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Poly(vinyl chloride) ion-selective electrodes for Piribedil determination

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Abstract

Piribedil (PD) ion-selective electrodes have been constructed from poly(vinyl chloride) matrix membrane containing piribedil-tetraphenylborate (PD-TPB) as the electroactive component with dibutylphthalate or dioctylphthalate as the plasticizing solvent mediator. The electrodes displayed a linear response over the concentration range 2.0×10^{-5} to 10^{-2} M PD. The working pH ranges of the electrodes were 3.5–6.4 and 3.0–6.0, and the isothermal coefficients of the cells were 0.00129 and 0.00096 V/°C, respectively. The electrodes were used for the determination of the diprotonated PD species, the most successful being that based on dioctylphthalate solvent mediator. The electrodes show a linear response over the concentration range of 8.0×10^{-6} to 10^{-2} M PD, with Nernstain slope 30 mV/PD concentration decade when preconditioned by soaking in distilled water for 30 min. The electrodes exhibit good selectivity for the PD with respect to a large number of inorganic cations and organic substances of biological fluids. Piribedil is determined successfully in pure solutions and in tablets or in biological fluids using the standard additions and potentiometric titration methods. The membrane withstood soaking in distilled water for more than 5 months.

Keywords: Piribedil; Ion-selective electrode; PVC membrane; Potentiometric determination; Tablets; Biological fluids

1. Introduction

Piribedil (PD) is an alkoxybenzyl-4-(2-pyrimidinyl)piperazine derivative with vasodilatory activity [1]. Piribedil has proved active in patients with Parkinson's disease, particularly in the control of tremors [2]. The drug is not cited in any pharmacopoeia. Methods for the analysis of piribedil or its basic metabolites in biological specimens have used gas chromatography with a nitrogen-sensitive detector [3] or combined with mass spectrometry [4], spectrophotometry [5,6] and high-performance liquid chromatography [7]. In the present work, plastic membrane electrodes based on the incorporation of piribedil-tetraphenylborate (PD-TPB) as the electroactive

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component in poly(vinyl chloride) (PVC) with dibutylphthalate (DBP) or dioctylphthalate (DOP) as the plasticizing solvent mediator were prepared. The results showed that the use of dioctylphthalate as plasticizing solvent mediator increases, to a large extent, the life span of the electrode. Also, it is a good plasticizing solvent mediator for the construction of electrode selective for the diprotonated species when the measurements are carried out in distilled water.

2. Experimental

2.1. Electrochemical system

Potentiometric measurements were carried out with a HI 9321 Hanna Microprocessor pH/mV meter at constant temperature. The electrochemical system may be represented as follows: Ag/AgCl/filling solution/membrane/test solution//KCl salt bridge//Ag/AgCl

2.2. Reagents and materials

Piribedil was obtained from Servier Egypt Industries, under licence of les laboratories Servier, France.

All reagents used were chemically pure grade and doubly distilled water was used throughout. Dibutylphthalate and dioctylphthalate (Merck), sodium tetraphenylborate (May & Baker),

Table 1
Composition of the different PD-TPB representative membranes and slopes of the corresponding calibration graphs at 25 ± 1°C

Membrane	Composition (%(w/w))				Slope (mV/decade)	RSD[a] (%)
	Ion-pair	DBP	DOP	PVC		
PD-TPB/DBP						
I	1.0	49.5	–	49.5	58.0	0.57
II	3.0	48.5	–	48.5	58.0	0.30
III	5.0	47.5	–	47.5	58.0	1.70
IV	10.0	45.0	–	45.0	52.0	0.74
V	15.0	42.5	–	42.5	52.0	0.86
PD-TPB/DOP						
I	1.0	–	49.5	49.5	55.0	0.76
II	3.0	–	48.5	48.5	55.5	1.51
III	5.0	–	47.5	47.5	56.5	1.25
IV	10.0	–	45.0	45.0	54.0	0.85
V	15.0	–	42.5	42.5	51.0	0.76
PD-TPB/DBP[b]						
I	1.0	49.5	–	49.5	39.0	0.80
II	3.0	48.5	–	48.5	40.0	0.63
III	5.0	47.5	–	47.5	38.0	0.28
IV	10.0	45.0	–	45.0	40.0	0.76
V	15.0	42.5	–	42.5	40.0	0.57
PD-TPB/DOP[b]						
I	1.0	–	49.5	49.5	28.0	0.97
II	3.0	–	48.5	48.5	28.0	0.73
III	5.0	–	47.5	47.5	30.0	0.57
IV	10.0	–	45.0	45.0	31.0	0.64
V	15.0	–	42.5	42.5	33.0	1.25

[a] Relative standard deviation (four preparations).
[b] The measurements were carried out in distilled water.

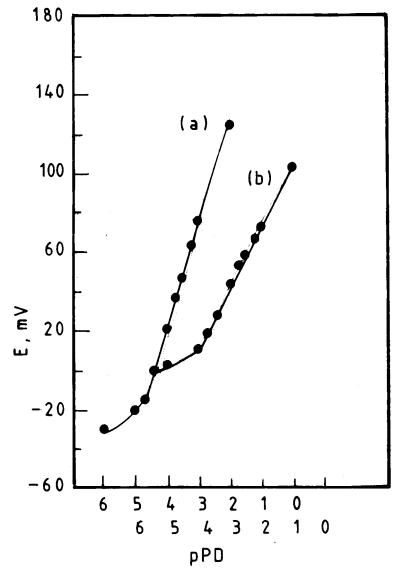

Fig. 1. Calibration curves of PD-TPB/DOP electrode in phosphate buffer (pH 5) (a) and distilled water (b).

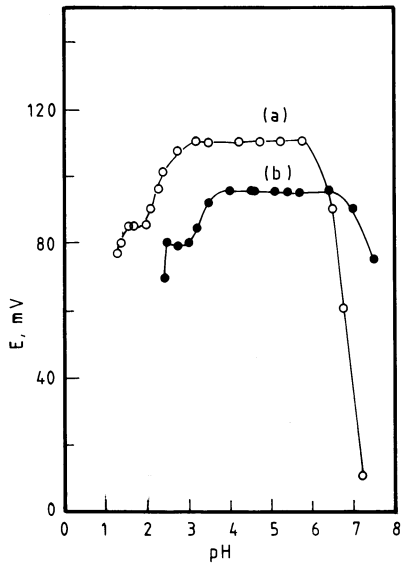

Fig. 2. Effect of pH of the test solution (10^{-3} MPD) on the potential of PD-TPB/DOP (a) and PD-TPB/DBP (b) electrodes.

poly(vinyl chloride) of relatively high molecular weight (Aldrich), and tetrahydrofuran (Lab-Scan Analytical Science) were used.

Stock piribedil solution of 0.01 M was prepared by dissolving 0.2983 g piribedil in 4 ml of 0.5 M HCl, and diluting with water to 100 ml. Sodium tetraphenylborate solution of 0.01 M was freshly prepared by dissolving 0.342 g of the pure salt in 20 ml hot distilled water and diluting to 100 ml. Phosphate buffer (pH 5.0; 0.1M) was prepared by mixing appropriate quantities of 0.1 M potassium dihydrogen orthophosphate with 0.1 M disodium hydrogen orthophosphate to obtain a solution of pH 5.0

2.3. Potentiometric determination of PD

The standard additions method [8] was applied, in which small increments of standard PD solution (0.01 M) were added to 50 ml aliquot samples of various concentrations from pure drug or sample solution equivalent to 1.49–29.83 mg PD in water or phosphate buffer pH 5 solution. The change in potential at (25 ± 0.1°C) was recorded for each increment and used to calculate the concentration of PD in the sample solution.

2.4. Potentiometric titration of PD

An aliquot of PD, pure or sample solution prepared previously containing 1.49–29.83mg PD was transferred into a 100-ml beaker and diluted to about 50 ml with water, then titrated with standard solution of 0.01 M TPB. The volume of titrant at end point was obtained using the differential method.

2.5. Analysis of trivastal tablets

The contents of less than 30 tablets were weighed and finely powdered. An accurately weighed amount of the powdered equivalent to 149.1 mg PD was transferred to a beaker and extracted with 4 ml of 0.5 M HCl for 10 min and diluted with water. The mixture was filtered through a Whatman filter paper No.41 and washed with water. The filtrate and washings were collected in a 100-ml standard measuring flask and diluted to volume with water. Different volumes of the solution (1.491 mg PD/ml) were taken and subjected to the standard additions and potentiometric titration methods.

2.6. Determination of PD in biological fluids

Different concentrations of PD (0.3–3.0 mg) and 5 ml plasma or urine were transferred to a 100-ml beaker, diluted to 50 ml with water or phosphate buffer (pH 5) solution, then subjected to the standard additions method.

2.7. Preparation of PD-TPB ion pair

The PD-TPB ion pair was prepared by mixing 100 ml of 0.01 M solution of PD·HCl with 200 ml of 0.01 M solution of sodium tetraphenylborate. The white precipitate was filtered, washed thoroughly with water and dried at room temperature. The composition of the precipitate was investigated by elemental analysis (calculated percentages of C, H, N and Cl for the 1:1 ion pair were 73.35, 6.15, 8.55 and 5.41, while the found percentages amounted to 74.9, 6.1, 8.6 and 5.5%, respectively). These results indicated the formation of a 1:1 ion-pair (PD:TPB). The melting point of the compound was 119–121°C.

2.8. Preparation of membranes

Five membranes of different compositions were tried (Table 1). Each of the resulting mixture (0.35 g) was dissolved in 10 ml tetrahydrofuran (THF), poured into a 7.5 cm Petri-dish and the THF allowed to evaporate at room temperature. Membranes about 12 mm in diameter and 0.2 mm thick were cut out and glued to the polished end of PVC tubes by means of a PVC–THF solution. The electrodes were then filled with a mixture of 10^{-2} M NaCl and 10^{-2} M PD as the internal solution.

Table 2
Selectivity coefficients ($-\log K^{\mathrm{Pot}}_{\mathrm{PD},J^+}$) for the PD-responsive electrodes

Interferent	PD-TPB/DBP		PD-TPB/DOP		PD-TPB/DOP[a]	
	Method I[b]	Method II[c]	Method I	Method II	Method I	Method II
Li^+	2.48	2.69	2.36	2.30	1.98	0.20
Na^+	2.41	2.39	2.44	2.30	1.89	0.30
K^+	2.26	2.39	2.18	2.39	2.12	0.10
NH_4^+	3.20	2.69	3.06	2.52	1.98	0.69
Zn^{2+}	3.32	3.30	2.87	2.39	1.05	2.69
Co^{2+}	3.39	3.30	2.82	2.39	3.79	2.52
Mg^{2+}	3.10	2.80	3.21	3.11	2.98	2.71
Cu^{2+}	3.58	2.39	2.89	2.39	3.63	2.52
Ni^{2+}	3.20	3.30	2.81	2.30	3.67	3.39
Pb^{2+}	3.70	2.52	2.90	2.39	3.67	2.52
Ba^{2+}	3.64	3.39	2.93	2.52	3.52	3.39
Al^{3+}	3.93	3.88	3.71	3.74	3.82	3.22
Glucose	2.71	2.63	2.60	2.68	2.98	0.84
Lactose	2.51	2.64	2.48	2.63	2.55	0.76
Sucrose	2.95	2.83	2.91	2.74	2.69	0.45
Starch	2.56	2.73	2.26	2.37	2.43	0.57
L-Asparagine	2.40	3.39	2.47	2.39	2.93	0.52
α-Alanine	2.71	2.69	2.73	2.52	3.03	0.69
Valine	2.54	2.52	2.58	2.39	3.10	0.69
Glycine	2.64	3.39	2.76	2.52	3.29	1.00
D,L-Threonine	2.67	2.52	2.88	2.69	2.96	0.69

[a] The measurements were carried out in distilled water.
[b] Method I, separate solution method.
[c] Method II, mixed solution method.

Table 3
Performance characteristics of PD electrodes at different temperatures

Electrode	Temperature (°C)	Slope (mV/decade)	Usable concentration range (pPD)	$E°$ (mV)
PD-TPB/DBP	25	58.0	4.7–2.0	226
	30	58.0	4.6–2.0	229
	40	58.0	4.4–2.0	236
	50	58.0	4.4–2.0	242
	60	61.0	4.2–2.0	254
	70	63.0	4.2–2.0	263
PD-TPB/DOP	25	56.5	4.8–2.0	225
	30	56.5	4.8–2.0	225
	40	57.0	4.4–2.0	226
	50	58.0	4.4–2.0	239
	60	59.5	4.0–2.0	245
	70	62.0	4.1–2.0	258
PD-TPB/DOP[a]	25	30.0	5.1–2.0	179
	30	31.0	5.1–2.0	183
	40	31.0	5.1–2.0	183
	50	32.0	5.1–2.0	191
	60	32.0	4.8–2.0	191
	70	30.0	4.8–2.0	196

[a] The measurements were carried out in distilled water.

2.9. Construction of the calibration graphs

The PD/TPB and Ag/AgCl electrodes were immersed in 50 ml distilled water or phosphate buffer (pH 5), suitable increments of standard PD solution, so as to cover the concentration range 2×10^{-5} to 10^{-2} M PD, were added and the electromotive force values were recorded after each addition, with constant stirring at 25 ± 0.1°C. The electrode potentials, E_{elec}, were plotted versus pPD (Fig. 1). The process was repeated at 25, 30, 40, 50, 60 and 70°C.

2.10. Selectivity of the electrode

The selectivity coefficients K^{Pot}_{PD,J^+} were evaluated by both the separate solution method [9] and the mixed solution method [10].

3. Results and discussion

3.1. Composition of the membranes

The effect of diverse electroactive materials (based on the ion exchangers) on the electrode function has been studied. Several compositions were investigated for PD-TPB/DBP and PD-TPB/DOP membrane electrodes (Table 1). For each composition, the electrode was repeatedly prepared four times. The preparation process was

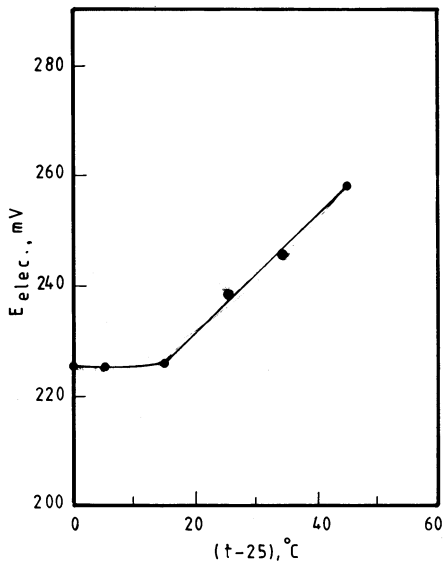

Fig. 3. Variation of E_{elec} of PD-TPB/DOP with temperature.

Table 4
Analytical data for the PD electrodes (temperature, 25°C)

Electrode	Usable concentration range (pPD)	Linear regression		Correlation coefficient (r)
		Intercept ± RSD[a]	Slope ± RSD[b]	
PD-TPB/DBP	4.7–2.0	230.78 ± 0.86	54.26 ± 0.69	0.999
PD-TPB/DOP	4.8–2.0	262.32 ± 1.27	55.41 ± 0.76	0.993
PD-TPB/DOP[c]	5.1–2.0	167.74 ± 0.87	31.10 ± 0.57	0.998

[a] Relative standard deviation of the intercept ($n = 6$).
[b] Relative standard deviation of the slope ($n = 6$).
[c] Measurements carried out in distilled water.

Table 5
Tests of precision of the standard additions (I) and potentiometric titration (II) methods on samples of pure piribedil

Method	Piribedil			Standard error	Confidence limits ($P = 0.05$)
	Taken (mg/50 ml)	Found ± S.D.[a] (mg/50 ml)	RSD (%)		
Method I					
PD-TPB/DBP	1.49	1.49 ± 0.02	1.27	0.008	1.49 ± 0.02
	4.47	4.48 ± 0.02	0.45	0.009	4.47 ± 0.02
	8.95	8.90 ± 0.13	1.46	0.058	8.90 ± 0.16
PD-TPB/DOP	1.49	1.51 ± 0.02	1.19	0.008	1.51 ± 0.02
	4.47	4.47 ± 0.03	0.76	0.015	4.47 ± 0.04
	8.95	8.95 ± 0.11	1.23	0.049	8.95 ± 0.13
PD-TPB/DOP[b]	1.49	1.50 ± 0.01	0.66	0.004	1.50 ± 0.01
	4.47	4.46 ± 0.02	0.45	0.009	4.46 ± 0.02
	8.95	8.95 ± 0.12	1.34	0.054	8.95 ± 0.15
Method II					
PD-TPB/DOP[b]	8.95	9.07 ± 0.03	0.33	0.013	9.07 ± 0.04
	14.91	14.88 ± 0.07	0.47	0.031	14.88 ± 0.09
	29.83	29.84 ± 0.22	0.74	0.098	29.84 ± 0.27

[a] Standard deviation ($n = 5$).
[b] Measurements carried out in distilled water.

highly reproducible, as revealed by the low relative standard deviation values of the slopes obtained. The results in Table 1 show that the best membrane compositions are those containing 5% ion-exchanger with slopes of 58 and 56.5 mV/decade in phosphate buffer (pH 5) for PD-TPB/DBP and PD-TPB/DOP electrodes, respectively, and their usable concentration range was 2.0×10^{-5} to 10^{-2} M PD.

When the measurements were carried out in distilled water instead of phosphate buffer (pH 5), it was found that the electrodes become selective to the diprotonated species with slopes of 30 and 38 mV/concentration decade (Table 1), and the usable concentration ranges of 8×10^{-6} to 10^{-2} M and 3×10^{-5} to 10^{-2} M PD for PD-TPB/DOP and PD-TPB/DBP electrodes, respectively. In all subsequent studies, electrodes made of membranes having 5% ion-exchanger were used. The PD-TPB/DOP electrode is more suitable for the determination of diprotonated species of PD.

3.2. Effect of pH

The effect of pH of the test solutions (10^{-4} and 10^{-3} M PD) on the electrode potentials was

investigated. The variation in potential with pH change was followed by addition of small volumes of hydrochloric acid and/or sodium hydroxide (0.1–1.0 M) to the test solutions. Fig. 2 shows the variation in the potential of the two electrodes with pH, using a test solution of 10^{-3} M PD as representative curves. It is evident that the electrodes do not respond to pH changes in the range 3.5–6.4 and 3.5–5.8 for PD-TPB/DBP and PD-TPB/DOP, respectively. At pH values higher than these ranges, the decrease in the potential readings is most probably attributed to the formation of the free PD base in solution, leading to decrease in the concentration of PD cation. The decrease in potential readings at pH values lower than 3.5 may be due to penetration of H^+ ion into the membrane surface or the formation of PD diprotonated species.

Phosphate buffer (pH 5.0; 0.1 M) was found to be suitable for the PD electrode and then selected for all subsequent studies.

3.3. Selectivity of the electrode

The influence of some inorganic cations, sugars and amino acids on the PD electrode was investigated. The selectivity coefficients K^{Pot}_{PD,J^+} of the electrodes (Table 2) reflect a very high selectivity of the investigated electrodes for the PD cation. The inorganic cations do not interfere because of differences in ionic size, mobility and permeability. Also, the smaller the energy of hydration of the cation, the greater the response of the membrane. The electrodes exhibit good tolerance towards the common excipients of the tablets, i.e magnesium, stearate, talc, starch, lactose, glucose and sucrose. (The tolerance amounts to 10^3 on average.)

3.4. Effect of soaking

Freshly prepared electrodes must be soaked in 10^{-3} M PD solution to activate the surface of the

Table 6
Standard additions (method I) and potentiometric titration (method II) methods for determination of PD in Trivastal tablets and in biological fluids

Sample	Taken (mg/50 ml)	Found ± S.D. (%)[a]				Spectrophotometric method [6]
		Method I			Method II	
		PD-TPB/DBP	PD-TPB/DOP	PD-TPB/DOP[b]	PD-TPB/DOP[b]	
Trivastal tablets[c] (20 mg/tablet)	2.98	100.0 ± 0.47	100.2 ± 0.46	99.89 ± 0.41	100.2 ± 0.62	99.8 ± 0.40
		$t = 0.72$	1.46	0.35	1.21	(2.306)[d]
		$F = 1.38$	1.32	1.05	2.40	(6.39)[d]
	5.96	99.6 ± 0.45	100.1 ± 0.54	99.9 ± 0.60	99.95 ± 0.65	100.2 ± 0.71
		$t = 1.66$	0.25	0.72	0.58	
		$F = 2.45$	1.73	1.40	1.68	
	8.95	100.2 ± 0.61	100.0 ± 0.52	99.9 ± 0.57	100.1 ± 0.63	100.3 ± 0.67
		$t = 0.24$	0.81	1.01	0.48	
		$F = 1.20$	1.66	1.38	1.13	
Urine	0.3	100.5 ± 0.60	99.3 ± 0.53	99.8 ± 0.21		
	3.0	100.1 ± 0.71	99.9 ± 0.46	100.2 ± 0.52		
Plasma	0.3	99.7 ± 0.32	99.5 ± 0.36	99.40 ± 0.49		
	3.0	99.71 ± 0.43	99.3 ± 0.23	99.7 ± 0.26		

[a] Standard deviation ($n = 5$).
[b] Measurements carried out in distilled water
[c] Trivastal tablets from Servier Egypt Industries (under licence of les laboratories Servier, France).
[d] Theoretical values of t and F at 95% confidence level.

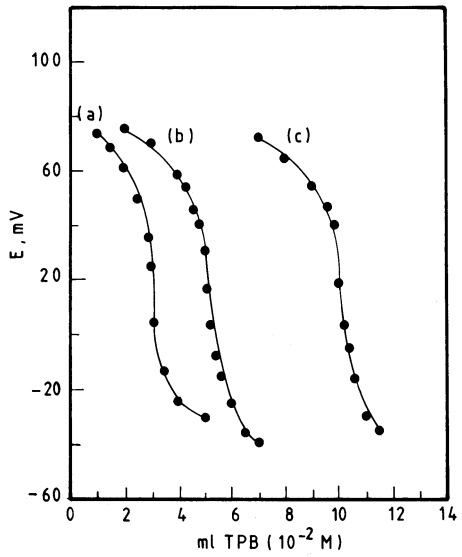

Fig. 4. Potentiometric titration of 50 ml solution containing: (a) 8.95 mg, (b) 14.91 mg and (c) 29.83 mg PD using 10^{-2} M NaTPB solution and PD-TPB/DOP electrode.

membrane to form a thin layer at which ion exchange occurs. This preconditioning process depends on diffusion and equilibration at the interface. Fast establishment of equilibrium is certainly a sufficient condition for fast potential response [11]. For PD-TPB/DBP and PD-TPB/DOP, the presoak times were at least 30 min for each electrode type. The response times of the electrodes were nearly instantaneous in relatively concentrated solutions. While in dilute solutions, about 20–30 s were necessary to reach stable potential readings.

Nevertheless, continuous soaking of the electrodes in 10^{-3} M PD affects negatively their responses to the PD cation; this is attributed to leaching of the active ingredients (ion-exchanger(s) and plasticizer) to the bathing solution. For the PD-TPB/DBP electrode, the slope of the calibration graph decreased gradually to about 53 mV/concentration decade after 5 days, and the electrode became insensitive to PD species after 13 days. On the other hand, the PD-TPB/DOP electrode has a longer life time, where the slope of the calibration graph decreased gradually to reach about 51 mV/concentration decade after 7 weeks, and 47 mV/concentration decade after 9 weeks. For PD-TPB/DOP in distilled water, the slope of the calibration graph increased gradually to reach about 33 mV/concentration decade after 5 months, and then decreased to reach 19 mV/concentration decade after 8 months. The decrease in the efficiency of the electrode is due to a diminished PD ion-exchange rate on the membrane gel layer–test solution interface, which is responsible for the membrane potential. There are two possible reasons for this decrease in the exchange rate: (i) leaching of PD-TPB ion pair from the gel layer of the membrane into the bathing solution, and (ii) poisoning of the electrode surface. A trial to regenerate the exhausted electrodes, by dipping alternately in 10^{-2} M PD and TPB solutions for 1 h three times, was unsuccessful.

3.5. Effect of temperature

Calibration graphs (electrode potential, E_{elec}, versus pPD) were constructed at test solution temperatures (25, 30, 40, 50, 60 and 70°C) for the two electrodes. The slope, usable concentration range and the standard potential ($E°$) of the electrode at each temperature are given in Table 3. For the determination of the isothermal coefficients ($dE°/dt$) of the cells, the standard electrode potentials $E°$, obtained from the calibration graphs as the intercepts at $pPD = 0$, are plotted versus $t - 25$ (Fig. 3), where t is the temperature of the test solution (°C). A straight-line plot is obtained according to the following equation [12]:

$$E^{o} = E^{o}_{(25)} + (dE^{o}/dt)(t - 25)$$

The slopes of the straight lines obtained represent the isothermal coefficients of the cells (amounting to 0.00129, 0.00096 and 0.00010 V/°C) for PD-TPB/DBP, PD-TPB/DOP and PD-TPB/DOP (in water), respectively, revealing a fairly high thermal stability of the cells within the temperature range investigated.

3.6. Analytical applications

The results (found values versus taken) were subjected to linear regression analysis, in order to establish whether the presented electrodes exhibit

any fixed or proportional bias. The slopes and intercepts of the regression lines are tabulated in Table 4 that do not differ significantly from the ideal values, revealing the absence of systematic differences between the determined and expected concentrations within the investigated range. The correlation coefficients were between 0.993 and 0.999, indicating good linearity.

Five replicate determinations at different concentration levels were carried out to test the precision of the methods (Table 5). The relative standard deviations were found to be less than 1.5%, indicating reasonable repeatability and reproducibility of the selected method.

The electrodes can be used for the determination of PD in trivastal tablets and in biological fluids (Table 6) using the standard additions and potentiometric titration methods. The potentiometric titration method is carried out in aqueous medium, and the end point was determined from the titration curve using the first derivative method. Fig. 4 is a representative example for the titration of PD solutions using PD-TPB/DOP electrode. Phosphate buffer solution (pH 5) is not suitable for this method because it gives flat curves.

The low of determination found in both aqueous solutions and body fluids for PD with the present electrodes was nearly 3.0 μg/ml.

To compare the proposed method with a reference method, PD in tablets was assayed by the spectrophotometric method for the determination of PD using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone reagent [6]. Statistical comparison for the results of the proposed and reference methods (Table 5) was performed with regard to accuracy and precision using Student's *t*-test and the *F*-ratio test [13]. At 95% confidence level, the calculated *t* and *F* values did not exceed the critical values, indicating that there is no significant difference between the proposed methods and the spectrophotometric method with regard to accuracy and precision.

Piribedil can be determined in urine and plasma by using potentiometric determinations, (results are presented in Table 5). About 99.30–100.50 and 99.30–99.71% PD were obtained in urine and plasma, respectively. The proposed method can therefore be applied to the determination of PD alone and in pharmaceutical preparations or in biological fluids without fear of interferences caused by the excipients expected to be present in tablets or the constituents of body fluids.

In comparison with the existing spectrophotometric methods [5,6], the proposed method is simpler, more rapid, less laborious, cheaper and much more accurate.. In chromatographic methods [3,4,7], many steps of extraction with some solvents and time consuming for sample preparation are required.

4. Conclusion

The proposed PD-selective electrodes based on the PD-TPB ion-pair as the electroactive compound might be a useful analytical tool for the in vitro and in vivo determinations of PD in the range from 10^{-5} to 10^{-2} M, and therefore an alternative to spectrophotometric methods. The standard additions principle was used to evaluate the accuracy of the proposed methods and test for interference (Tables 5 and 6). Also, it was observed that the use of DOP as plasticizing solvent mediator increases, to a large extent, the life span of the electrodes.

References

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