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Electrochemical Reduction of Carbamazepine in Ethanol and Water Solutions Using a Glassy Carbon Electrode.

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The electrochemical reduction of carbamazepine in ethanol and water using a glassy carbon electrode has been studied. In all experimental conditions of scan rate and concentration of carbamazepine an irreversible cathodic wave was observed by cyclic voltammetry (CV). Electrochemical parameters and a plausible EqC mechanism have been reported from the electrochemical measurements and digital simulation. The values of thermodynamic E1/2 were correlated with solvent polarity parameters that it can be interesting for biological, pharmaceutical and forensic purposes. Limits of Detection (LOD) for DPV are 1.1 and 9.0 μg/mL ($4.65x10^{-6}$ and $3.81x10^{-5}$ M) in ethanol and water, respectively. The precision and recoveries obtained for tablets and plasma samples showed that the method could be successfully used for analysis.

Keywords: Carbamazepine; electrochemical reduction; cyclic voltammetry; differential pulse voltammetry; glassy carbon electrode

1. INTRODUCTION

Carbamazepine (CBZ, scheme 1) is a highly lipophilic neutral tricyclic compound. This molecule is an antiepileptic drug used for some conditions, such as epilepsy and bipolar disorder. CBZ, as one of the most widely used antiepilectic drugs, is prescribed in the treatment of psychomotor, generalized tonic-clonic seizures and complex partial seizures [1,2]. It is usually administered orally in tablet or suspension form presenting 85% compound bioavailability.

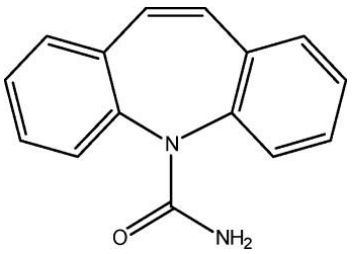
The drug is usually analysed in tablets and biological samples, such as plasma or urine, using liquid chromatographic methods. Liquid chromatographic methods using both UV-Vis [3] and mass spectrometry detectors [4] are the most common techniques of choice for forensic and clinical laboratories and they offer the highest selectivity and sensitivity for its detection. However they are

time consuming and in some cases expensive to purchase and with considerable running costs, especially for small laboratories.

Recently, several electrochemical studies of the CBZ have been reported for the characterization of redox properties and the analytical determination in commercial formulations and biological fluids. In most cases, these studies are concerned with the oxidation properties of the molecule with different modified and unmodified carbon electrodes [5-13].

However, none of the reported papers directly refer to the characterization of the electrochemical reduction of CBZ. The detection of CBZ using reduction potentials in solid electrodes is important and presents certain advantages when compared to the oxidation processes as avoids all the surface oxidation processes associated to these types of substrates (metallic and non-metallic) when performed in protic solvents such as ethanol or water.

In a previous publication, we reported the electrochemical reduction of carbamazepine in dimethylformamide and acetonitrile using a glassy carbon electrode [8]. In this work, we have studied the reduction process in ethanol and water solutions using the same working electrode. The use of glassy carbon substrate offers a double advantage. First, a quantitative measure of the environment polarity in which carbamazepine is located in different matrices within the biological, forensic and pharmaceutical fields as the half-wave potential is very sensitive to the polarity of the solvent. On the other hand, our study offers an alternative to other analytical methods for the CBZ determination. Therefore these solid electrodes present analytical characteristics that make them suitable for fast analysis.



Scheme 1

2. EXPERIMENTAL

Carbamazepine (CBZ) (99% purity), tetra-ethyl ammonium perchlorate (TEAP) (98% purity) and lyophilised human plasma were purchased from Sigma-Aldrich (Darmstadt, Germany). Ethanol, chloroform and acetic acid were also purchased from Sigma-Aldrich. Methanol and dichloromethane were of HPLC grade and were purchased from Fluka. Tegretol tablets containing 200 mg of carbamazepine were purchased from Novartis (Varese, Italy).

Cyclic Voltammetry (CV) and Differential Pulse Voltammetry (DPV) analyses were performed with a potentiostat CHI 900b (CH Instrument, Austin, US) attached to a PC fitted with control software for data acquisition. DPV conditions for all experiments were: pulse amplitude 0.05 V, pulse width 0.05 s and pulse period 0.2s. Experimental optimisation and experimental parameters were

calculated using DigiSim 3.03 software. A three electrode configuration was used: graphite electrodes acting as working electrodes, a Saturated Calomel Electrode (SCE) used as a reference electrode and a platinum electrode acted as a counter electrode. The working electrode used for the different experiments was a 3mm diameter glassy carbon electrode from Bioanalytical Systems (Kenilworth, UK). The working electrode was polished with 0.05 μm slurry, rinsed and sonicated in 18 MΩ Milli-Q water (Millipore, Mariland, US) and dried before use. Nitrogen was bubbled in the electrochemical cell for 20 min before analysis.

Liquid-liquid extraction was performed to extract the carbamazepine from the plasma and tablet samples. Plasma samples were spiked with carbamazepine to obtain 8 mg/L concentration (mid therapeutic range) and chloroform added (1:20 ratio) to extract the carbamazepine. Tablets were crushed in a mortar and pestle and the powder mixed with chloroform to extract the drug. In both cases the chloroform was removed using a nitrogen evaporator and the sample reconstituted with water or ethanol prior to voltammetry.

3. RESULTS AND DISCUSSION

3.1. Cyclic voltammetry

3.1.1. Ethanolic solutions.

Figure 1 shows the different voltammograms obtained by cyclic voltammetry (CV) corresponding to the electrochemical reduction of 472 μg/mL (2 mM) solution of carbamazepine (CBZ) using a 3 mm glassy carbon electrode at different sweep rates. The solvent used was ethanol and the supporting electrolyte was 0.1M TEAP. Only one cathodic peak was observed in the direct scan and none in the reverse scan indicating an apparent irreversible nature of the electrode reaction with a reduction peak shifting to a negative direction when the scan rate increases.

The voltammetric signal is partially overlapped with the background response of the buffer. The measurement of current peak was carried out by subtracting the corresponding signal off the discharge current. The current function $Ip/v^{1/2}$ is practically independent of the scan rate (only a decrease of 5-10% at the higher scan rates was observed) which is the typical behaviour of a diffusion-controlled process [14].

The voltammetric profile observed indicates that the product of the electrochemical reaction is not electroactive, at least in this time window, in contrast with the results recently obtained by us in dimethylformamide (DMF) and acetonitrile (ACN) [8]. The electrochemical reduction of carbamazepine in DMF and ACN using a glassy carbon electrode is consistent with an electrochemical-chemical mechanism (EC) involving a two electron transfer followed by a first order reaction, the conformational isomerisation of the 10,11-dihydrocarbamazepine reaction product, CBZ_R.

In the present case, the obtained values of the current intensity correspond to a two-electron process to produce the 10,11 C-C saturated bond. This was confirmed by comparing these with the limiting current obtained for CBZ in these other solvents. Also, we cannot reject an EC mechanism

though the absence of the anodic wave might be an indication that the chemical reaction step is more rapid than that observed for DMF and ACN, as emphasized by other authors in water solutions [5]. On the other hand, we observed an electrochemical reaction with a rate-limiting electron transfer as evidenced through the variation of the peak potential with the scan rate. As a consequence of all these facts, we can conclude that a wide time scale exists for the chemical reaction to take place and therefore the associated oxidation wave is not observed.

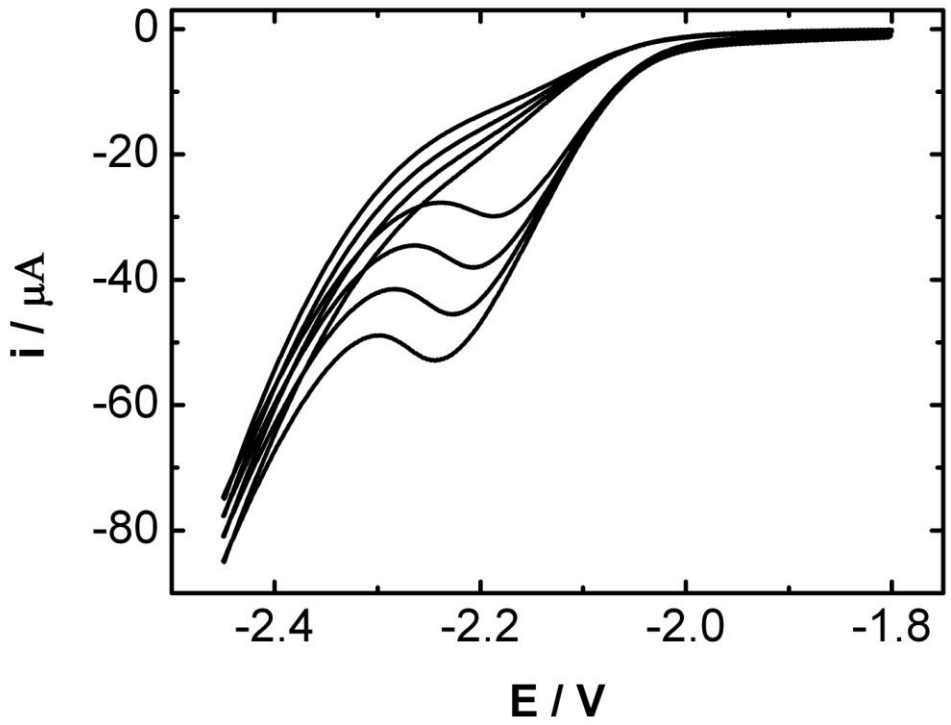


Figure 1. Cyclic voltammetry of CBZ 472 μg mL^{-1} in ethanol solution containing 0.1 M TEAP at several scan rates: 0.04, 0.08, 0.14, 0.2 V/s. Inset shows variation of peak potential versus logv

The presence of 0.5 mM of acetic acid delays the supporting electrolyte signal. The interaction between the acetate and tetraethylammonium ions [15] on electrode surface could explain this observation. This fact permits obtaining the best shape of the wave for CBZ in ethanol solution, which made possible obtaining more accurate and precise measurements to calculate electrochemical parameters (Figure 2).

In these experimental conditions the CBZ response to variations in the sweep rate is similar to that obtained previously where an anodic peak in the reverse scan could not be observed in any case. When the scan rate increased (at $v \geq 1$ V/s) the overlap of the reduction wave with that of the supporting electrolyte could be observed.

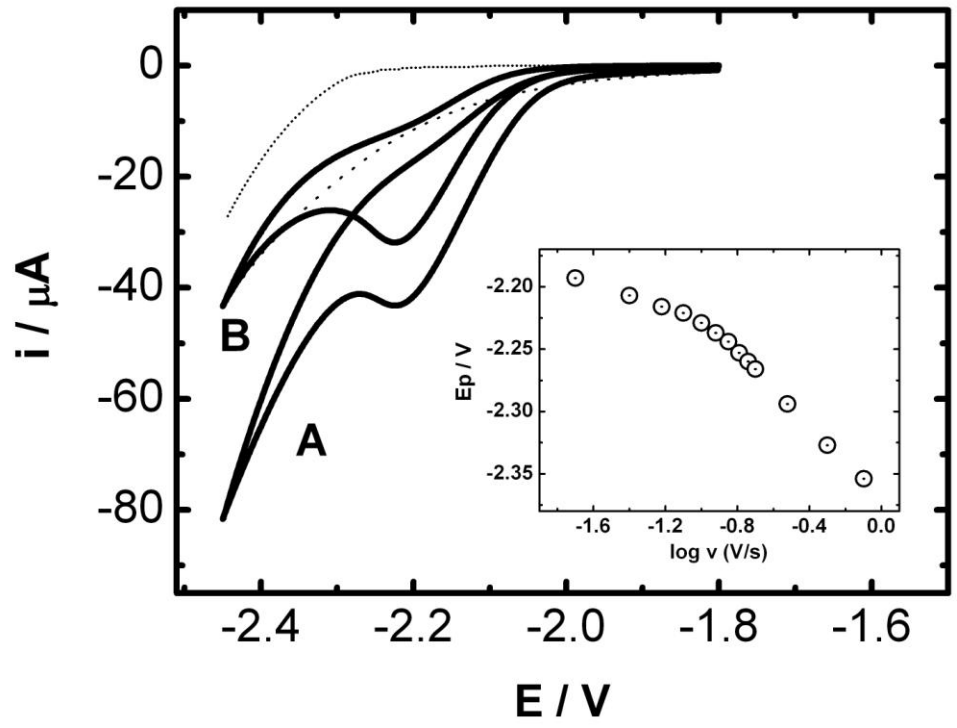


Figure 2. Cyclic voltammetry of CBZ 472 μg mL^{-1} in ethanol solution containing: (A) 0.1 M TEAP (B) 0.1 M TEAP and 0.5mM acetate iones. Scan rate, 0.1 V/s. The dotted lines represent the corresponding blank responses. Inset shows variation of peak potential versus logv

Also, no important dependency of the function $I_p/v^{1/2}$ with the scan rate was observed and only a slight decrease to high speeds was detected. The peak potential vs logv plot shows a typical profile of the curve of a quasi-reversible electron transfer [14] (inset figure 2). It is interesting to emphasize that the peak potential does not change with the addition of acetic acid as a proton donor (Figure 2), which might be indicative of a slow first-step electronic transfer. On the other hand, the study of CBZ in ethanol in the range 24 to 470 μg·mL^{-1} (10^{-4} to $2 \cdot 10^{-3}$ mol L^{-1}) yielded a linear relationship between current intensity and CBZ concentration indicating a first order electrochemical reaction with respect to the concentration of the depolarizer. Likewise, the peak potential is independent of the concentration. Our results support an electrochemical-chemical reaction mechanism (EC) for the electrochemical reduction of CBZ in ethanol according the following scheme:

$$CBZ_O + 2e^- + 2H^+ \underset{}{\overset{k_h}{\rightleftharpoons}} CBZ_R \qquad E_{1/2}$$

$$CBZ_R \xrightarrow{k} CBZ_{R'}$$

whereas CBZ_R is 10,11-dihydrocarbamazepine and $CBR_{R'}$ an electro-inactive conformational isomer. In ethanol solutions, the protonation step to obtain the product of the first electronic transfer is known to play a major role in yielding a two electron product [16,17]. The second electronic transfer

takes place at higher potentials than the first one, producing the observed bi-electronic wave. The first step of the previous scheme is overall named E although two fast protonations and the second electron transfer are included.

In order to obtain the electrochemical parameter corresponding to the reduction of CBZ in ethanol according to the mechanism proposed in the previous scheme, we used a digital simulation (DigiSim 3.0) to adjust the i-E curves of the voltammograms at several sweep rates. Some approximate parameters input were: (i) the diffusion coefficient obtained from coefficient viscosity correction at the values in other solvent studied [8], as well as the similar values for another tricyclic compounds [18,19]; (ii) the potential $E_{1/2}$ obtained, in a first approximation, by extrapolation to scan rate zero of the peak potential in the study with the scan rate and (iii) $\alpha = 0.5$, as the transfer coefficient. The calculated values for the parameters, with the best adjustment from the profiles of the voltammograms (see Figure 3), were: $\alpha = 0.54 \pm 0.07$, $D = (3.95 \pm 0.35) \cdot 10^{-6}$ cm^2/s and $E_{1/2} = -2.120 \pm 0.002$ V vs SCE. The heterogeneous electron transfer rate constant $k_h = (8.83 \pm 0.61) \cdot 10^{-4}$ cm/s and the homogeneous chemical reaction rate constant $k \geq 28.1$ s-1 were also calculated (according to the range of scan rate studied). These were consistent with a quasi-reversible electron transfer and a subsequent reaction (EqC) about two orders of magnitude higher than those values obtained in aprotic solvents [8]. The k_h value calculated should give an anodic peak at potential 0.2 V or highest, far from the cathodic peak obtained in scan-rate ranges studied. The conformational isomerisation reaction prevents the observation of this signal according to the limit value for the homogeneous chemical constant determined by digital simulation.

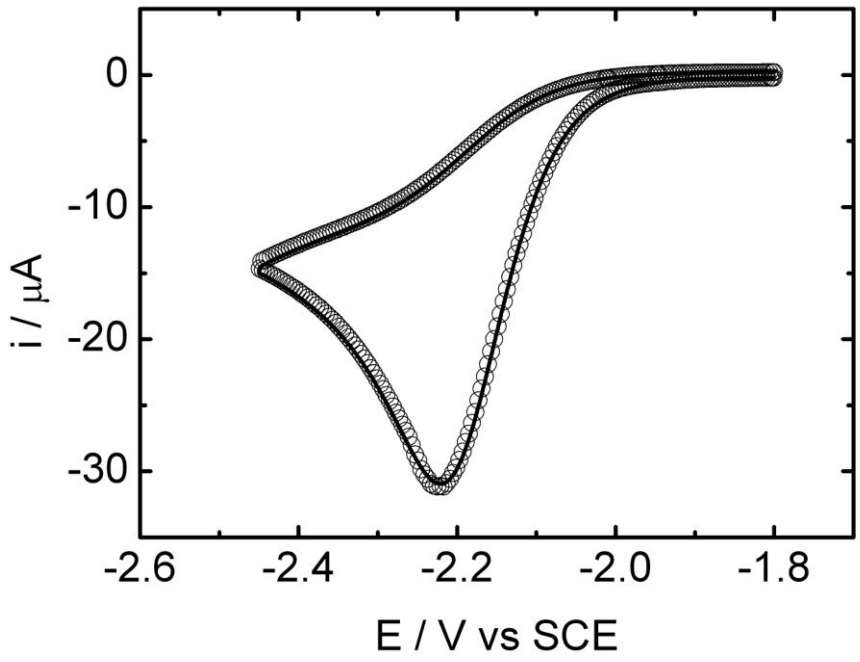


Figure 3. Digital simulation of voltammogram of CBZ 472 μg mL^{-1} in ethanol solution containing 0.1 M TEAP and 0.5mM acetate iones. The current of the supporting electrolyte was subtracted. Scan rate, 0.1 V/s; (o) experimental voltammogram; (-) theoretical i-E curve.

3.1.2. Water solutions

The electrochemical behaviour of CBZ on glassy carbon electrodes in water solutions was also studied. Due to the low solubility of CBZ in water, a stock solution was prepared first in ethanol and the final composition of the ethanol:water solution was 10:90 (v/v) with a CBZ concentration of 472 μg/mL (2 mM). The supporting electrolyte was a 0.1 M tetraethylammonium perchlorate and the final pH of the solution was 7.03, close to that of physiological fluids.

The electrochemical behaviour observed in CV is similar to that found in ethanol. CBZ shows irreversible i-E curves under all the experimental conditions studied and corresponding to the bielectronic reduction of a double bond 10,11C=C present in the heterocycle of the molecule [5]. As in ethanol, the current function $Ip/v^{1/2}$ is independent of the scan rate which is the typical behaviour of a diffusion-controlled process. In the same way, the peak potential vs logv plot shows a typical curve for a quasi-reversible electron transfer [14]. Figure 4 shows the voltammograms obtained at different sweep rates and the inset shows E_P versus logv.

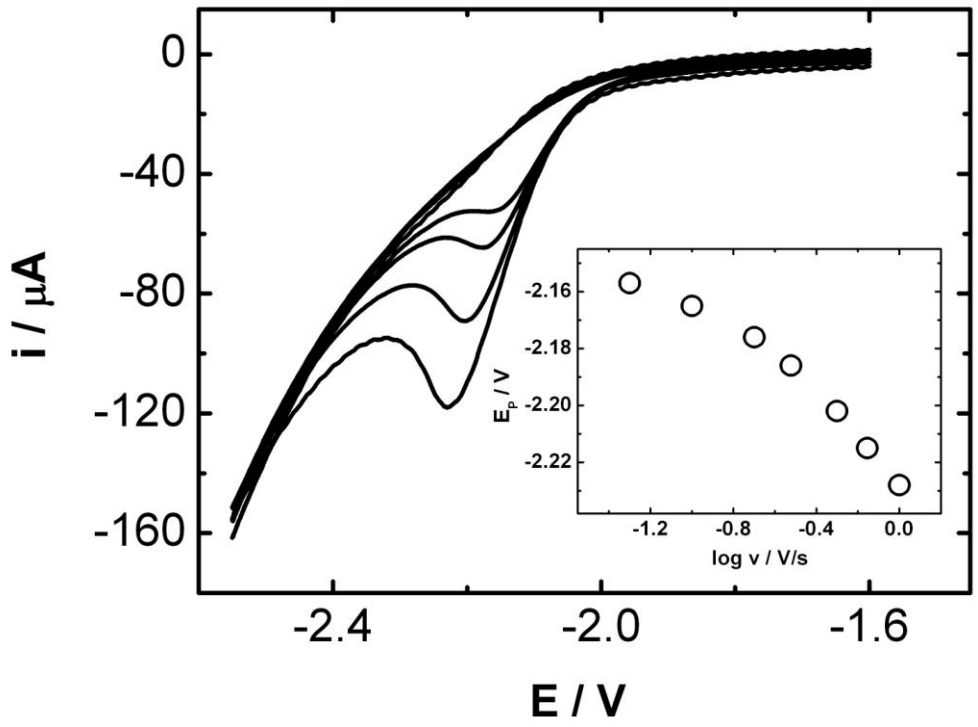
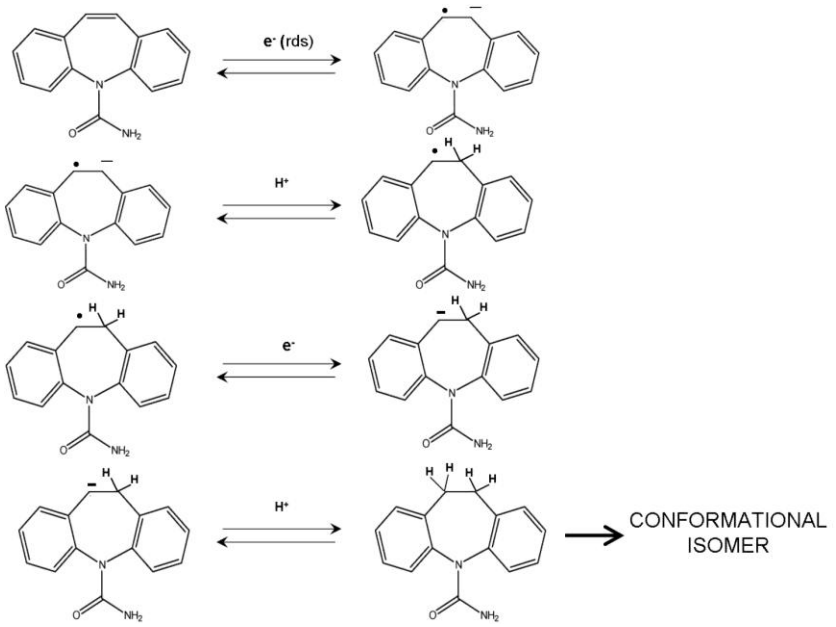


Figure 4. Cyclic voltammetry of CBZ 350 μg mL^{-1} in water solution (10% ethanol) containing 0.1 M TEAP at several scan rates: 0.1, 0.2, 0.5, 1.0 V/s. Inset shows variation of peak potential versus logv

Also, the pH did not produce any changes in neither the peak potential nor in the maximum current in agreement with a first electronic slow step (6≤pH≤10 interval, measurement not shown in this paper).

The mechanism scheme proposed for the electrochemical reduction of carbamazepine in water solutions is the same than that suggested for an ethanol solution with an electrochemical E overall step including the transfer of two electrons and two protons and the following chemical reaction being the conformational isomerization of the reduction product (EqC, Scheme 2).



Scheme 2

The study using digital simulations lead to the following electrochemical parameters: $E_{1/2}$=-2.042 V vs SCE, α = 0.51±0.08 y D = (4.44±0.52)·10^{-6} cm^2/s. Also, the heterogeneous electron transfer rate constant k_h = (4.35±0.57)·10^{-4} cm/s and the homogeneous chemical rate constant $k \geq 22.8 s^{-1}$ are compatible with the suggested mechanism within the scan rate studied.

It is interesting to highlight that the behavior observed in ethanol and water relative to the hydrogenation of the double bond C=C of CBZ is similar to that found in other substances with this electroactive group [20], with a initial reduction to a radical anion, rapid protonation, subsequent reduction to an anion and followed by also fast protonation yielding the C-C saturated bond.

3.2. Differential Pulse Voltammetry (DPV)

Figure 5 shows the voltammograms obtained for CBZ using DPV under the same experimental conditions as those used in CV. The cathodic peak potentials obtained were -2.121 and -2.057 V for ethanol and water respectively. This shows good agreement with the values obtained for $E_{1/2}$ in CV.

For both solvents it can be observed that the value obtained for the anodic peak current is much lower than that obtained for the cathodic peak. In both cases the characteristic of DPV curves are corresponding to a charge transfer control electrochemical process [21].

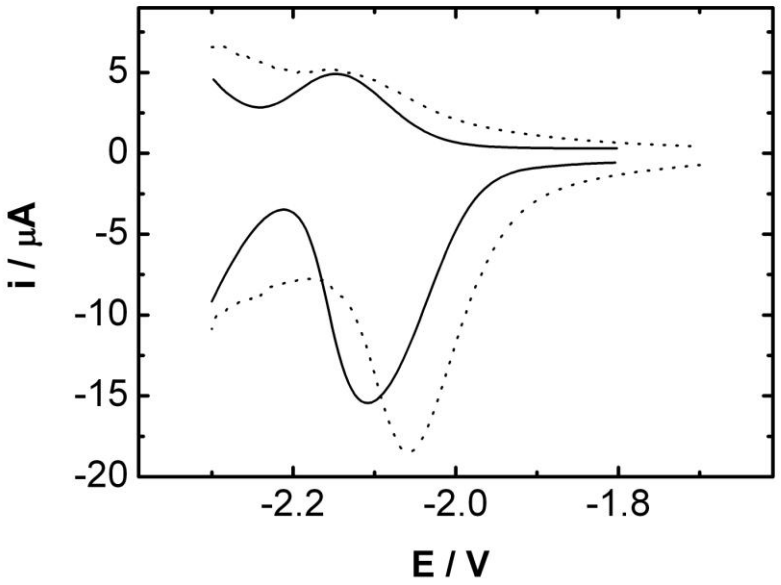


Figure 5. DPV of CBZ 472 μg mL^{-1} ($2 \cdot 10^{-3}$ $mol \cdot L^{-1}$) in ethanol (solid line) and water (dots line).

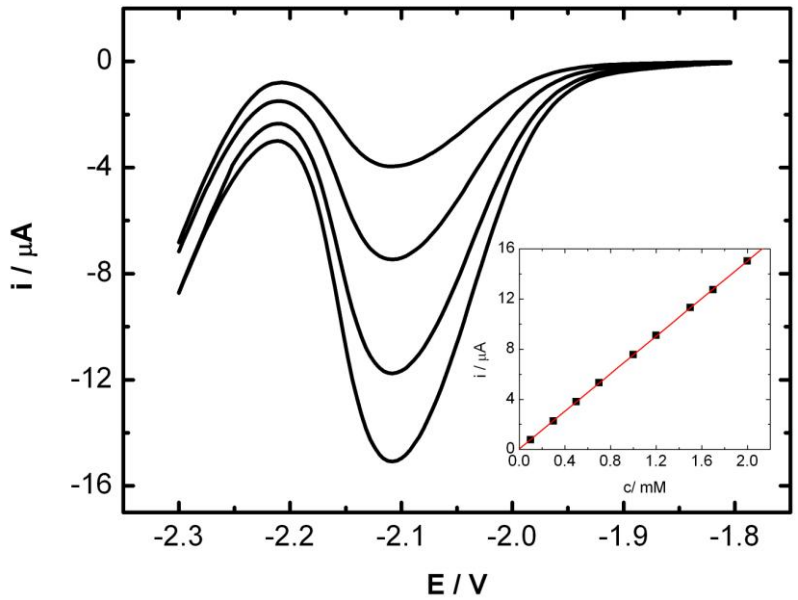


Figure 6. DPV of CBZ at several concentrations in ethanol. From top to bottom: 0.5, 1, 1.5, 2.0, $mol \cdot L^{-1}$. Inset: Plot of the cathodic peak current vs concentration.

Figure 6 shows some DPV curves obtained when CBZ was analysed in ethanol in a range of concentrations from 24 to 470 $\mu g \cdot mL^{-1}$ (10^{-4} to $2 \cdot 10^{-3}$ $mol \cdot L^{-1}$). The signal obtained for the different experiments increased linearly with CBZ concentrations. Peak potential is independent of the CBZ concentration according to the proposed mechanism. The correlation coefficient obtained for the line of best fit in the case of ethanol is $r^2 = 0.9993$ and $r^2 = 0.9974$ when water is used as solvent. The limits

of detection obtained for both ethanol and water were 1.1 y 9 μg/mL, respectively. In water solutions the proximity between the signal of CBZ and the discharge of the supporting electrolyte increases the limit of detection. The addition of acetic acid in ethanol leads to a better sensitivity and a lower limit of detection. The limit of quantitation was calculated to be 10.77 and 2.11 μg/mL for water and ethanol, respectively. Precision expressed as % RSD (n=5) was also calculated and was 3.32 and 2.17, respectively. The linear range was calculated 11-600 μg/mL and 3-500 μg/mL.

These limits of detection in aqueous solutions are higher than those reported in similar experimental conditions for several authors when they studied the electro-oxidation of CBZ [10-11]. The anodic signal of the electro-oxidation of CBZ is between three and four times over the cathodic one of the electro-reduction. Moreover the proximity of signal of the discharge of supporting electrolyte at negative potential explains these results. On the other hand a similar LD to that found in other solvents is found in ethanol solutions where the presence of acetic acid decreases the background current with increasing the sensitivity of the electrochemical signal.

3.3. Solvent effect

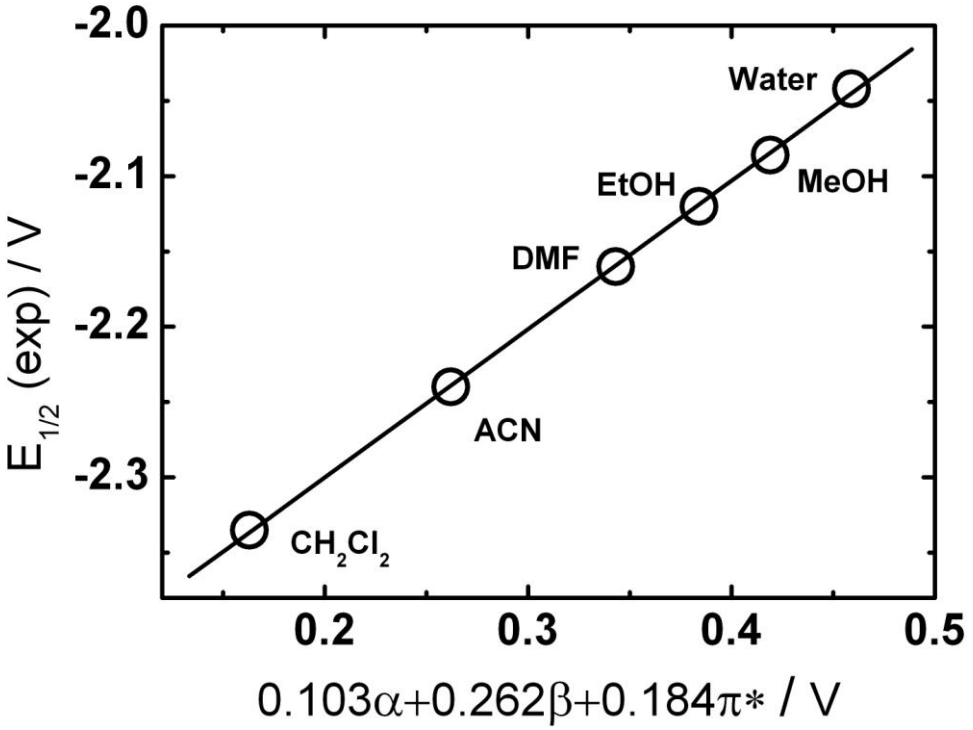


Figure 7. Variation of experimental $E_{1/2}$ with the linear combination found by regression methods for Kamlet-Taft solvent polarity parameters. The $E_{1/2}$ values for dichloromethane and methanol corresponding to measurement not shown in this paper.

There are many physicochemical, biological, toxicological and pharmacological properties that can be studied by polarity measures [22]. In this sense, we found that potential $E_{1/2}$ for CBZ in the solvents studied (in this work and those solvents of the ref [8]) is sensitive to the solvent polarity.

Kamlet-Taft approach represent a linear combination of the dipolarity /polarizability effect (π^*), hydrogen-bond donor parameter (α) and hydrogen-bond acceptor parameter (β) contributing to de overall solvent polarity [23,24].

$$SP = SPo + a\alpha + b\beta + p\pi^* \quad (2)$$

where SP is the solute property, and the regression coefficients SPo, a, b and c measure the relative susceptibilities on the solute property to the indicated solvent parameter.

In our system, linear multiple regression methods were carried out by using Microcal OriginPro (version 7) computer software. The correlation between the reduction potential and solvatochromic parameters via equation (2) is excellent (R^2=0.9994) and given by $E_{1/2}$ = -2.503(±0.004) + 0.104(±0.003)α + 0.257(±0.005)β + 0.188(±0.003)π^*. Figure 7 shows the representation of the experimental $E_{1/2}$ versus the linear combination of Kamlet-Taft parameters where a regression coefficient of 0.99986 is obtained. This behaviour allows a best knowledge about the interaction between CBZ with different environment, and it could be interesting for the study of the drug with forensic purposes.

3.4. Application to tablets and biological samples

Table 1. Precision and recovery values for carbamazepine in plasma (12 mg/L) and carbamazepine tablets (200mg).

Sample	Average[1] (n=3)	% RSD[1]	% Recovery[1]
Tablet A[2]	208.2/203.6	6.01/4.23	104.1/101.8
Tablet B[2]	211.6/204.1	5.45/5.12	105.8/102.0
Tablet C[2]	203.3/202.1	5.72/4.21	101.6/101.0
Tablet D[2]	209.0/201.2	5.27/3.45	104.5/100.6
Plasma A[3]	11.59/12.32	4.35/3.18	96.6/102.7
Plasma B[3]	12.71/12.34	5.96/4.05	105.9/102.8
Plasma C[3]	12.81/12.67	4.89/4.15	106.7/105.6

[1] water values/ethanol values
[2] units mg
[3] units mg/L

Table 1 summarises the precision and recovery obtained in the analysis of a set of tablets containing 200 mg of carbamazepine and spiked plasma samples containing the maximum recommended therapeutic dose (12µg/mL). As observed, the precision expressed as % RSD is not greater than 6% in all cases and the average recovery for the tablets was 104.00±1.75 and 101.35±0.66 % in water and ethanol respectively and 103.06±5.61 and 103.70±1.65 % for the plasma samples in water and ethanol respectively.

4. CONCLUSIONS

The electrochemical reduction of carbamazepine in ethanol and water using a glassy carbon electrode by CV and DPV has been achieved. The reduction process is consistent with a EqC mechanism involving a bielectronic charge transfer and the following chemical reaction of conformational isomerization of carbamazepine. Electrochemical parameters, such as half-wave potential, transfer coefficient and diffusion coefficient, as well as, the heterogeneous electron transfer rate constant and a limit value of the homogeneous chemical reaction rate constant of the posterior reaction have been determined from voltammetric measurements and digital simulation. Sensitivity of $E_{1/2}$ to solvent polarity was analysed as a useful tool to know the chemical environment in which carbamazepine is found within different matrices in the context of forensic and pharmaceutical analysis. Analytical characteristics, such as LOD, precision, % recovery and calibration ranges have also been presented for both solvents. The analysis in plasma and tablets demonstrates the applicability of the proposed methodology in real samples.

ACKNOWLEDGEMENTS
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