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Preparation of Unique Potentiometric Carbon Paste Sensor for Determination of Diazepam in Pharmaceutical applications

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In this study, the effect of various produce conditions on the construction and general performance of a novel modified carbon paste electrode for the determination of diazepam was discussed. Diazepam - tetraphenylborate (DZP-TPB) ion pairs have been prepared and used as electro active materials. The electrode shows a stable, potentiometric response for diazepam in the concentration range 1×10^{-2} - 5×10^{-5} M at 25 °C independent of pH in the range 3 – 5. The electrode passed near Nernstian cationic slope of 58.6±0.2 mV and lower detection limit of 8×10^{-7} M with a fast response time of 5-10s. Selectivity coefficients for diazepam relative to a number of interfering substances have been investigated. There is a negligible interference from the studied cations. These results have been obtained using the proposed electrodes by using a (HPLC) reference method showed that the ion-selective electrode technique is sensitive, reliable and can be used with very good accuracy and high % recovery without pretreatment procedures of the samples to minimize interfering matrix effects.

Keywords: Diazepam; Tetraphenylboratet; carbon paste; potentiometric sensor

1. INTRODUCTION

Benzodiazepines are psychoactive therapeutic compounds possess sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnesic actions [1, 2], which are useful in a variety of indications such as alcohol dependence, seizures, anxiety, panic, agitation and insomnia. They slow down the activity of the central nervous system. Benzodiazepines are classified as short, intermediate or long-acting. Short and intermediate-acting benzodiazepines are preferred for the treatment of insomnia. Longer-acting benzodiazepines are recommended for the treatment of anxiety.

Diazepam(7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiapin) (fig.1) [3], first synthesized by Leo Sternbach[4] is used to treat a wide range of conditions, and has been one of the

most frequently prescribed medications in the world since its launch in 1963.Diazepam (DZP) is a benzodiazepine with a rapid onset of action [5] and high efficacy rates which is important for managing acute seizures, anxiety attacks and panic attacks; benzodiazepines also have a relatively low toxicity in overdose[6]. Diazepam commonly used in intravenous anesthesia induction, anticonvulsant , muscle spasms, restless legs syndrome, alcohol withdrawal, benzodiazepine withdrawal, opiate withdrawal, sedation and hypnotic medication [7-9]. Diazepam occurs as solid white or yellow crystals with a melting point of 131.5 to 134.5 °C. It is odorless, and has a slightly bitter taste. The diazepam as being very slightly soluble in water, soluble in alcohol and freely soluble in chloroform.

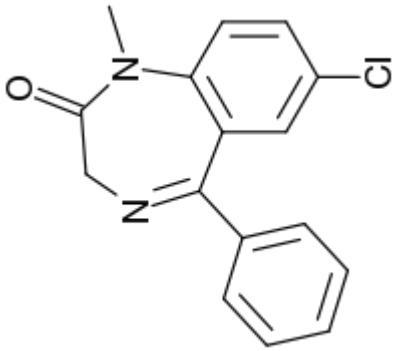

Figure 1. Structural formula of Diazepam.

Several analytical methods have been published for the determination of DZP with or without its metabolites in different biological fluids. These techniques utilized high performance liquid chromatography (HPLC)[10-17], spectrophotometry[18-21], thin layer chromatography [22], gas chromatography [23-25], polarography [26-28], fluorimetry [18,29,30],IR spectrometry [31], solid-phase micro extraction (SPME) [32], capillary zone electrophoresis (CZE) [33,34] and potentiometry [35,36]. In this work, we introduce a very simple and inexpensive (potentiometric) method in determination of diazepam in a wide concentration range and in presence of variety of metal ions with minimum number of interferences. This method, potentiometric characterization, and analytical application of a novel diazepam-modified carbon paste electrode based on the use of diazepam-tetraphenylborate (DZP-TPB) as electro active material and dioctylphthalate (DOP) as plasticizer.

2. EXPERIMENTAL

2.1. Materials

Pure diazepam were purchased from Cambrex. Tablet diazepam 10 mg was obtained from Loghman pharmacy. All Reagents used were chemically pure grade and doubly distilled water was used throughout. Sodium tetraphenylborate (Na-TPB), graphite powder, acetic acid, sodium acetate, hydrochloric acid, mineral oil and methanol were obtained from Merck. O-nitrophenyloctylether (o-NPOE) was obtained from Fluka. Bis (2-ethylhexyl) adipate (DOA), dioctylsebacate (DOS) and

dioctylphthalate (DOP) were obtained from Aldrich. All other solutions used in interference studies and electrode applicability were prepared from analytical grade salts (all from Aldrich or Merck).

2.2. Apparatus

All potentiometric measurements were made at 25±1°C unless otherwise stated using a Metrohm potentiometer (pH meter /Ion meter model of 781) and a combined Metrohm pH electrode (model 9101) was used for pH measurements. Saturated calomel electrode (SCE) was used as a reference electrode. The electrochemical system is represented as follows:

Hg, Hg_2Cl_2(s), KCl (sat.)‖sample solution ⎪carbon paste electrode⎪Cu

2.3. Standard solutions

2.3.1. Diazepam standard solutions

Stock solutions (1×10^{-2} M) were prepared by dissolving the proper weight of 142.35 mg diazepam drug into 20.0 ml 1×10^{-2} M HCl. A 2.0M HCl solution was added drop wise with continuous stirring till complete drug dissolution was achieved. The pH was adjusted to about 4 with dilute NaOH solution. The resulting solution was then made up to 50 ml in a measuring flask using the 1×10^{-2}M HCl. Working solutions of each drug in the concentration range (1×10^{-2} to 1×10^{-5} M) were prepared by serial accurate dilution with the 1×10^{-2}M HCl solution.

2.3.2. Tetraphenylborate solution (TPB)

A 2×10^{-2}M sodium tetraphenylborate solution was prepared by dissolving 342mg into 50ml de-ionized water. The resulting solution was standardized by potentiometric titration against 2×10^{-2}M silver nitrate solution using a silver/silver sulfide electrode in conjunction with a double-junction saturated calomel electrode.

2.3.3. Interfering ions solutions

A 10^{-3}M standard solution each of cobalt nitrate, cadmium nitrate, calcium nitrate, nickel nitrate, aluminium nitrate, chormium nitrate, barium nitrate, iron sulfate, copper chloride, lead nitrate, zinc nitrate, fructose, sucrose, galactoside and uric acid were prepared by dissolving the proper weights into 100 ml of de-ionized water. A 500 ppm starch solution was prepared by dissolving 50 mg into 100 ml de-ionized water.

2.4. Preparation of diazepam-TPB ion pair complexes

A 2×10^{-2}M of diazepam drug solution was prepared by dissolving the proper weight into 25 ml aliquots of 2×10^{-2}M HCl. Equal volume of 2×10^{-2} M, tetraphenylborate (TPB) solution was added drop wise with continuous stirring. The resulting precipitate were left over night to settle down, filtered through G-4 sintered-glass crucibles, washed with distilled water till no chloride ion was detected in the filtrate and dried under vacuum for 48 h.

2.5. Preparation of the diazepam-modified carbon paste electrode

The diazepam-modified carbon paste electrode (DZPCPE) was prepared by mixing weighed amounts of DZP-TPB as electro active material, graphite powder, plasticizer and methanol thoroughly until obtaining a uniformly wetted paste. Portions of the resulting Composite material were then packed in the end of a disposable polyethylene syringe (3 mm i.d., 1ml), the tip of which had been cut-off with a razor blade. Electrical contact to the carbon paste was made with a copper wire. Fresh surface was obtained by applying manual pressure to the carbon paste. The resulting fresh surface was polished on a filter paper until it had a shiny surface. The electrode surface was polished gently with smooth tissue of paper when the diazepam solution is changed from high concentration to a dilute solution. The newly prepared indicator electrode was conditioned by soaking in a 1×10^{-2} M aqueous diazepam solution for 1h and stored in the same solution when not in use.

2.6. Procedure

The diazepam-modified carbon electrode was calibrated by immersion in conjunction with the reference electrode in a 50 ml beaker containing 9 ml of acetate buffer solution of pH 4. Then 1 ml aliquot of diazepam solution of concentration ranging from 1×10^{-2} to 5×10^{-5} M was added with continuous stirring and the potential was recorded after stabilization to ±/0.2 mV. A calibration graph was then constructed by plotting the recorded potentials as a function of -log [diazepam]. The resulting graph was used for subsequent determination of unknown diazepam concentration.

2.7. Determination of diazepam in diazepam tablet

Diazepam was determined in diazepam injection solution (10 mg/1gr) by transferring the contents of one tablet of diazepam into a 100 ml measuring flask, and making up to the mark with water. Fifty and hundred microliters aliquots of the solution were transferred to the measuring cell containing 9.0 ml of acetate buffer, and the e.m.f. of the electrode systems was measured. The concentration of diazepam was calculated from the previous calibration graph as in the procedure. Alternatively, the standard addition technique was used for the determination of diazepam by monitoring the potential of the drug solution before and after the addition of a known concentration of

the diazepam solution. The determination of diazepam content in diazepam ampoule and tablet has been carried out using HPLC methods [37] after appropriate dilution of the diazepam concentration.

2.8. Determination of diazepam in Biological Fluids

Different quantities of diazepam and 1mL serum were transferred to a 50mL measuring flask and completed to the mark with 1×10^{-4} M HCl to give solutions of pH values ranging from 4 and concentrations of 1×10^{-2} to 1×10^{-5} M diazepam. These solutions were subjected to the standard addition method for the potentiometric determination of diazepam.

2.9. Selectivity of the Sensor

Potentiometric selectivity factors of the electrode were evaluated by applying the matched potential method (MPM) [38]. According to this method, the activity of (CPM) was increased from $a_A = 1\times10^{-4}$ M (reference solution) to $a'_A = 2\times10^{-4}$ M, and the change in potential (ΔE) corresponding to this increase were measured. Next, a solution of an interfering ion of concentration a_B in the range 1×10^{-1} at 1×10^{-2} M is added to new 1×10^{-4} M (reference solution) until the same potential change (ΔE) was recorded. The selectivity factor, $k_{A,B}^{MPM}$ for each interferent was calculated using the following equation:

$$K_{A,B}^{MPM} = (a'_A - a_A)/a_B$$

3. RESULTS AND DISCUSSION

Tetraphenylborate was used as an ion-pairing agent for the preparation of an electro active ion association complex for diazepam. The elemental analysis of the sparingly soluble complex of DZP-TPB showed that the composition of the complex is 1:1 (diazepam: tetraphenylborate). The dry powder of the formed ion-pair was used for the preparation of the new diazepam-modified carbon paste electrode. [39- 41]

3.1. Response characteristics of modified and unmodified carbon paste electrode

The unmodified electrode showed no significant response under the optimum conditions (Fig. 2). As can be seen, the electrode without ion-pair modifier and ion-pair modifier gave a working concentration range of 1×10^{-2} to 1×10^{-5} with a slope of 24.2 and 47.4 mV of the analyte.

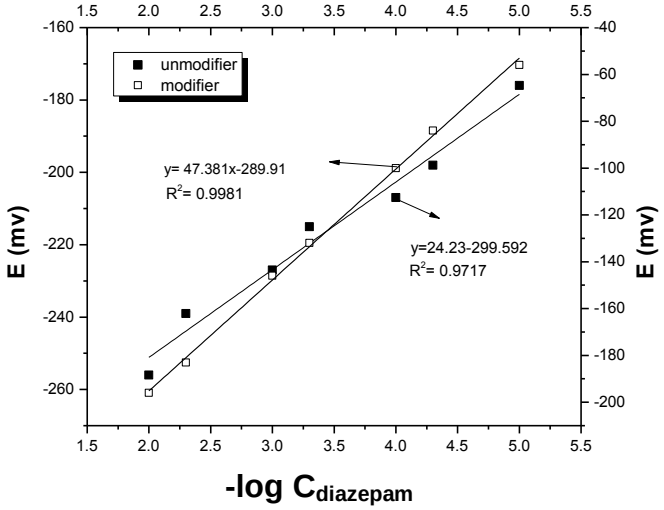

Figure 2. Response of modified and unmodified carbon paste electrode under the optimum conditions. *Conditions:* buffer acetate with pH = 4, 5% modifier

3.2. Optimization of the amount of modifier in the electrode

It is known that the sensitivity and linearity for a given electrode depend significantly on the amount of the ion-pair in the membrane composition. Thus, the influence of the percent of DZP-TPB in the carbon paste composition was investigated. Preliminary experiment showed that carbon paste electrode which does not contain the ion-pair modifier with slope 4.1 has no response towards the analyte. For this purpose, five electrodes were prepared that contain the ion-pair modifier in 5, 10, 12, 15, and 20%, while the other components have been kept unchanged, and the results are summarized in Table 1. The resulting slopes and correlation coefficients are 47.4 (0.998), 53.3 (0.993), 58.6 (0.998), 51.4 (.984) and 41.7 (0.989) mV per decade. These results show that for the electrode that contains 12% of the modifier, a Nernstian slope has been obtained. A nonlinearity in the electrode response has been observed with electrodes that contain less or higher ratios of the modifier. Since the electrode with 12 % of ion-pair has a good slope and wide range of linearity, this percentage was chosen as the optimum amount for the diazepam electrode.

Table 1. General characteristic of some different composition of DZPCPE

Composition of the modified chemical (%)	slope	Range of determination (M)	Lower LOD (M)	Correlation coefficient, r
5	47.4±0.3	1×10^{-2} - 1×10^{-5}	1.0×10^{-6}	0.998
10	53.3±0.1	1×10^{-2} - 1×10^{-5}	5.0×10^{-6}	0.993
12	58.6±0.2	1×10^{-2} - 1×10^{-5}	8.0×10^{-7}	0.998
15	51.4±0.2	1×10^{-2} - 1×10^{-5}	5.0×10^{-6}	0.994
20	41.7±0.3	1×10^{-2} - 1×10^{-5}	8.0×10^{-6}	0.989

Conditions: buffer acetate with pH = 4, plasticizer DOP 40%

3.3. Effect of plasticizer on the potential response

Next five electrodes were prepared that contain the ion-pair modifier 12%, Graphite powder 48% and different plasticizer (mineral oil, DOS, DOA, o-NPOE, and DOP) 40% the results are summarized in Table 2. The results show that for the electrode that contains DOP as plasticizer, a Nernstian slope has been obtained. Fig. 3 shows that the linear ranges of the electrode that contain ion-pair complex 12%, Graphite powder 48% and DOP plasticizer 40% is in the Range of 1×10^{-2} - 1×10^{-5} M. The limit of detection (LOD) is 8×10^{-7}M, respectively. The least-squares equation obtained from the calibration data is

E (mv) = - (58.6±0.2) Log [diazepam] – 329.165

Table 2. General characteristic of different plasticizer of DZPCPE

Composition of the plasticizer chemical (%)	slope	Range of determination (M)	Correlation coefficient, r
DOS	52.8±0.2	1×10^{-2} - 5×10^{-5}	0.993
DOP	58.6±0.2	1×10^{-2} - 1×10^{-5}	0.998
DOA	51.1±0.3	5×10^{-3} - 1×10^{-5}	0.991
o-NPOE	45.9±0.3	5×10^{-3} - 1×10^{-5}	0.975
mineral oil	47.6±0.3	5×10^{-3} - 1×10^{-5}	0.989

Conditions: buffer acetate with pH = 4, 12% modifier, 48% graphite powder, 40% plasticizer

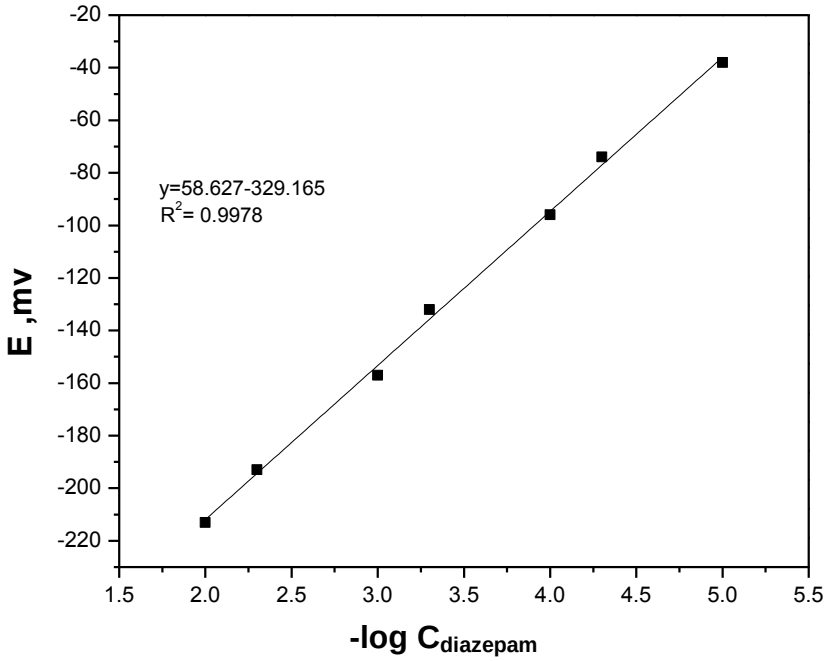

Figure 3. Calibration graph

3.4. Repeatability or reproducibility

The repeatability of the method has been examined by measuring the potential response of different concentrations of diazepam over a wide time interval of 1 week. The repeatability of the measuring solution has been found to be within ±/1 mV over a week.

3.5. Effect of pH

The behavior of the electrode in relation to the variation of pH (2–7.5) at concentration of 1×10^{-4}M of diazepam was studied (Fig. 4). For measuring the pH, adjustments were made with the concentrated hydrochloric acid or sodium hydroxide solutions. It can be seen from Fig.4 that the variation in potential due to pH change is considered acceptable in the pH range 3 – 5. However, there is an observed drift at pH values lower than 3 which may be due to H^+ interference. On the other hand, the potential increases gradually at pH values higher than 5. This is possibly attributed to the diazepam the base form with lower solubility causing the electrodes potentials to decrease. The potentiometric curves of diazepam in buffer solutions with different pH values are illustrated in Fig. 5. According to Fig. 5 pH 4 offered a better slope and a wider linear range than in the other pH values.

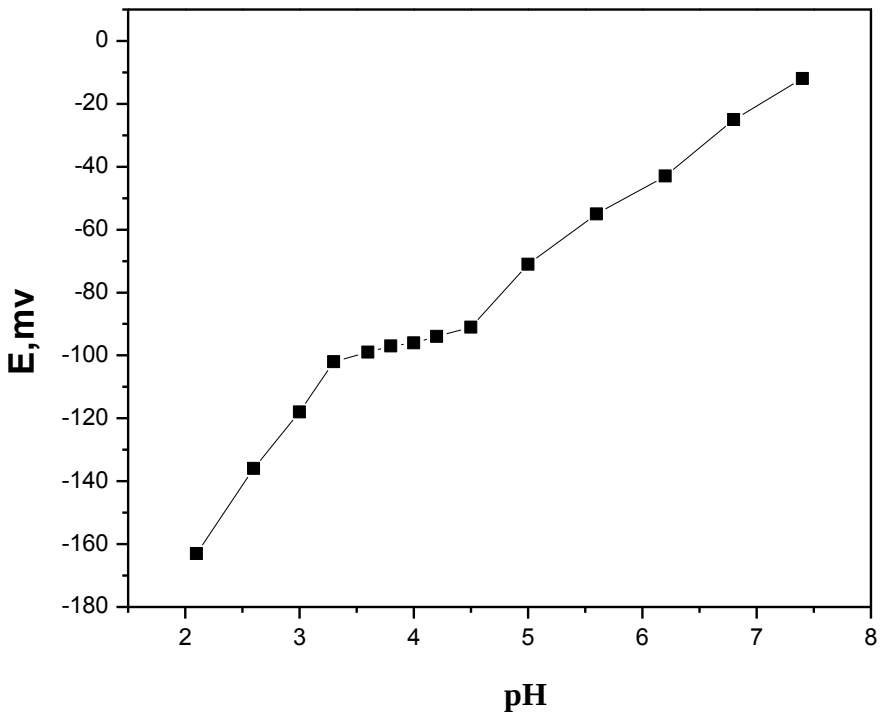

Figure 4. The pH effect on potential response of the diazepam electrode (conditions: 10 % ion-pair modifier, diazepam concentration was 1.0×10^{-4} M).

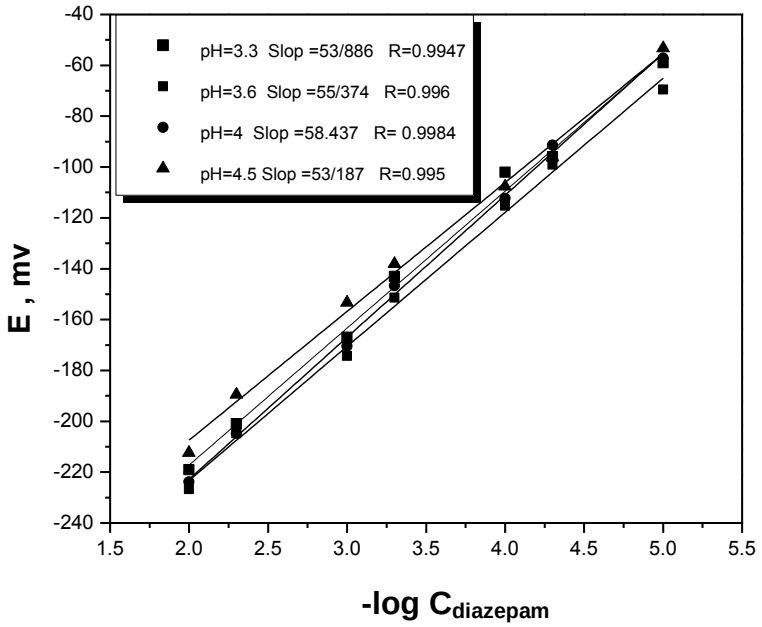

Figure 5. Potentiometric curves of the proposed electrode at various pH buffers (conditions: 10% ion-pair modifier, diazepam concentration was 1.0×10^{-4}M)

3.6. Effect of response time

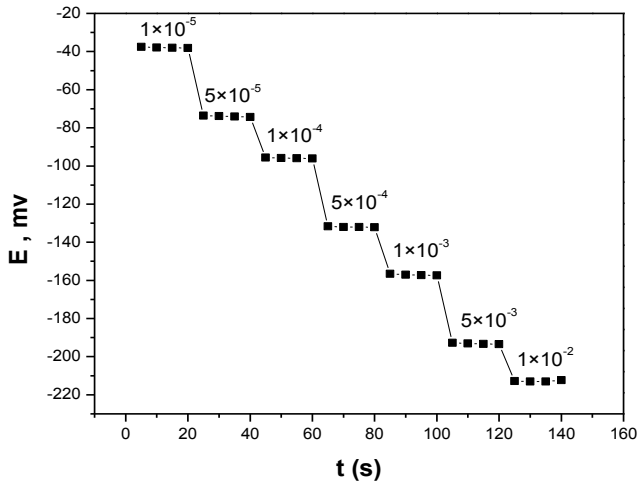

Figure 6. Dynamic response characteristics of diazepam carbon paste electrode for different concentration diazepam.

The dynamic response time of the modified electrode was measured according to IUPAC recommendation [42]. The response time of the electrode is defined as the time required for the electrode to reach a stable potential within ±1 mV of the final equilibrium value after successive immersions of the sensor of a series of diazepam solutions, each having difference in concentration,

was studied, The static response time of the diazepam carbon paste electrode was 3-8 s over the concentration range (1×10^{-2} to 1×10^{-5} M) is shown in Figure 6, at lower concentrations, The response time was delayed and reached to 10 s and no change is observed up to 3 minutes. The repeatability of the potential reading of the electrode was examined by subsequent measurements (high to- low cycles) in 1×10^{-4} M diazepam solution immediately after measuring the first set of solutions at 5×10^{-5} M diazepam is show in figure 7.

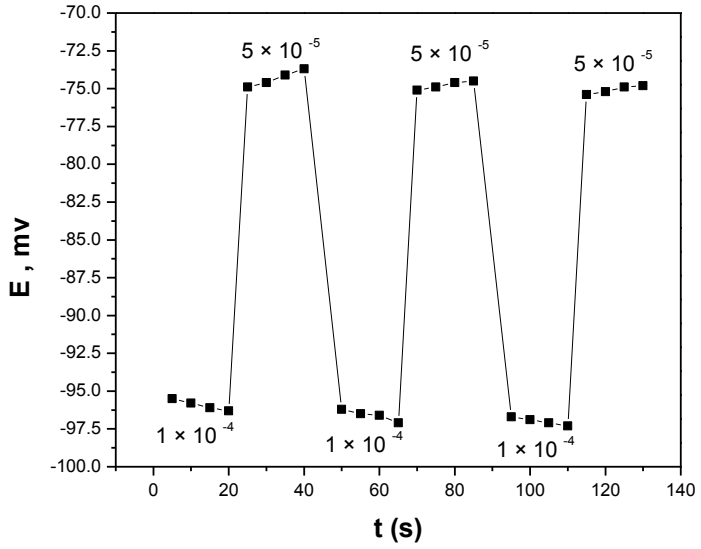

Figure 7. Dynamic response characteristics of diazepam carbon paste electrode for several high- to-low cycles.

3.7. Potentiometric Selectivity

The potentiometric selectivity coefficient of an electrode, as one of the most important characteristics, is defined by its relative response for the primary ion over the other ions present in the solution [43]. The selectivity coefficients of the modified carbon paste electrode towards many inorganic cations, drugs, carbohydrates were evaluated by the matched potential method (MPM) [37]. This method measures selectivity coefficients of ionic and nonionic species; it has an advantage of removing limitations imposed by Nikolsky –Eisenman equation while calculating selectivity coefficients by other methods. These limitations include non- Nernstian behavior of interfering ions and problems of inequality of charges of primary and interfering ions [44]. The values of the selectivity coefficients are listed in Table 3; they reflect a very high selectivity of this electrode for drug over most of the tested species. The results listed in Table 3 reveal that there were no significant interferences from any of the tested substances. Overall, the designed electrode is useful for the intended measurements.

Table 3. Potentiometric selectivity coefficients of some interfering ions

Interferent, J	$k^{pot}_{diazepam,j}$	Interferent,J	$k^{pot}_{diazepam,j}$
Ca^{+2}	1.01×10^{-3}	Fe^{+2}	5.5×10^{-4}
Pb^{+2}	9.1×10^{-4}	Al^{+3}	3.1×10^{-3}
Cd^{+2}	8.7×10^{-4}	Cr^{+3}	9.3×10^{-4}
Zn^{+2}	6.5×10^{-4}	sucrose	8.9×10^{-3}
Ni^{+2}	7.1×10^{-4}	glucose	7.8×10^{-3}
Cu^{+2}	6.2×10^{-4}	fructose	1.08×10^{-2}
Ba^{+2}	1.2×10^{-3}	uric acid	1.01×10^{-2}
Co^{+2}	6.1×10^{-4}		

3.8. Pharmaceutical preparations

Diazepam in pharmaceutical preparation (tablet) were analyzed and their concentrations were determined using the proposed electrode. The results are listed in Table 4. Applying least-squares method for three determinations gave a 95% confidence level for the slopes and intercepts.

The regression line equation (taken versus found) for the proposed carbon paste electrode can be represented by:

Y=0.9842(±0.0058) X – 0.0976(±0.147)

R=0.9999

Where X is the average reference assay and Y is the average of the proposed method. Correlation coefficient values of 0.9999 were obtained. The relative mean errors obtained ranged from1.15 to 1.68% with % recovery from 98.31 to 98.84% (Table4).

These results indicate that the proposed electrode can be used to determine diazepam in pure samples or in pharmaceutical preparations with high accuracy, precision and high % recovery without pretreatment procedures of the samples to minimize interfering matrix effects.

Table 4. Determination of diazepam in pharmaceutical preparations using carbon paste electrode

Taken / µg ml^{-1}	Diazepam carbon paste electrode (DZPCPE)		Reference HPLC method	
	Found[a]/ µg ml^{-1}	% Recovery	Found[a]/ µg ml^{-1}	% Recovery
142.4	140.75	98.84	141.2	99.16
28.48	28.1	98.67	28.2	99.02
14.24	14.0	98.31	14.1	99.02

4. CONCLUSION

In the present work, a novel modified carbon paste electrode was constructed for determination of diazepam. It offers a simple, accurate, selective, and specific tool for quantitative determination of

diazepam content in its pharmaceutical preparation, diazepam tablet. The sensor demonstrated advanced performances with a fast response time, a lower detection limit of 8×10^{-7} M and potential responses across the range of 1×10^{-2} - 1×10^{-5} M. The sensor enabled the diazepam determination in pharmaceutical formulations. This sensor respond based on ion-exchange mechanism. The best performance of carbon paste electrode was achieved by the ion-pair modifier 12%, Graphite powder 48% and plasticizer DOP 40%. A carbon paste electrode was designed to improve the analytical responses. And also a response of this developed method was compared with HPLC method.

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