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ORIGINAL ARTICLE

Electrochemical study of indapamide and its complexation with β-cyclodextrin

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Abstract Electrochemical oxidation of indapamide has been investigated at glassy carbon electrode using cyclic and differential pulse voltammetry (DPV). Indapamide exhibited two well resolved signals which attributed to the oxidation of indoline ring and benzamide moiety in phosphate buffers in the pH range of 2.7–10.1. The oxidation processes have been shown to be irreversible and diffusion controlled. The formation of an inclusion complex of indapamide with β-cyclodextrin (β-CD) has been investigated by cyclic, differential pulse voltammetry as well as UV–Vis spectrophotometry. The stability constant of the complex was determined to be 6199 and 2717 M^{-1} using differential pulse voltammetry and UV–Vis spectrophotometry, respectively.

Keywords Cyclodextrin · Indapamide · Voltammetry · Spectrophotometry

Indapamide, (4-chloro-N-(2-methyl-1-indoline) 3-sulfamoylbenzamide), is an oral diuretic antihypertensive drug. Indapamide effectively reduces arterial blood pressure of patients with mild to moderate hypertension [1]. The diuretic and natriuretic effects are mainly due to the structure of *O*-chlorobenzenesulfonamide, a molecule present in various diuretics. However, a varied side chain gives the drug its characteristic properties. Indapamide presents an indolinyl ring and uniquely exhibits free radical scavenging activity [2–4]. In accordance with its antihypertensive properties, indapamide was shown to have excellent efficacy in protecting against target organ damage (heart, kidneys, brain). Indapamide lowers the response to sympathetic nerve stimulation and exhibits calcium antagonist properties [5]. It has been reported that indapamide reduces vascular smooth muscle cell proliferation by a mechanism which involves a decrease in the intracellular Ca^{2+} movements that might link with the mitogen-activated protein kinase (MAPK) pathway, altering cell-cycle progression [6].

Cyclodextrins are oligosacharides obtained from enzymatic hydrolysis of starch. The β-cyclodextrin (β-CD) is one of the most abundant natural oligomers and corresponds to the association of seven glucose units with cavity, which exhibits a hydrophobic character whereas the exterior is strongly hydrophilic. Cyclodextrins are well known in supramolecular chemistry as the most efficient molecular hosts [7–10] capable of encapsulating, with a degree of selectivity, a range of guest molecules via non covalent interactions in hydrophobic cavities. Cyclodextrins and their derivatives have received considerable attention in the pharmaceutical field for the past few years [11–15] due to their extensive use in drug delivery processes. In addition, it can be used to enhance solubility, chemical stability, and bioavailability of the drugs.

However, to our knowledge only few studies dealing with diuretics inclusion complexes with cyclodextrins have been appeared in the literature. Improvement of dissolution properties and bioavailability of furosemide by complexation with β-cyclodextrin has been reported [16, 17]. Thin-layer chromatography has been used for studying the inclusion complexation of some sulphonamidic diuretics with different structures (chlorthalidone, hydrochlorothiazide, furosemide, indapamide and acetazolamide) with natural and semisynthetic cyclodextrins [18].

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The present study deals with the voltammetric investigation of indapamide and its inclusion complex with β-cyclodextrin on glassy carbon electrode. We have taken advantage of the electroactivity of indapamide molecule to design a differential pulse voltammetric procedure in order to obtain the stability constant of the inclusion complex. For comparative purpose, we have also applied a spectrophotometric method for the stability constant calculation.

Experimental

Materials and reagents

Indapamide powder was obtained from ADCO, Egypt. β-CD was purchased from Sigma Chemical Company (St. Louis, USA). Phosphate buffer solutions (*o*-phosphoric acid 85%, potassium dihydrogen phosphate KH_2PO_4, 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 (1.0×10^{-2} M) of indapamide were prepared by direct dissolution in methanol and stored under refrigeration at 4 °C. 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. 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.

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, $\Phi = 3$ 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 Gerate, Germany) digital pH-meter with glass combined electrode.

Procedure

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. Indapamide solutions were introduced into the cell and the anodic sweep was repeated under different conditions. All experiments were carried out at the room temperature.

Procedures for calculating stability constant (K_s)

Differential pulse voltammetry experiment was performed for 3.0×10^{-5} M of indapamide in 0.2 M phosphate buffer pH 2.7: methanol, 90:10 (v/v) containing various concentrations of β-CD ($0.0 - 1.5 \times 10^{-3}$ M). The differential pulse voltammetry conditions used were as follows: potential range from +0.2 to +0.7, pulse amplitude = 50 mV, pulse width = 0.2 s, sample width = 0.02 s and pulse period = 0.5 s.

Absorption spectra were recorded in the range of 200–350 nm, the concentration of indapamide was fixed at 7.0×10^{-5} M and the β-CD concentration was changed from 0 to 4.0×10^{-3} M. For the calculation of stability constant, the change of absorption of indapamide was measured at 284 nm as a function of β-CD concentration.

Results and discussion

Voltammetric behaviour of indapamide

Effect of pH

Figure 1 represents some cyclic voltammograms of indapamide at different pH values. At pH 2.7, we could notice that, in the forward scan, two well-resolved anodic peaks were obtained, while, in the reverse sweep, no cathodic peaks were observed which indicates that the indapamide oxidation is irreversible. Moreover, the anodic scan has been reversed after the first peak and no peak was observed in the cathodic direction, confirming the irreversibility of the anodic process. In general, pH is one of the main variable that strongly influence the shape of voltammograms. Thus, the electrochemical oxidation behaviour of indapamide at the glassy carbon electrode was critically examined over a wide range of pH (2.7–10.1) in phosphate buffer. The peak potential (E_p) and the peak

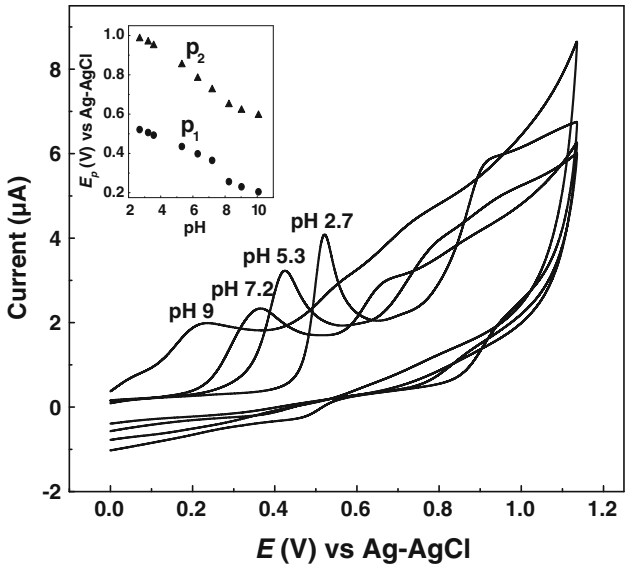


Fig. 1 Cyclic voltammograms of (1.0×10^{-4} M) indapamide at GCE in phosphate buffer at different pH values, scan rate 50 mVs^{-1}. Inset is the plot of E_p versus pH

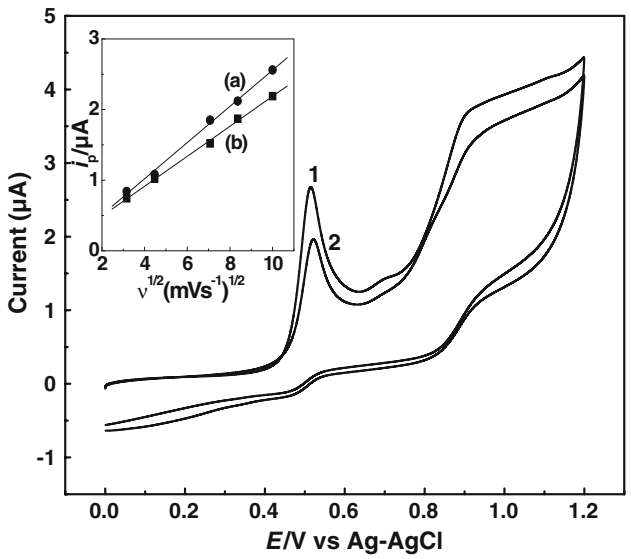


Fig. 2 Cyclic voltammograms for 7.0×10^{-5} M indapamide solution obtained in 0.2 M phosphate buffer pH 2.7: methanol, 90:10 (v/v) using a scan rate of 50 mVs^{-1}. (*1*) Without β-CD, (*2*) with 4.0×10^{-3} M β-CD. *Inset* is the plot of i_p versus $v^{1/2}$; *a* without β-CD, *b* with 4.0×10^{-3} M β-CD

current (i_p) of both voltammetric peaks were dependent on the pH.

As shown in the inset of Fig. 1, the anodic potentials of both peaks were shifted to less positive values by increasing the pH, implying the involvement of protons in the current-limiting electrode process. From the linear regression analysis of the experimental data, two zones can be distinguished for each peak. An estimated ΔE_p/pH of 34.8 mV/pH was obtained between pH 2.7 and 7.0, and 28.0 mV/pH between pH 8.2 and 10.1 for the first anodic peak, suggesting a $2e^-/1H^+$ oxidation process over the entire pH range. Whereas, for the second anodic peak the slope was 58.1 mV/pH between pH 2.7 and 8.2, indicating an equal number of electrons and protons involved within this pH range, while at higher pH the slope decreased to 29.3 mV/pH, suggesting a $2e^-/1H^+$ oxidation process. The intersection observed in the plot at about pH = 8.2, can be attributed to the deprotonation of the drug as it is previously reported that indapamide behaves as a weak acid, exhibiting a pKa of 8.8 ± 0.2 at 25 °C [19]. The peak current of indapamide in acidic solution was higher than that in basic solution and its maximum value was at pH 2.7. The first oxidation peak (p_1) was more pronounced while the second one (p_2) was less distinct at the tested pH range. Thus, the present study was focused on the first oxidation peak.

Effect of scan rate

The influence of the scan rate on the CV of indapamide 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_{p1}) when the scan rate was increased.

The linear relationship existing between peak current i_{p1} and the square root of the scan rate (inset of Fig. 2) predict a diffusion-controlled regime over the range of the scan rate studied.

The αn_a value (where α is the charge transfer coefficient and n_a is the number of electrons involved in the rate determining step) has been 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 $47.7/\alpha n_a$ mV for totally irreversible diffusion controlled process [20]. The αn_a value obtained at pH 7.2 was 0.59. The αn_a value can be calculated also by another approach, from the Tafel slope expression ($b = 2.303RT/\alpha n_a F$) [20] where Tafel slope (b) can be obtained using the following equation for totally irreversible diffusion controlled process [21]:

$$E_p = \frac{b \log v}{2} + \text{constant}$$

when E_p was plotted versus log v for scan rates in the range 10–250 mVs^{-1} at pH 7.2, a straight line was obtained with a slope of 0.055 V, so, $b = 2 \times 0.055 = 0.11$ V. The αn_a value was estimated as 0.53. Thus, the results obtained from the two different methods are in good agreement.

From αn_a values and the slopes of the E_p-pH plot, number of protons were calculated to be one proton involved in the anodic process. The first anodic reaction involved 1 H^+, 2 e^-,

taking into account the structure of indapamide, could be attributed to the oxidation of the 2,3-dihydroindol (indoline) ring [22]. The second voltammetric peak could be attributed to the oxidation of the benzamide moiety [23].

Complexation of indapamide with β-cyclodextrin

Cyclic voltammetry experiments

The inclusion phenomena of indapamide with β-CD were investigated by cyclic voltammetry. As shown in Fig. 2, the addition of β-cyclodextrin to 7.0×10^{-5} M indapamide solution in phosphate buffer pH 2.7 causes changes in the voltammogram of the latter. With adding β-CD, the anodic peak potential slightly shifted to more positive potential by 15 mV, 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,

$$\mathrm{In} + \beta - \mathrm{CD} \rightleftharpoons \mathrm{In} - \beta - \mathrm{CD}$$

where In is the indapamide molecule and In–β-CD is the association complex between indapamide 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 the first oxidation peak current (i_{p1}) both without and with β-CD. CV peak currents were proportional to the square root of scan rates in the range of 10–150 mVs^{-1} both without and with β-CD (inset of Fig. 2), since the relation between the peak current and $v^{1/2}$ (at 25 °C) is given by the equation: $i_p = (2.99 \times 10^5)\mathbf{n}(\alpha n_a)^{1/2}ACD^{1/2}\,v^{1/2}$ [24], where A is the electrode area (cm^2), C is the concentration (M), D is the diffusion coefficient (cm^2/s) and v is the scan rate (V/s). The slope of the linear plot of i_p versus $v^{1/2}$ without β-CD (0.2563 μA $mV^{-1/2}$ $s^{1/2)}$ was more than that with β-CD (0.2122 μA $mV^{-1/2}$ $s^{1/2}$), suggesting that the diffusion coefficient of the free form of indapamide was larger than that of the complexed form of indapamide with β-CD. On the other hand, The positive shift in the E_{P1}, which is more pronounced in DPV (Fig. 3), reveals that part of the indoline component in the indapamide molecule was included in the β-CD cavity, which may make the nitrogen of the indoline moiety close to the rim of the β-CD, giving only a small shift in the oxidation potential; while the other part of the indapamide molecule remains out side (Scheme 1). Otherwise, if the other side of the indapamide was included in the β-CD cavity there would not be any change in the first anodic peak potential. This proposed site of interaction indicates that hydrophobic interaction play an important role in complexation with β-CD, where the nonpolar methyl indoline component [25] is more favorable to leave the hydrophilic environment of the aqueous solution and to interact with the hydrophobic cavity of the β-CD.

Table 1 shows that with increasing scan rate (v) the ratio of the anodic peak current to $v^{1/2}$ become smaller, which is expected for a CE mechanism [20]. This indicates that the inclusion complex dissociates first to indapamide and β-CD followed by oxidation of the free indapamide.

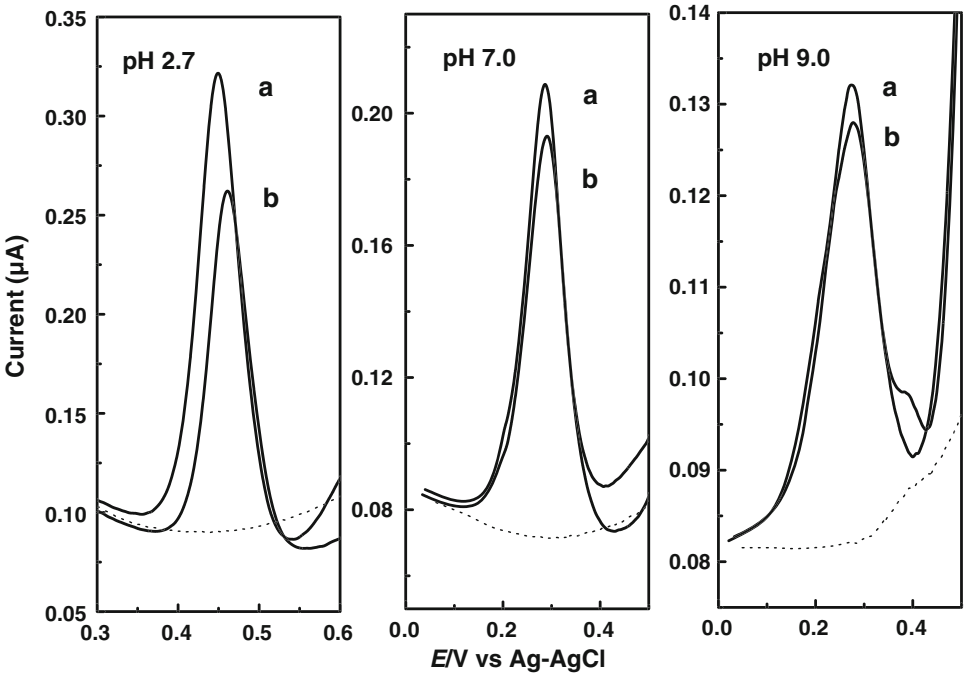
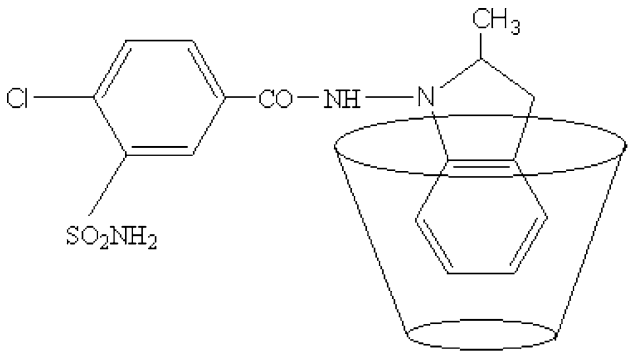


Fig. 3 Differential pulse voltammograms (DPVs) of 1.0×10^{-5} M indapamide in phosphate buffer at different pH values in the absence (**a**) and (**b**) presence of 1.0×10^{-3} M β-CD at GCE, *pulse amplitude* 50 mV, *pulse width* 0.2 s, *sample width* 0.02 s and *pulse period* 0.5 s. The *dotted lines* represent the background voltammograms



Scheme 1 The proposed structure of the 1:1 inclusion complex of indapamide with β-CD

Table 1 The ratio of the anodic peak current (i_p) to the square root of the scan rate at different scan rates (v)

v (mV/s)	10	20	70	100
$i_p/v^{1/2}$ (μA/(mV/s)$^{1/2}$)	0.24	0.23	0.22	0.21

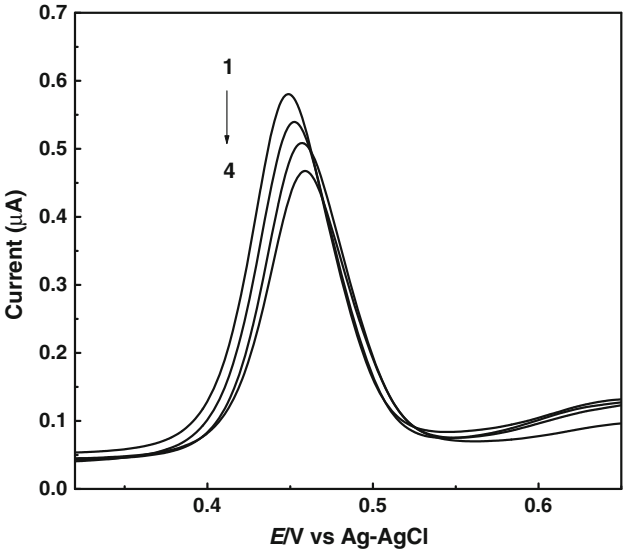


Fig. 4 DPV curves for 3.0×10^{-5} M indapamide solution obtained in 0.2 M phosphate buffer pH 2.7: methanol, 90:10 (v/v) in absence (*1*) and presence of (*2*) 1.0×10^{-4} M, (*3*) 4.0×10^{-4} M, (*4*) 1.5×10^{-3} M β-CD

Differential pulse voltammetry experiments

Effect of pH on complexation

The formation of inclusion complex between indapamide and β-CD are markedly affected by pH value of the solution. Figure 3 shows the effect of the pH (2.7, 7.0 and 9.0) of the medium on the first anodic peak of indapamide upon addition of definite amount of β-CD. The decrease in the peak current and the positive shift observed reflect the difference in the strength of the interaction at the different pH values studied. Weak interaction was observed at pH 9.0 (about 13 mV shift in the E_p) where the indapamide molecule was in its ionized form [19]. This is could be explained on the basis of the hydrophobic mode of interaction discussed above. It has been reported that the complexation strength of molecules to cyclodextrins decreases with an increase in the hydrophilicity of the substrate [26–28]. This is attributed to the much simplified rule of "like-dissolves-like." With an increase in the hydrophilicity of the substrate, by addition of charge upon ionization (at pH 9.0), an improved interaction with the polar solvent occurs, lowering the cyclodextrin complexation strength. While, strong interactions were observed at phosphate buffer pH 2.7 (about 22 mV shift in the E_p) compared to media with other pH values. Therefore, phosphate buffer pH 2.7 was employed throughout this study.

Calculation of the stability constant of the inclusion complex

The inclusion phenomenon of indapamide with β-CD was also studied by differential pulse voltammetry because it provides higher sensitivity and better peak resolution compared to cyclic voltammetry (Fig. 4). The differences in the peak currents using DPV are more pronounced, obtaining more accurate results for the calculation of the stability constant Fig. 5.

For the equilibrium:

$$\mathrm{In} + \beta - \mathrm{CD} \rightleftharpoons \mathrm{In} - \mathrm{CD}$$

the stability constant (K_S) is:

$$K_S = \frac{[In - CD]}{[In][CD]} \quad (1)$$

the observed diffusion coefficient (D_{obs}) can be calculated according to [29, 30] as:

$$D_{obs} = \frac{D_{In}[In] + D_{In-CD}[In - CD]}{[In] + [In - CD]} \quad (2)$$

where D_{In}, D_{In-CD} are the diffusion coefficients of free indapamide and inclusion complex.

For DPV, we know [24] that:

$$i_p = \frac{nFAD^{1/2}C}{\sqrt{\pi t_m}}\left(\frac{1-\sigma}{1+\sigma}\right) \quad (3)$$

where A is the electrode area, C is the concentration of the guest, D is the diffusion coefficient of the diffusing species, t_m is the time after application of the pulse, and $\sigma = \exp[(nF/RT)(\Delta E/2)]$, ΔE is the pulse amplitude.

From Equ. (1), (2), and (3), the relationship between current and stability constant is obtained:

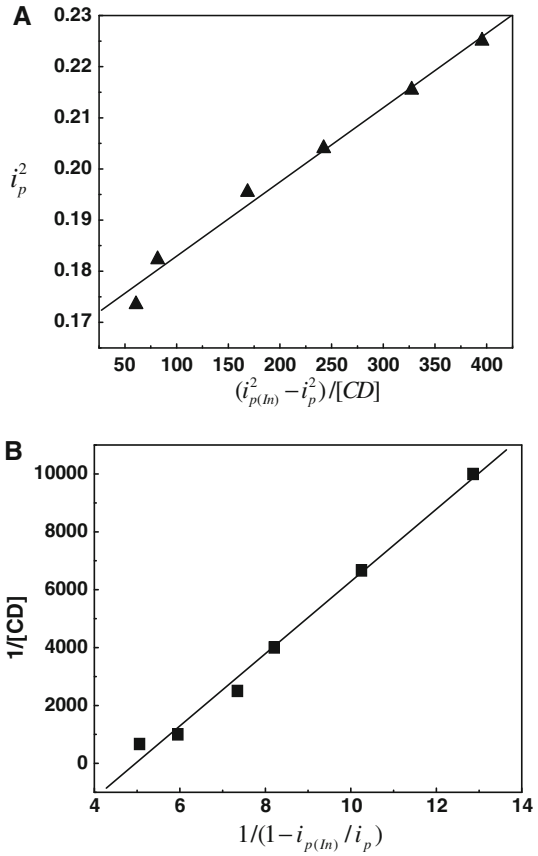


Fig. 5 **a** The plot of i_p^2 versus $(i_{p(In)}^2 - i_p^2)/[CD]$, **b** The plot of 1/[*CD*] versus $1/(1\text{-}i_{p(In)}/i_p)$

$$i_p^2 = \frac{1}{K_S[CD]}(i_{p(In)}^2 - i_p^2) + i_{p(In-CD)}^2 \quad (4)$$

Where i_p is the observed current (after adding CD), $i_{p\,(In-CD)}$ and $i_{p(In)}$ are the peak currents of the inclusion complex and free In, respectively, i_p and $i_{p(In)}$ can be determined from the experiments. The value of K_S can be obtained from the reciprocal of the slope of the linear plot of i_p^2 versus $(i_{p(In)}^2 - i_p^2)/[CD]$.

In our work, the stability constant for the inclusion complex of indapamide with β-CD was calculated to be 6320 M^{-1} according to Eq. (4) by regression analysis as shown in Fig. 5a

The stability constant can be also obtained using the following equation:

$$1/[CD] = K_S\frac{(1-A)}{1 - i_{p(In)}/i_p} - K_S \quad (5)$$

Which can be deduced according to references [31–33] and used previously in various reports [34–37], where A is a proportional constant. The condition of using this equation is that a 1:1 association complex is formed and [CD] is much larger than the total concentration of indapamide in solution.

According to Eq. (5), the stability constant can be obtained from the y-intercept of the linear plot of 1/[CD] versus $1/(1\text{-}i_{p(In)}/i_p)$ by regression analysis as shown in Fig. 5b to be 6199 M^{-1}, indicating a 1:1 association complex. However, the K_S value obtained using both equations are in good agreement.

Spectrophotometric experiment

The formation of inclusion complex between indapamide and β-CD could be further confirmed by a spectroscopic experiment. The absorption spectra of indapamide in the absence, and presence, of β-CD are shown in Fig. 6. Although the maximum absorption wavelength of indapamide was at 240 nm, the slight change in the absorbance at 240 nm can not be used to obtain accurate results for the stability constant calculations. Therefore, the band at 284 nm was used for the calculations. It was noticed that upon addition of β-CD, the absorption of indapamide at 284 nm was decreased which confirms the formation of the inclusion complex of indapamide with β-CD. The stability constant, K_S, of this complex can be determined according to the Benesi-Hildebrand equation [38]. Under the condition of 1:1 inclusion complex formation with an excess of the concentration of β-CD compared with the total concentration of indapamide in solution, the equation can be represented as follows [29, 39]:

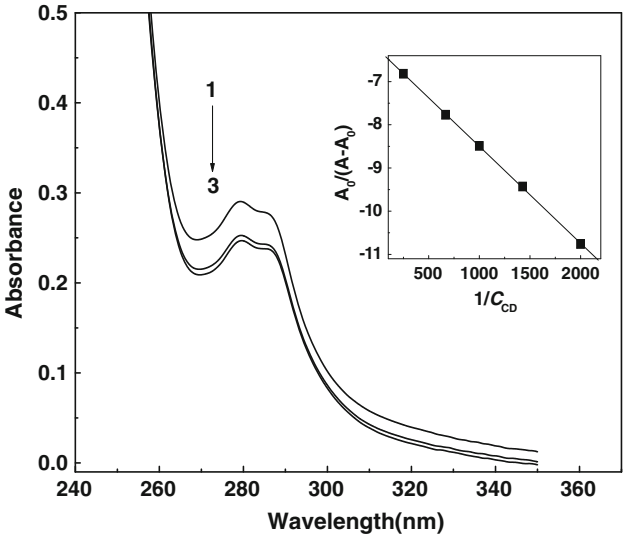


Fig. 6 Absorption spectra of indapamide (7.0×10^{-5} mol/L) in 0.2 M phosphate buffer pH 2.7: methanol, 90:10 (v/v) in the absence (1) and presence of various concentrations of β-CD: (*2*) 1.5×10^{-3}, (*3*) 4.0×10^{-3} M. *Inset* is the plot of $A_o/(A-A_o)$ versus $1/C_{CD}$

$$\frac{A_0}{A - A_0} = \frac{\varepsilon_G}{\varepsilon_{H-G} - \varepsilon_G} + \frac{\varepsilon_G}{\varepsilon_{H-G} - \varepsilon_G K_S[CD]} \quad (6)$$

where A_o and A are the absorbances of the free guest and the complex, ε_G and ε_{CD-G} are the absorption coefficients of the guest and complex, respectively.

According to Eq. (6), from an $A_o/(A-A_o)$ versus 1/[CD] plot (inset of Fig. 6), the ratio of the intercept to the slope gives the value of stability constant of 2717 M^{-1}.

From our results, we can notice that the two electrochemical approaches give the close results for the stability constant (6320 and 6199 M^{-1}), while the spectrophotometric method depending on measuring another experimental property (changes of the absorbance) does not give the same result (2717 M^{-1}). The probable reason could be the use of different techniques as it is a fact that the stability constants of the host–guest complexes significantly depends upon the technique used for their evaluation as previously reported with various techniques [36, 40, 41].

Conclusion

The effect of β-CD on the voltammetric behavior of indapamide showed a positive shift in the first anodic peak potential and a decrease in the peak current. From these changes, we can assume that part of the hydrophobic indoline component of the indapamide molecule was located inside the cavity of β-CD and the diminution of the peak current was due to the diminution in the diffusion coefficient of indapamide as a consequence of the formation of an inclusion complex with β-CD. From the voltammetric and the spectrophotometric results, it may be concluded that indapamide forms 1:1 type inclusion complexes with β-CD and the obtained stability constants were 6199 and 2717 M^{-1}, respectively.

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