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(RESEARCH ARTICLE)

Improvement of performance of anti-cancer (dacarbazine) drug sensor utilizing tetraphenylborate anion

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Abstract

A sensor for dacarbazine, an anticancer drug denoted DAC, is presented. A dacarbazine-modified carbon paste electrode was fabricated and improved by incorporation of sodium tetraphenylborate as an additive. Dacarbazine–phosphotungstate, a salt of dacarbazine abbreviated DAC-PT, was used in a carbon paste electrode as an ion-pair. Incorporation of sodium tetraphenylborate abbreviated STPB as an additive distinctly improved the slope from 43.7±0.3 to 55.6±0.3 mV per decade of DAC ion. The present electrode exhibits linearly over a wide concentration range from 1.80×10^{-6} to 1.0×10^{-2} M with a notably small detection limit of 8.9×10^{-7} M in a significantly fast response time (~ 5 s). These measurements are independent of the pH of the test solution in the pH range 3.2 to 9.5. The present sensor has distinct selectivity toward the drug ion over other common inorganic ions, sugars, amino acids, and drugs. This sensor was satisfactorily used as an indicator in potentiometric titrations and determination of dacarbazine in pharmaceutical preparations and urine samples.

Keywords: Carbon paste electrodes; Dacarbazine; Anticancer drug; Potentiometry; Ion selective electrode

1. Introduction

Dacarbazine (DAC), 5-(3,3-dimethyl-1-triazenyl) imidazole-4-carboxamide shown in Figure 1**,** is a highly lipid-soluble and light-sensitive agent used as an antineoplastic drug to treat various cancers [1]. A derivative of dacarbazine, dacarbazine citrate, is soluble in water. Dacarbazine is one of the most commonly drugs in chemotherapy used for treating various cancers. However, its short half-life in blood circulation, low response rate and high side effects [2] curtail its determination by currently used methods and makes worthy finding an alternative for this purpose.

Several analytical techniques have been used to evaluate dacarbazine in pharmaceutical products such as HPLC [3, 4], LC-UV [5, 6], LC-MS [7] and polarographic methods [8]. These methods have been useful and provided valuable results. However, they are long, costly in training the working personnel and maintenance of analytical equipment. Moreover, they produce chemical waste [9]. Therefore, development of a cheap, simple, sensitive, selective, fast and accurate is strongly desired and motivated this research. Chemically modified carbon paste electrodes are alternative as they were extensively used in electrochemical analysis for miscellaneous applications work [10–15]

Carbon paste electrodes (CPEs) circumvent most of the common aberrations in liquid membrane electrodes as transport into or out of the inner filling solution hampers the membrane response [16]. CPEs have good characteristics such as miniaturized size, lower detection limit, simple design, flexible use and low cost. In addition, providing fresh

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paste makes electrode renewal possible thus improving the analytical results. Therefore, CPEs caught attention and were utilized for in a variety of sensing and detection applications [10–14]Clearly, the function of a CPE basically depends on its structure. Directly follows from this fact that the nature and amount of the lipophilic additive in this electrode strongly influence the response of the membrane ion-selective sensor by reducing the membrane resistance, improving the response behavior and selectivity and in some cases, where the extraction capability is poor, increasing the sensitivity of the membrane sensors[17–20].

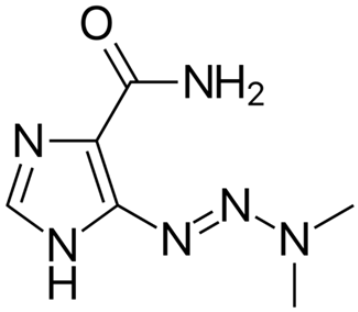

Figure 1 The chemical structure of Dacarbazine

This work involved fabrication of a new CPE for dacarbazine using DAC-PT ion-pair as for sensing the drug and improving its function by incorporation of sodium tetraphenylborate as an additive which improved the slope from 43.7±0.3 to 55.6±0.3 mV per decade. Remarkable results were obtained with the present electrode in determination of micromolar concentrations of DAC. Thus, the present electrode is useful for determination of this anticancer medication.

2. Experimental

2.1. Reagents

All reagents are analytical grade. Distilled water was used throughout experiments. Dacarbazine citrate (10 mg/mL) was manufactured by Lipomed (Switzerland), Medac (Germany) and Bionic (India). DAC solutions with the same concentration made by these sources were purchased from local stores. The plasticizers: dioctyl phthalate (DOP), dibutyl phthalate (DBP), dioctyl sebacate (DOS) and tris(2-ethylhexyl) phosphate (DOPh) as well as graphite powder (G, 99.9%, < 45μM) and Paraffin oil were purchased from Sigma-Aldrich (CH-9471 Buchs-Germany). Phosphotungstic acid (PTA) H3[PW12O40], sodium tetraphenylborate (STPB) Na[C24H20B], glutamic acid, aspartic acid, histidine, glycine, glucose, sucrose, fructose, galactose, maltose, lactose dextrose and other metal salts were obtained from Sigma-Aldrich (CH-9471Buchs-Germany). Ranitidine, chlorpheniramine maleate, tramadol hydrochloride, ephedrine hydrochloride, levocetirizine, paracetamol, diclofenac potassium, ibuprofen, tinidazole, lidocaine hydrochloride, metoclopramide, oxaloplatein and gemcetabine hydrochloride, doxorubcin hydrochloride, 5-flurouracil, cytrabine hydrochloride (anti-cancer drugs) were available from local drug stores (Gaza-Palestine).

2.2. Equipment

Potentiometric automatic titrator AT-400 was used for potential measurements, pH measurements were made on a digital pH meter (TOA Electronics HM-60V). CHNS Elemantal Analyzer (VARIO EL III Germany) was used for analysis of DAC-PT ion pair. A saturated calomel electrode (SCE) from Sigma-Aldrich was used for potential measurements in cell assemblies:

Hg, Hg2Cl2(s), KCl(sat) ||sample solution| carbon paste electrode.

2.3. Preparation of ion-exchanger complex

The ion-exchanger DAC-PT was made by mixing 10 mL of 0.01M DAC and 10 mL 0.0033M PTA according to a previously reported method [21]. An instant reaction occurred and produced sparingly soluble material that precipitated in the reaction vessel. The precipitate was collected, washed, dried and characterized by CHNS Elemental Analyzer that gave the following results:

Elemental analysis calculated for $C18H_{33}N_{18}O_{43}W_{12}P$: C = 8.48; H = 0.99; N = 3.44 was found: C = 8.89; H = 0.98; N = 3.46

2.4. Preparation of carbon paste electrode

The desired amounts of graphite, the selected plasticizer, lipophilic additive and the ion-pair making a total of 1.0 g were intimately mixed in a petri dish to make a homogenous paste. This paste was packed at the end of a small syringe cut at one end. Electrical contact was attained by a stainless-steel screw that was moved down to squeeze the paste against a smooth paper to ensure smoothness of the surface. The electrode was repeatedly used for potential determination until its deterioration indicating saturation of the surface layer. This layer is skimmed off to replenish the electrode activity.

2.5. Effect of interfering ions

The selectivity of the electrode was tested by the separate solution method (SSM) and the modified separate solution method (MSSM). SSM measures the potential of a certain interferent and the drug, one at a time, to obtain the net effect of each species [22, 23]. The equation 1

Equation 1. $$\log K_{DJ^{2+}}^{pot} = \frac{E_J - E_D}{S} + (1 - \frac{Z_D}{Z_J}) \log a_D$$

is used to measure the selectivity coefficient where EJ and ED are the measured potentials of the interfering ion and the drug respectively. S is the slope of the calibration graph. zD and zJ are the charge of DAC and interfering species respectively.

MSSM requires construction of the calibration curve of every selected ion and that of the drug ion separately. The selectivity coefficient may be obtained from the equation 2 by extrapolation of the line representing the potential versus log of the concentration to 0 [24, 25].

Equation 2. $$\log K_{DJ}^{pot} = \frac{E_J - E_D}{S_D}$$

This method eliminates any effect caused by the ionic charge as the above equation has no consideration of the charge of the ion involved in the measurement.

2.6. Analytical application

2.6.1. Calibration graph method

Proper amounts of DAC were added to 50.0 mL of water to make solutions comprising a concentration range from 2.0 × 10−7 to 1.0 × 10−2 M of the drug and the potential was recorded using the present electrode. As the present solutions are very dilute, the activity can be used instead of the concentration since the activity coefficients become very close to unity. The potential was plot versus logarithm of DAC activity and used for subsequent determinations of unknown DAC.

2.6.2. Potentiometric titration method

A 10.0-mL of 1.0 10-2 M DAC solution was transferred to a 25 mL beaker and potentiometrically titrated against 1m M PTA and STPB one at a time. The end point was taken from a plot of the measured potential vs. volume of titrant.

2.6.3. Analysis of drug in spiked urine samples

The concentration of DAC-spiked urine samples was made by mixing 5.0 mL down to 0.25 mL of urine and diluting with water to 25.0 mL to get 1.0×10−5 M, 1.0×10−4 M and 1.0×10−3 M DAC solutions respectively. The concentrations were measured by the calibration curve method. Each analysis was repeated three times and the standard deviation of the results was evaluated.

3. Results and discussion

The recommendation of the IUPAC [26] indicate many important factors in the performance of the electrode such as composition of the electrodes, the amount of ion-exchanger, plasticizer, lipophilic ion and g/p ratio. The operational conditions such as pH, temperature, response time of the electrode are also effective.

3.1. Optimizing the composition of the sensor

A lipophilic ion-pair, incorporating the drug cation with a counter anion, that has good solubility in the paste matrix was made and incorporated in each electrode to prevent leaching from the paste into the sample solution [27]. The sensor gave good response to the drug with changes in concentrations of DAC ions as electrodes comprising variable amounts (0.0, 1%, 2%, 3%, 4%, and 5%) of DAC-PT were tested. The composition of ion- exchanger DAC-PT with best response, that is closest to Nernstian behavior, was 4% . This electrode showed good slope, concentration range, detection limit and response time. Increasing the percentage of ion-pair (>4%) and decreasing it (<4%) give poor sensitivity to the electrode response of DAC as shown as in Table 1. The sensitivity and selectivity of the electrode depend on the composition and the relative amounts of the ingredients of the electrode, basically graphite and plasticizer [28]. Electrodes comprising graphite/plasticizer (g/p) ratios of (0.80 - 1.20) were tested. The sensor with the lowest detection limit and the closest Nernstian slope contains g/p = 1.00. It was chosen for full characterization of this electrode. The plasticizer should preferably have high lipophilicity, solubility, molecular weight, stability and suitable properties such as polarity to allow high mobility of ion-pair in the paste. Therefore, five plasticizers with a range of properties were tested namely: DBP: D.C = 6.4, log P_{LTC} = 4.5, DOP: D.C = 5.1, log P_{LTC} = 7.1, DOPh: D.C = 4.8, log P_{LTC} = 10.2, DOS: D.C = 4.2, log P_{LTC} = 10.1 and paraffin oil: D.C = 4.6. DOP gives better, stable and reproducible results as shown as in Table 1. It seems that DOP, has relatively moderate properties, produced the best results. This is due to its ability to extract drug ions from the aqueous solution to the organic paste phase.

In addition, the sensitivity of the electrode may be increased by selected additives based on their physicochemical properties. As for the ingredients of the paste, it is the hydrophobicity that makes this additive compatible with the other components of the electrode [20]. These additives reduce ohmic resistance and improve response behavior and selectivity. It is relevant to assess the effect of tetraphenylborate anion in improving the response of the present electrode. We would to present a suggested explanation to this behavior. In essence, TPB^- retards or reduces penetration of Cl^-, the counter ion of the drug, into the paste. TPB- is more bulk and less polar than Cl^- thus it is more effective in neutralization of the bulk drug cations in the surface layer of the paste, in line with the notion "like dissolve like". This effect amounts to a less effective positive charge there and a bigger net difference in the concentration of the drug cations across the paste-sample interphase. The net effect is a better electrode response. Furthermore, additives to the electrode may catalyze the exchange kinetics at the sample-electrode interface [18].

Sodium tetraphenyl borate was found notably effective for this purpose and was utilized to optimize the DAC-electrode design as a lipophilic anion exchanger which is anticipated to result in a well-defined and reproducible phase boundary potential at the interface [29]. More explicitly, electrodes containing various amounts of STPB: 0.0, 0.05, 0.1 and 0.2 w/w %, were tested. The electrode containing no additive showed a slope of 43.7±0.3 mV per decade. This slope was notably improved on incorporation of STPB. The best response, 55.6±0.3 mV per decade, was attained on incorporating 0.1% STPB to the electrode as shown in **Fig. 2**. The results obtained using the present electrode as well as reports in the literature [30, 31] support the explanation provided above.

The composition of the electrode that produced the optimum response is 4 wt % (DAC-PT), 47.95 wt% graphite, 47.95 wt% DOP, and 0.1 wt% STPB produced effective, accurate, fast and cheap sensor that may be efficiently utilized for analysis of the drug.

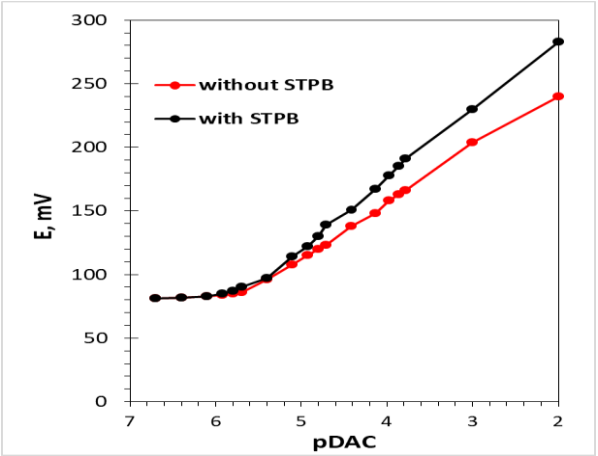

Figure 2 The calibration curve with and without STPB for proposed electrode.

Table 1 Composition and slope of calibration curve for proposed electrode.

No.	I.P	Composition%							S	C.R.	LOD	R.S.D%	R (s)
		g/p	I.P	g	p	STPB	[Surf.] mM	Temp					
Effect of different plasticizers													
1	DAC-PT	1.00	100	49.50	49.50 (DBP)	-	-	25 °C	28.6±0.4	8.56×10^{-6}-1.00×10^{-2}	7.48×10^{-6}	1.05	7
2	DAC-PT	1.00	1.00	49.50	49.50 (DOP)	-	-	25 °C	33.1±0.7	8.00×10^{-6}-1.00×10^{-2}	6.80×10^{-6}	1.11	8
3	DAC-PT	1.00	1.00	49.50	49.50 (DOPh)	-	-	25 °C	32.3±0.5	1.78×10^{-5}-1.00×10^{-2}	1.00×10^{-5}	1.05	9
4	DAC-PT	1.00	1.00	49.00	49.00 (DOS)	-	-	25 °C	27.2±0.6	1.91×10^{-5}-1.00×10^{-2}	1.21×10^{-5}	1.52	10
5	DAC-PT	1.00	1.00	49.50	49.50 (Parrafin oil)	-	-	25 °C	18.7±0.5	2.87×10^{-5}-1.00×10^{-3}	2.28×10^{-5}	1.05	9
Effect of DAC-PT ion pair													
6	DAC-PT	1.00	0.00	50.00	50.00 (DBP)	-	-	25 °C	20.9±0.7	1.43×10^{-5}-1.00×10^{-2}	1.10×10^{-5}	1.72	9
7	DAC-PT	1.00	1.00	49.50	49.50 (DBP)	-	-	25 °C	38.6±0.4	1.20×10^{-5}-1.00×10^{-2}	1.00×10^{-5}	1.05	8
8	DAC-P	1.00	2.00	49.00	49.00 (DBP)	-	-	25 °C	36.9±0.3	7.90×10^{-6}-1.00×10^{-2}	2.20×10^{-6}	1.52	7
9	DAC-PT	1.00	3.00	48.50	48.50 (DBP)	-	-	25 °C	42.9±0.5	2.25×10^{-6}-1.00×10^{-2}	1.23×10^{-6}	1.37	10
10	DAC-PT	1.00	4.00	48.00	48.00(DBP)	-	-	25 °C	43.7±0.3	2.18×10^{-6}-1.00×10^{-2}	1.02×10^{-6}	1.52	5
11	DAC-PT	1.00	5.00	47.50	47.50(DBP)	-	-	25 °C	39.9±0.5	2.56×10^{-6}-1.00×10^{-2}	2.02×10^{-6}	1.37	10
Effect of amount Na-TPB additive													
12	DAC-PT	1.00	4.00	47.975	47.975(DBP)	0.05	-	25 °C	50.9±0.5	7.18×10^{-6}-1.00×10^{-2}	3.84×10^{-6}	1.54	8
13	DAC-PT*	1.00	4.00	47.95	47.95 (DBP)	0.1	-	25 °C	55.6±0.3	1.80×10^{-6}-1.00×10^{-2}	8.90×10^{-7}	1.52	5
14	DAC-PT	1.00	4.00	47.90	47.90 (DBP)	0.2	-	25 °C	51.7±0.6	7.90×10^{-6}-1.00×10^{-2}	4.00×10^{-6}	1.37	10

I.P: ion-pair, g: graphite, p: plasticizer, S: slope (mV/decade), C.R.: concentration range, LOD: limit of detection, R.S.D % relative standard deviation R(s): response time(s)
*:selected composition

3.2. Effect of acidity

The response of the present electrode was studied for 1.0×10^{-4} and 1.0×10^{-5} M DAC solutions in the pH range 2.0 to 11.0 where 0.1 M solutions of HCl or NaOH were utilized for adjustment of pH of the test solutions. The results, shown **in Fig. 3**, prove the electrode are useful in the pH range 3.2 to 9.5. The measured potential increases in more acidic solutions and decreases in basic solutions.

To explain this behavior, consider the hydrolysis of $HDAC^+$ cation given in the following equilibrium:

$HDAC^+ + H_2O \rightleftharpoons DAC + H_3O^+$

This is reasonably linked to the effect of the accumulating hydronium ion on the electrode behavior. There is a big concentration of hydronium ions at low pH that shifts the above equilibrium to the left. Thus, more drug cations accumulate in solution and at the analyte solution-electrode interphase. This building up of bigger charge difference across the interphase leads to a bigger electrode potential difference and an increase in the measured potential in acidic solutions. At high pH the OH^- added to the analyte solution react with the drug cations forming DAC and water. That means consumption of a part of the drug cations in solution and a decrease of its concentration in solution. Lower charge difference across the analyte solution-paste interphase develops and a thus lower corresponding potential difference is measured in basic solutions. A similar situation and explanation was encountered in a few recently reported sensors [32].

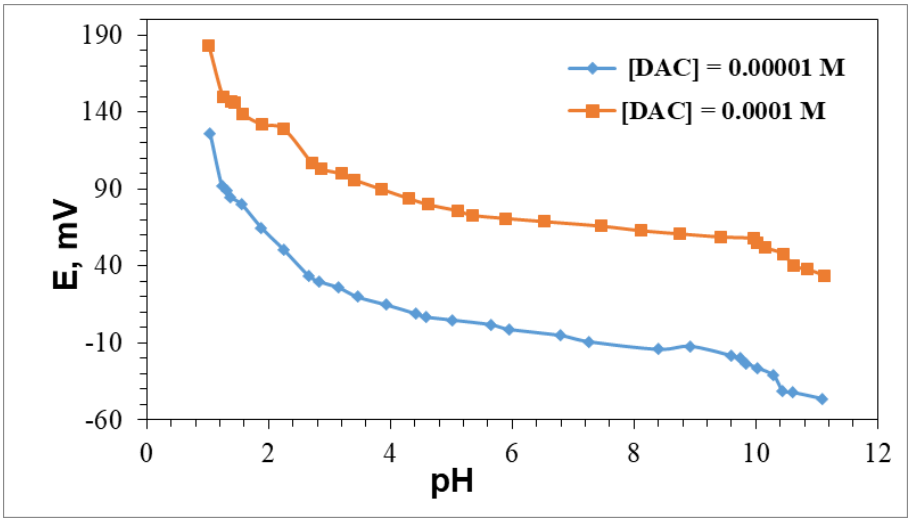

Figure 3 Effect of acidity of the test solution on the response of the electrode

3.3. Effect of other ions

An ion-selective electrode is designed such that it selectively senses and measures the concentration of a specified ion in a test solution. Therefore, its selectivity is crucial for proper function to achieve the intended goal. Selectivity of an ion-selective electrode quantitatively depends on the equilibria at the sample-electrode interface. In addition, it depends on the structure and composition of the ion-pair. Other ions present in solution affect the response of the electrode according the simplified Nicolsky-Eisenman equation [17]

Acceptable selectivity coefficients range from very small values indicating negligible interference to less than unity indicating the electrode is selective to the intended species. A selectivity coefficient greater than unity indicates that the electrode responds to the interfering ion more than the primary ion, in which case the electrode is not selective as required. Eisenman equation holds for calculation of selectivity coefficients for ions of the same charge but gives erroneous results for ions with different charges.

Therefore, an alternative approach must be used to measure selectivity for ions with different charge. The modified separate solution method [24] provides the answer. It was employed to assess the selectivity of other species likely present in preparations of this drug

The electrode was tested in presence of substances administered with DAC for cancer treatment protocols such as sugars, amino acids and some electrolytes as well as other excipients commonly encountered in pharmaceutical

preparations. Measurements listed in Table 2 show that the present sensor display high selectivity for DAC over common drugs and other species. This is a consequence of the similarity in composition of the paste and better compatibility with the drug ion in the analyte that amounted to enhanced response of the electrode. The interferents marginally affect the electrode due to diminished similarity between them. Organic cations and electrolytes do not interfere as they are normally small in size and have high charge to size ratio. In contrary, DAC is more bulk and thus the differences in ionic size, permeability and mobility of its ions over interferents supports the response of the electrode. Notably, the MSSM produced better results than the SSM for the first gives what is considered unbiased thermodynamic selectivity coefficients.

In the results, collected in Table 2 for SSM method, some compounds such as sugars, amino acids and some drugs were tested for interference but showed no effect on the measured potential. No data was listed in the relevant positions. These materials are not ionic and consequently do not interact with ionic materials present in solution.

Table 2 Selectivity coefficients $\log K$ $\log K^{pot}_{D,J^{Z+}}$ for DAC-PT electrode

Interfering species	SSM	MSSM
Na^{+1}	-3.00	-4.37
K^{+1}	-3.12	-4.49
Mg^{+2}	-1.98	-4.34
Ca^{+2}	-2.13	-4.49
Glucose	-	-4.58
Glactose	-	-4.56
Fructose	-	-4.46
Sucrose	-	-4.24
Maltose	-	-4.13
Lactose	-	-4.27
Dextrose	-	-4.21
Glycine	-	-4.24
Histidine	-	-4.41
Glutamic Acid	-	-3.70
Aspartic Acid	-	-3.54
Chloropheniramine	-	-3.80
Acetaminophen (Paracetamol)	-	-4.29
Ibuprofin	-	-4.61
Tindazol	-	-3.95
Metocopramide	-	-3.57
Levocetirizine .2HCl	-1.65	-3.84
Diclofenac Potassium	-4.06	-4.58
Lidocaine HCl	-2.31	-3.66
Ratidine HCl	-2.01	-3.28
Tramadole HCl	-2.19	-3.48
Oxaliplatine	-4.25	-4.34
5-Flurouracil	-4.07	-5.29
Doxorubcin HCl	-2.46	-3.80
Gemcitabine HCl	-2.43	-3.77
Cytrabine HCl	-2.28	-3.57

3.4. Effect of temperature

To study temperature effect on the electrode, calibration graphs were constructed for solutions at 15, 25, 35 and 45 ^{o}C from which the characteristics of the electrodes corresponding to each temperature were obtained. Differences in the performance characteristics at different temperatures were insignificant indicating high thermal stability of the electrode.

3.5. Response time

Response time is the time elapsed between the addition of a given amount of the analyte and the time when a stable potential response is attained by the electrode over several 10-fold concentration increments. It is considered an important characteristic of an electrode as a short response time is an attractive property of the electrode. Response time is normally measured over concentration increments from 10^{-5} to 10^{-2} M as shown in **Fig. 4**. It was found ~5 seconds which is attractively short and indicates a good quality of the present electrode. Apparently, it follows directly from fast exchange kinetics between drug and the ion-pair at the electrode surface.

To examine the reversibility of an electrode, its potential is measured alternately in solutions containing 1.0×10^{-4} M and 1.0×10^{-5} M. The results indicate that equilibrium is reached in a notably short time ~ 7-10 s. Relevantly, there is a slight decrease of the measured potential with time apparently due to memory effect and partial saturation of the surface of the electrode.

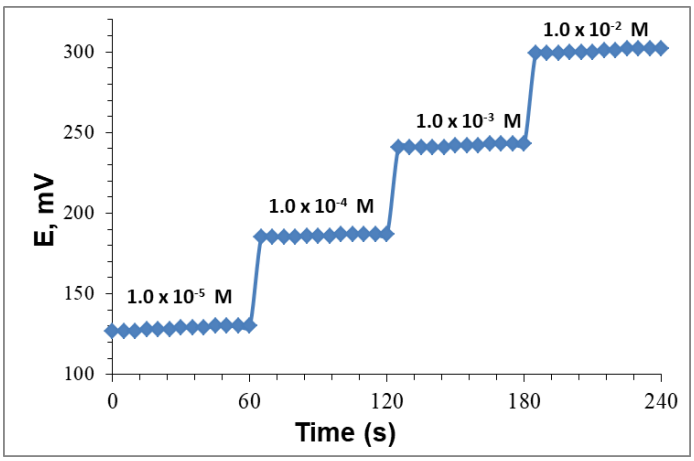

Figure 4 Dynamic responses of the proposed electrode obtained by successive increase of Dacarbazine ion

3.6. Analytical applications

The applicability of the present electrode is appealing. This was proved by implementing it in analysis of biological and pharmaceutical preparations. Results of analyses of these samples were accurate and dependable which culminate their usefulness in the desired analytical work.

3.6.1. Determination of drug ions in urine and ampoules

Potentiometry with ion-selective electrodes (ISE) is getting increased applications as analytical tools for drug determination. Therefore, it is inspiring to check and establish the applicability of the present electrode in determination of DAC in biological samples such as urine and pharmaceutical preparations. This goal was attained by using the calibration curve and potentiometric titration methods.

The present electrode was used to determine the drug DAC in various ampoules and urine samples. The daily dose of DAC is 500 mg, out of which about 20% [33] (≈ 100 mg) is excreted into the urine. Considering a daily total volume of urine to be 2L and the molar mass of the drug to be 182.2 g/mol, an estimated concentration of 2.74×10^{-4} M is accumulated. This concentration lies the linear concentration range covered by the present electrode.

Experimentally, spiking 0.25 mL samples of the urine resulted in about 99% recovery but using larger samples lowered percent recovery due to matrix effects of urine samples. These findings, collected in **Table 3** indicate accuracy, reproducibility and dependability of the proposed electrode for determination of the drug in urine samples. This result paid was paid for in the fabrication of this electrode.

3.6.2. Determination of dacarbazine in ampoules

The proposed electrode was utilized for determination the drug (ampoule) by calibration curve method. As can be seen in Table 3, the accuracy, precision and recovery of DAC drug is almost quantitative.

3.6.3. Statistical treatment of results

The analytical results utilizing the present electrode was assessed by comparison with those reported spectrophotometrically [34]. The precision was checked using F-test and the accuracy by applying the t-test. The outcome of this comparison is shown in Table 3 where the calculated F and t-values show no significant difference in precision. The accuracy of the results obtained by using the present electrodes with a confidence level is above 95%.

Table 3 Analysis of DAC in ampoules and urine samples using proposed electrode

Samples	M		X %	R.S.D%	F-Value	t-Value
	Taken	Found				
Ampoules						
DAC Lipomed Switzerland	4.00×10^{-4}	3.92×10^{-4}	98.00	0.31	3.08	2.01
DAC Medac Germany	4.00×10^{-4}	3.89×10^{-4}	97.25	0.59	3.44	1.97
DAC Bionic India	4.00×10^{-4}	3.95×10^{-4}	98.75	0.92	2.98	2.13
Urine	4.00×10^{-4}	3.97×10^{-4}	99.25	0.46	3.29	2.47

X: recovery, RSD: relative standard deviation. The critical value of F = 9.28 and the critical value of t= 3.18. The number of replicate measurements = 5.

3.6.4. The potentiometric titration method

A potentiometric titration is a valuable analytical technique where there is a remarkable change in the concentrations of a reactant and a big shift in the electrode potential over addition of a small measured amount of titrant. Accordingly, the present electrode was successfully tested as indicator in potentiometric titration of 10.0 mL-samples of 0.01M drug with a 0.01 M solution of PTA & STPB. A plot representing titration of 10.0 mL of 0.01 M solution of DAC is given in **Fig. 5**. A steep potential jump indicates the end point and completeness of this titration. The added titrant instantly combines with the drug and produces an ion-pair complex with gradual depletion of drug ions in solution and a concomitant decrease in the corresponding measured potential. Thus, the present electrode is dependable indicator to determine the amount of the drug in solutions.

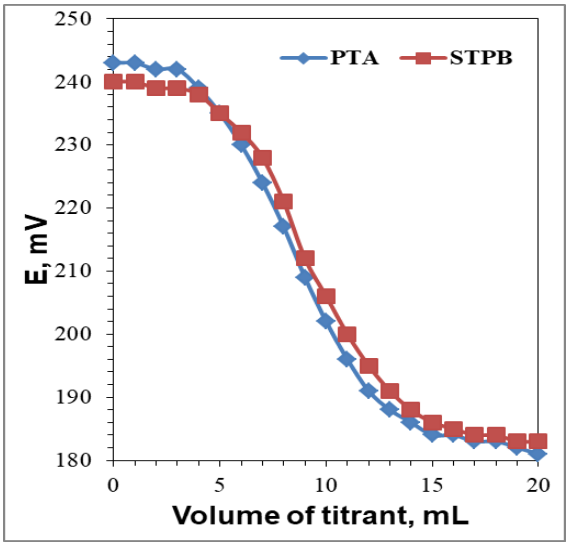

Figure 5 Potentiometric titration curve 10.0 mL 1.0 × 10−2 M solution DAC ion with 1.0 × 10−2 M solution STPB and PTA as titrants using DAC-PT electrode.

4. Conclusion

A dacarbazine-modified carbon paste electrode was fabricated and distinctly improved by incorporation of sodium tetraphenylborate as an additive. Dacarbazine–phosphotungstate, DAC-PT, ion-pair was used in a carbon paste electrode. Incorporation of sodium tetraphenylborate distinctly improved the slope from 43.7±0.3 to 55.6±0.3 mV per decade of DAC ion. This electrode functions linearly over a wide concentration range from 1.80×10^{-6} to 1.0×10^{-2} M with a notably small detection limit of 8.9×10^{-7} M. The sensor has distinct selectivity toward the drug ion over other commonly encountered species. This proved dependable for determination of dacarbazine in pharmaceutical preparations and urine samples.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

References

[1] Sun M, Nie S, Pan X, et al. (2014). Quercetin-nanostructured lipid carriers: Characteristics and anti-breast cancer activities in vitro. Colloids Surfaces B Biointerfaces, 113, 15–24.

[2] Almousallam M, Moia C and Zhu H. (2015). Development of nanostructured lipid carrier for dacarbazine delivery. Int Nano Lett, 5, 241–248.

[3] Fiore D, Jackson AJ, Didolkar MS and Dandu VR. (1985). Simultaneous determination of dacarbazine, its photolytic degradation product, 2-azahypoxanthine, and the metabolite 5-aminoimidazole-4-carboxamide in plasma and urine by high-pressure liquid chromatography. Antimicrob Agents Chemother, 27, 977–9.

[4] Safgren SL, Reid JM, Rios R and Ames MM. (2001). Validated high-performance liquid chromatographic assay for simultaneous determination of dacarbazine and the plasma metabolites 5-(3-hydroxymethyl-3-methyl-1-triazeno)imidazole-4-carboxamide and 5-(3-methyl-1-triazeno)imidazole-4-carboxamide. J Chromatogr B Biomed Sci Appl, 754, 91–96.

[5] Beitz C, Bertsch T, Hannak D, et al. (1999). Compatibility of plastics with cytotoxic drug solutions—comparison of polyethylene with other container materials. Int J Pharm, 185, 113–121.

[6] Lunn G and Sansone EB. (1987). Reductive destruction of dacarbazine, procarbazine hydrochloride, isoniazid, and iproniazid. Am J Heal Pharm, 44, 2519–2524.

[7] Stewart JT, Warren FW, King DT, et al. (1997). Stability of ondansetron hydrochloride, doxorubicin hydrochloride, and dacarbazine or vincristine sulfate in elastomeric portable infusion devices and polyvinyl chloride bags. Am J Heal Pharm, 54, 915–920.

[8] Rodriguez JRB, Garcia AC, Ordieres AJM and Blanco PT. (1989). Electrochemical oxidation of dacarbazine and its major metabolite (AIC) on carbon electrodes. Electroanalysis, 1, 529–534.

[9] Saadeh SM, Abu-Shawish HM, Abed-Almonem KI, et al. (2012). A new potentiometric thiosalicylamide-functionalized polysiloxane earbon paste electrode for lead(II) determination. J Electroanal Chem, 687, 11–17.

[10] Aglan RF, Hamed MM and Saleh HM. (2019). Selective and sensitive determination of Cd(II) ions in various samples using a novel modified carbon paste electrode. J Anal Sci Technol, 10, 7.

[11] Mardani L, Vardini MT, Es'haghi M and Ghorbani Kalhor E. (2020). Design and construction of a carbon paste electrode modified with molecularly imprinted polymer-grafted nanocomposites for the determination of thyroxin in biological samples. Anal Methods, 12, 333–344.

[12] Ghalwa NA, Abed Almonem KI, Al-Kashef ID, et al. (2020). Comparative effects of surfactants on the behavior of an anticancer drug potentiometric sensor. Anal Methods, 12, 679–686.

[13] Vytřas K, Svancara I and Metelka R. (2009). Carbon paste electrodes in electroanalytical chemistry. J Serbian Chem Soc, 74, 1021–1033.

[14] Shawish HMA, Tamous H, Saadeh SM and Tbaza A. (2018). Determination of Atomoxetine Hydrochloride in Biological Fluids Using Potentiometric Carbon Paste Electrode Modified by TiO2 Nanoparticles. Acta Chim Slov, 65, 811–822.

[15] Mohamed GG, Frag EYZ, Zayed MA, et al. (2017). Fabrication of chemically and in situ modified carbon paste electrodes for the potentiometric determination of chlorpromazine HCl in pure pharmaceutical preparations, urine and serum. New J Chem, 41, 15612–15624.

[16] Abu Shawish HM, Abu Ghalwa N, Al-Kashef ID, et al. (2019). Extraordinary enhancement of a 5-fluorouracil electrode by praepagen HY micellar solutions. Microchem J, 104316.

[17] Abu Shawish HM, Khedr AM, Abed-Almonem KI and Gaber M. (2012). A comparative study of solid and liquid inner contact benzalkonium chloride ion-selective electrode membranes. Talanta, 101, 211–9.

[18] Schaller U, Bakker E, Spichiger UE and Pretsch E. (1994). Ionic additives for ion-selective electrodes based on electrically charged carriers. Anal Chem, 66, 391–398.

[19] Wardak C. (2009). Ionic liquids as new lipophilic additives to the membrane of lead ion-selective electrodes with solid contact. Int J Environ Anal Chem ,89, 735–748.

[20] Tani Y and Umezawa Y. (2005). Ion-selective electrodes. Sens Lett, 3, 99–107.

[21] Khedr AM, Abu Shawish HM, Gaber M and Abed Almonem KI. (2014). Potentiometric determination of alkyl dimethyl hydroxyethyl ammonium surfactant by a new chemically modified carbon past electrode. J Surfactants Deterg, 17, 183–190.

[22] Umezawa Y, Bühlmann P, Umezawa K, et al. (2000). Potentiometric selectivity coefficients of ion-selective electrodes. Part I. Inorganic cations (technical report). Pure Appl Chem, 72, 1851–2082.

[23] Radu A, Peper S, Bakker E and Diamond D. (2007). Guidelines for improving the lower detection limit of ion-selective electrodes: A systematic approach. Electroanalysis, 19, 144–154.

[24] Bakker E, Pretsch E and Bühlmann P. (2000). Selectivity of potentiometric ion sensors. Anal Chem, 72, 1127–1133.

[25] Abu Shawish HM, Abed Almonem KI, Saadeh SM and Al-lham WS. (2016). Determination of haloperidol drug in ampoules and in urine samples using a potentiometric modified carbon paste electrode. Measurement, 78, 180–186.

[26] Buck RP and Lindner E. (1994). Recommendations for nomenclature of ionselective electrodes (IUPAC Recommendations 1994). Pure Appl Chem, 66, 2527–2536.

[27] Abu Shawish HM, Tamous H, Saadeh SM, et al. (2015). A new approach for decreasing the detection limit for a ketamine(I) ion-selective electrode. Mater Sci Eng C, 49, 445–451.

[28] Ceresa A, Bakker E, Hattendorf B, et al. (2001). Potentiometric polymeric membrane electrodes for measurement of environmental samples at trace levels: n requirements for selectivities and measuring protocols, and comparison with ICPMS. Anal Chem, 73, 343–351.

[29] Papp S, Bojtár M, Gyurcsányi RE and Lindfors T. (2019). Potential Reproducibility of Potassium-Selective Electrodes Having Perfluorinated Alkanoate Side Chain Functionalized Poly(3,4-ethylenedioxytiophene) as a Hydrophobic Solid Contact. Anal Chem, 91, 9111–9118.

[30] Yan R, Qiu S, Tong L and Qian Y. (2016). Review of progresses on clinical applications of ion selective electrodes for electrolytic ion tests: from conventional ISEs to graphene-based ISEs. Chem Speciat Bioavailab, 28, 72–77.

[31] Abu Shawish HM, Saadeh SM, Tamos H, et al. (2014). A novel coated silver ketamine(I) electrode for potentiometric determination of ketamine hydrochloride in ampoules and urine samples. Anal Chem Res, 2, 30–36.

[32] Gaber M, Abu Shawish HM, Khedr AM and Abed-Almonem KI. (2012). Determination of benzalkonium chloride preservative in pharmaceutical formulation of eye and ear drops using new potentiometric sensors. Mater Sci Eng C, 32, 2299–2305.

[33] Skibba JL, Beal DD, Ramirez G and Bryan GT. (1970). N-Demethylation of the antineoplastic agent 4(5)-(3, 3-dimethyl-1-triazeno) imidazole-5(4)-carboxamide by rats and man. Cancer Res, 30, 147–150.

[34] Cojocaru I, Ochiuz L, Ştpac A, et al. (2012). The validation of the UV spectrophotometric method for the assay of 5 fluorouracil. Farmacia, 60, 379–385.

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