixed with different amounts and diluted to 200 mL with doubly distilled water to obtain the required pH) were used. Stock solutions (5.0×10^{-3} M) of gliclazide were prepared daily by direct dissolution in methanol. Working solutions of the drug were obtained by transferring a sample of adequate volume of stock solution into 10 mL volumetric flask containing an appropriate amount of β-cyclodextrin dissolved in phosphate buffer (pH 7.2, 0.2 M). The mixed solution was diluted with phosphate buffer up to the final volume in away that the final solutions were composed of phosphate buffer: methanol, 90 : 10 (v/v). Then, the solution was shaken thoroughly for 20 min and allowed for equilibration at room temperature. All materials used without any further purification and doubly distilled water were used throughout the study.

2.2 Apparatus

The voltammetry experiments were performed using CHI610C Electrochemical Analyzer controlled by CHI Version 9.09 (USA). A three-electrode system was composed of a glassy carbon electrode (BAS model MF-2012, $\varnothing = 3$ mm) as working electrode, an Ag/AgCl/3 M KCl (BAS model MF-2063) reference electrode and a platinum wire (BAS model MW-1032) counter electrode. The glassy carbon electrode surface was polished with 0.3 and 0.05 μm alumina slurries and cleaned with water before each measurement.

The UV spectra were performed by the Perkin Elmer UV–VIS double beam spectrophotometer equipped with a PC for data processing (UV WinLab-ver 2.80.03, Perkin Elmer, USA). Spectra were recorded over the wavelength range from 200 to 350 nm at a scan speed of 240 nm min^{-1}. A quartz cell with a 1.0 cm path length was used. All pH measurements were performed on a CG 808 (Schott Geräte, Germany) digital pH-meter with glass combined electrode.

2.3 Procedure

2.3.1 Voltammetric Procedure

Voltammetric measurements were carried out in 10 ml of phosphate buffer. After background voltammograms had been recorded in the anodic direction from +0.0 V to +1.2 V. Gliclazide solutions were introduced into the cell and the anodic sweep was repeated under different conditions. All experiments were carried out at the room temperature, and peak heights were evaluated by means of the tangent method.

2.3.2 Procedures for Calculating Stability Constant (K_s)

Differential pulse voltammetry experiment was performed for 7.0×10^{-5} M of gliclazide in 0.2 M phosphate buffer pH 7.2 : methanol, 90 : 10 (v/v) containing various concentrations of β-CD ($0.0–4.0\times10^{-3}$ M). The current titration equation was described as follows [17,30]:

$$1/C_{CD} = K_s\,(1-A)(1-i/i_o)^{-1}-K_s \qquad (1)$$

Where, C_{CD} is the concentration of β-CD, KS is the apparent stability constant, i_o and i are the peak current without and with β-CD. A is the proportional constant. The condition of using this equation is that a 1 : 1 association complex is formed and C_{CD} is much larger than the total concentration of gliclazide in solution. In other words, if Equation 1 corresponds well to the experimental data, this may suggest that the complex of gliclazide with β-CD is a 1 : 1 association complex.

Solubility diagram was obtained according to Higuchi and Connors [31]. Briefly, excess amounts of solid gliclazide (40 mg) were added to 10 ml solutions (phosphate buffer pH 7.2 : methanol, 90 : 10 (v/v)) containing various concentrations of β-CD ($0.0–8.0\times10^{-3}$ M). The suspensions were shaken in screw-capped vials for three consecutive days at 25 °C, after 12 hours, the contents of each vial were centrifuged, filtered through a 0.45 μm membrane filter and suitably diluted and the gliclazide concentrations in the filtrates were measured by a UV-vis spectrophotometric method at 227 nm. The stability constant, K_s, was calculated from the phase solubility diagram according to the equation:

$$K_s = Slope/S_o \times (1-Slope) \qquad (2)$$

Where S_o is the solubility of gliclazide in the absence of β-CD and the slope means the corresponding slope of the phase solubility diagram, i.e., the slope of the gliclazide concentration versus β-CD concentration graph. The gliclazide concentration was obtained using calibration curve obtained in the same experimental conditions.

Calibration curve of gliclazide was constructed using a series of standard solutions in the range of (1.0×10^{-5}–5.0×10^{-5} M) prepared by appropriate dilutions of the stock solution of gliclazide with phosphate buffer pH 7.2 in a way that the final solutions were composed of phosphate buffer : methanol, 90 : 10 (v/v).

3 Results and Discussion

3.1 Voltammetric Behaviour of Gliclazide

3.1.1 Effect of pH

Cyclic voltammetry was used to investigate the electrochemical oxidation of gliclazide. Cyclic voltammetry experiments for 1.0×10^{-4} M gliclazide in phosphate buffer solutions over the pH range 2.7–11.8 were carried out on glassy carbon electrode. One oxidation peak was observed within the pH range 2.7–6.3 and a second oxidation peak was produced at more positive potential above pH 6.3. In the reverse sweep, no cathodic peaks were observed which indicates that the gliclazide oxidation is irreversible. The first oxidation process was more pronounced, sharper and better defined than the second process. Thus, the study was focused mainly on this oxidation peak.

Figure 1 shows the effect of pH on peak potential and peak current of the first anodic peak using cyclic voltammetry. The anodic peak potential is shifted to less positive values by increasing the pH with slope of −68 mV/pH in the range from 2.7 to 5.3 (this value is close to the Nernstian slope of 59 mV), indicating an equal number of electrons and protons involving in the electrode process. Thereafter the peak potential remains practically pH independent (Figure 1a). The intersection observed in the plot at pH 5.3 was very close to the reported pKa value of the sulfonylurea moiety in the gliclazide molecule [32]. The effect of solution pH on the peak enhancement is also shown in Figure 1b. The best results with respect to signal enhancement accompanied by sharper response was obtained with phosphate buffer at pH 5.3.

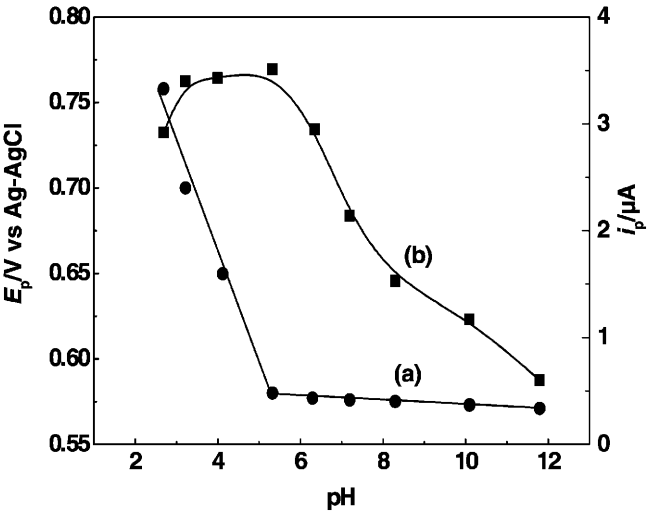


Fig. 1. Effect of pH on (a) the peak potential and (b) the peak current in phosphate buffer using CV at GCE. Gliclazide concentration, 1.0×10^{-4} M, scan rate 100 mVs^{-1}.

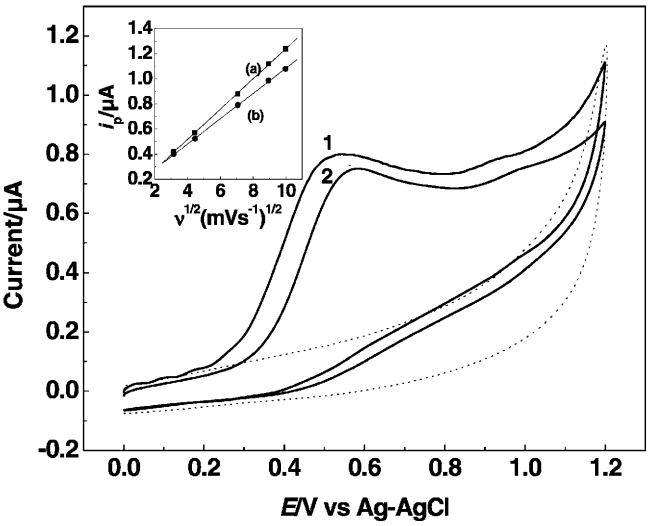


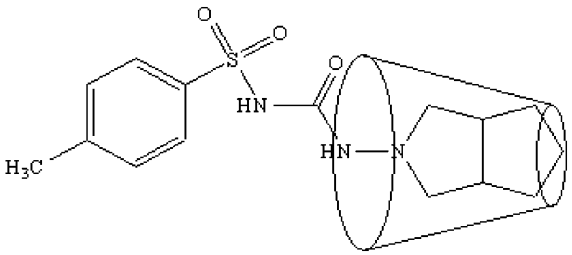
Fig. 2. Cyclic voltammograms for 7.0×10^{-5} M gliclazide solution obtained in 0.2 M phosphate buffer pH 7.2 : methanol, 90 : 10 (v/v) using a scan rate of 10 mV s^{-1}. (1) Without β-CD, (2) with 1.0×10^{-3} M β-CD. Inset is the plot of i_p versus $v^{1/2}$ (a) without β-CD, (b) with 1.0×10^{-3} M β-CD. The dotted line represents the voltammogram of the supporting electrolyte.

3.1.2 Effect of Scan Rate

The influence of the scan rate on the cyclic voltammogram of gliclazide was critically investigated. The data showed a positive shift in the peak potential of the first anodic wave, confirming the irreversible nature of the electrochemical process, with simultaneous increase in peak current (i_p) when the scan rate was increased. The linear relationship existing between peak current i_p and the square root of the scan rate (Inset of Figure 2), predicts a diffusion-controlled regime over the range of the scan rate studied.

In order to obtain information on the rate determining step, the αn_α value (where α is the charge transfer coefficient and n_α is the number of electrons involved in the rate determining step) was determined from a ($E_p - E_p/2$) value (where E_p is the peak potential and $E_p/2$ is the half-beak potential) which is equal to $47.7/\alpha n_\alpha$ mV for totally irreversible diffusion controlled process [33]. The αn_α value obtained for 1.0×10–^{4} M gliclazide at pH 5.3 was 0.45. The αn_α and the slope of the E_p–pH plot for acidic media most likely correspond to a one electron-one proton transfer.

By comparing the electrochemical oxidation behaviour of gliclazide with the related sulfonylureas such as, glibenclamide [34] and glipizide [35], we can conclude that the voltammetric oxidation peaks of gliclazide at GCE was attributed to the oxidation of hydrazide -CONH-NR moiety (where R is the azabicyclooctyl group), as previously reported at carbon paste electrode [36].



Scheme 1. The proposed structure of the inclusion complex of gliclazide with β-CD.

3.2 Complexation of Gliclazide with β-Cyclodextrin

3.2.1 Cyclic Voltammetry Experiment

As shown in Figure 2, the addition of β-cyclodextrin to 7.0×10^{-5} M gliclazide solution in phosphate buffer pH 7.2 causes changes in the cyclic voltammogram of the latter. With adding β-CD, the anodic peak potential slightly shifted to more positive potential, and at the same time, the anodic peak current decreased. These results are attributed to the formation of the inclusion complex according to the equilibrium of the following reaction

$$GC + \beta\text{-CD} \leftrightarrow GC/\beta\text{-CD}$$

Where GC is the gliclazide molecule and the GC/β-CD is the association complex between gliclazide and β-CD. The decrease of the peak current can be explained by the smaller diffusion coefficient of the inclusion complex with β-CD compared to the free drug. This explanation was confirmed by studying the effect of scan rate on peak current (i_p) both without and with β-CD. Cyclic voltammetry peak currents were proportional to the square root of scan rates in the range of 10–100 $mV\,s^{-1}$ (Inset of Figure 2), since the relation between the peak current and $\nu^{1/2}$ (at 25 °C) is given by the equation: $i_p=(2.99\times10^5)_n(\alpha n_\alpha)^{1/2}ACD^{1/2}\,\nu^{1/2}$ [37], where A is the electrode area (cm^2), C is the concentration (M), D is the diffusion coefficient (cm^2/s) and ν is the scan rate (V/s). The slope of the linear plot of i_p versus $\nu^{1/2}$ without β-CD ($0.12\,\mu A\,mV^{-1/2}s^{1/2}$) was more than that with β-CD ($0.1\,\mu A\,mV^{-1/2}\,s^{1/2}$), suggesting that the diffusion coefficient of the free form of gliclazide was larger than that of the complexed form of gliclazide with β-CD. On the other hand, it must be pointed out that even if an electroactive guest forms a stable inclusion complex with a CD host, electron transfer generally do not involve the encapsulated substrate. The CD-complex dissociation generally takes place before the electron transfer step as reported with several electroactive compounds [38–42]. In such case the positive shift observed in the E_p reveals that the oxidation center in the gliclazide molecule (hydrazide moiety), which is attached to the azabicyclooctyl group was included in the β-CD cavity (Scheme 1), which has been lead to more difficulty in its oxidation, while the other part (tolylsulfonamide group) of the molecule has a lower participation in the complexation phenomenon. This could be due to the ionization of the tolylsulfonamide group at the physiological pH 7.2 used [43], thus diminishing its affinity for the CD cavity. However, this way of interaction is in agreement with that reported in the liquid medium using ^1H NMR spectroscopy [44].

3.2.2 Differential Pulse Voltammetry Experiment

The inclusion phenomenon of gliclazide with β-CD was also studied by differential pulse voltammetry. This method that used for the stability constant calculation is applicable to any electroactive guest compound-CD systems in which the use of spectrophotometric method is difficult due to small spectral changes induced by addition of CDs (such as the studied compound). According to the decrease of peak currents with increasing the concentrations of β-CD, the following equation was obtained: $1/C_{CD}=156/(1-i/i_o)-839$, with a linear correlation coefficient (r) of 0.9983. This revealed that the inclusion complex of gliclazide with β-CD was a 1:1 association complex and the stability constant (K_s) was 839 M^{-1} as calculated from the y-intercept.

3.2.3 Phase Solubility Experiment

Figure 3 shows the absorption spectra of gliclazide without β-CD and shows as Inset the calibration curve with a linear regression equation of $A=0.0309+14983.9\,C$ (M) and correlation coefficient of 0.9998 and Figure 4 shows the phase solubility diagram of gliclazide with β-CD. The shape of the phase solubility diagram of gliclazide in phosphate buffer pH 7.2 : methanol, 90 : 10 (v/v) solutions containing various concentrations of β-CD obtained at 25 °C followed a BS type system [31]. The solubility of gliclazide was 9.86×10–^{4} M and it was rapidly raised as the concentration of β-CD increased (Figure 4a). When β-CD was continually increased, the solubility of gliclazide remained unchanged (the short plateau on Figure 4b). Instantaneously, the solubility of gliclazide was decreasing along with the augmentation of β-CD (Figure 4c). The slope of Equation 2. was calculated by the linear regression analysis method ($C=9.86\times10^{-4}+0.262C_{CD}$ (M)) with a correlation coefficient $r=0.9965$ from the initial upright portion of the solubility diagram (Figure 4a). In short, the phase solubility study suggested the formation of GC-β-CD inclusion complex with 1:1 molar ratio and the value of the stability constant obtained from Equation 2 was 360 M^{-1}.

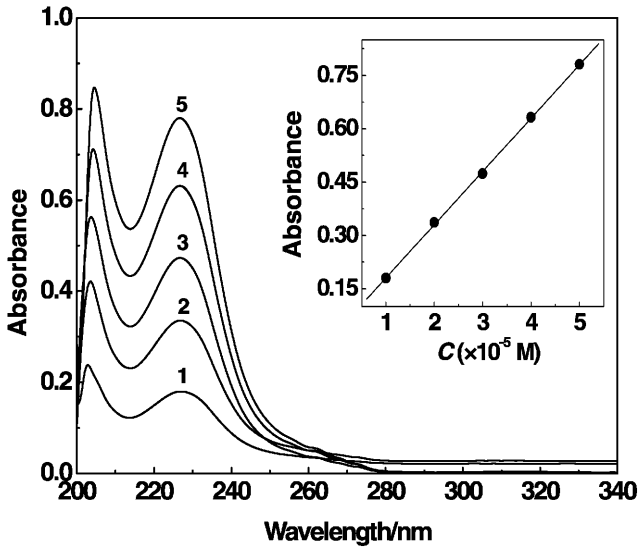


Fig. 3. Absorption spectra of various concentrations of gliclazide under the conditions of phosphate buffer pH 7.2 : methanol, 90 : 10 (v/v). Inset: Calibration curve.

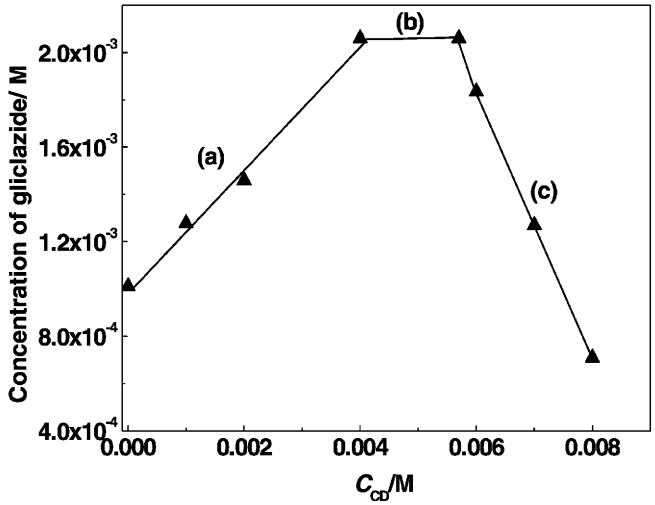


Fig. 4. Phase solubility diagram for gliclazide with increasing concentration of β-CD established by UV-vis method under the condition of phosphate buffer pH 7.2 : methanol, 90 : 10 (v/v).

From our results, we can notice that the electrochemical and the phase solubility methods do not give the close results for the stability constant because it is a fact that the stability constants of the host-guest complexes significantly depend upon the technique used for their evaluation as previously reported with various techniques [45–48]. In addition, all the values of the stability constant (K_s) obtained from previous reports using the phase solubility method [24,25,28,29] were different, may be due to the differences in the shaking time or the errors in the equilibrium attainments. The present voltammetric method can be considered as an alternative for the calculation of the stability constant in such kind of studies.

4 Conclusions

The effect of β-CD on the voltammetric behavior of gliclazide showed a positive shift in the first anodic peak potential and a decrease in the peak current. From these changes, we can assume that the azabicyclooctyl group in the gliclazide molecule was included in the β-CD cavity, which has been lead to more difficulty in the oxidation of hydrazide -CONH-NR moiety and the diminution of the peak current was due to the diminution in the diffusion coefficient of gliclazide as a consequence of the formation of an inclusion complex with β-CD. From the differential pulse voltammetry and the phase solubility results, it may be concluded that gliclazide forms 1 : 1 type inclusion complex with β-CD and the obtained stability constants were 839 and 360 M^{-1}, respectively.

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