Ion-selective electrode for the determination of trazodone in tablets

Sabry Khalil

Department of Chemistry, Faculty of Science, Cairo University, Fayoum Branch, 63514 - Fayoum, Egypt

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A coated wire trazodone-selective electrode based on incorporation of trazodone–tetraphenylborate ion pair in a poly(vinylchloride) coating membrane was constructed. The influences of membrane composition, temperature, pH of the test solution, and foreign ions on the electrode performance were investigated. The electrode showed a Nernstian response over a trazodone concentration range from 1.41×10^{-5} to 0.89×10^{-2} M, at 25 °C, and was found to be very selective, precise, and usable within the pH range 2.4–9.0. The standard electrode potentials, $E°$, were determined at 20, 25, 30, 35, 40 and 45 °C and used to calculate the isothermal temperature coefficient ($dE°/dT$) of the electrode. Temperatures higher than 45 °C seriously affected the electrode performance. The electrode was successfully used for potentiometric determination of trazodone hydrochloride both in pure solutions and in pharmaceutical preparations.

Trazodone or 2-[3-(4-*m*-chlorophenylpiperazin-1-yl)propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one is a triazolo pyridine derivative. The distinguishing property of trazodone is its capacity to act selectively on the system of emotional integration, correcting the two main mechanisms responsible for depression: (a) an excessive input of unpleasant information as for example in secondary depression and (b) an intrinsic defect in integration, as in endogenous depression. Trazodone also acts selectively on the serotoninergic system both at the central level, where it inhibits the uptake phenomenon, and at the vascular level, where its antiserotonin effect prevails since serotonin is involved in cerebral ischemia; this latter effect may prove to be useful in pathological conditions accompanied by a diminished cerebral blood flow.

Several methods have been reported for the determination of this important compound.[1–10] However, most of these methods involve several manipulation steps before the final result of the analysis is obtained. Although potentiometric methods of analysis using ion-selective electrodes are simple, cheap and applicable to samples, no selective electrode is, so far, available for the determination of trazodone.

The present work, thus, describes a new selective membrane electrode of the coated wire type, for determination of trazodone in pure solutions and in pharmaceutical preparations. This electrode is based on incorporation of an ion-pair complex of tetraphenylborate anion (TPB^-) with trazodone cation (TZH^+) in a poly(vinylchloride) matrix.

It is noteworthy that all previously reported investigations using poly(vinylchloride) (PVC) membrane selective electrodes for determination of species of pharmaceutical and/or medical importance have been carried out at only one temperature, mostly 20 or 25 °C. No attention has been paid to the higher temperature range, 25–45 °C, although many potentiometric measurements concerning biological media and fluids are made at such temperatures.[11] In this paper, the effect of the temperature of the test solution on the performance characteristics of the proposed coated wire electrode (CWE) is reported.

Experimental

Reagents and materials

All chemicals used were of analytical or pharmacopeial grade (can be used for manufacturing pharmaceutical preparations). Bi-distilled water was used throughout all experiments. The pharmaceutical preparations containing trazodone (Deprax, Trazolan and Trittico tablets) were obtained from local drug stores. The TZH–TPB ion pair was prepared by a method similar to that described previously.[12] The base component of the produced ion pair has been determined by the non-aqueous titration method.[13] The agreement between calculated and found values was very good confirming the postulated stoichiometry; the 1 : 1 (TZH : TPB) molar ratio stoichiometry was also confirmed by elemental analysis.

Construction of electrode

Spectroscopic pure copper wires of 2.0 mm diameter and 12 cm length were tightly insulated by polyethylene tubes leaving 1.0 cm at one end of the coating and 0.5 cm at the other end for connection. The coating solutions were prepared by dissolving varying amounts of powdered PVC, dioctylphthalate, DOP (plasticizer), and the TZH–TPB in the least amount of tetrahydrofuran possible (3–4 ml), Table 1. Prior to coating, the polished copper surface was washed with a detergent and water, thoroughly rinsed with de-ionized water, and dried with acetone. Then the wire was rinsed with chloroform and allowed to dry. Afterwards, the copper wire was coated by quickly dipping it into the coating solutions, (a), (b), (c), or (d), several times and allowing the film left on the wire to dry for about 2 min. The process was repeated several times until a plastic membrane of approximately 1.0 mm thickness was formed as measured by an electronic linear measuring gauge head, Tesa-GT41. The prepared electrodes were preconditioned by soaking them for 1.5 h in 10^{-3} M TZHCl solution daily.

Potentiometric studies and electrochemical system

Potentiometric measurements were carried out with an Orion (Cambridge, MA, USA) Model 701 A digital pH/mV-meter. A Techne circulator thermostat, Model C-100, was used to control the temperature of the test solution. The electrochemical system was as follows: Cu|membrane|test solution||KCl salt bridge|| KCl(sat.)|Hg_2Cl_2–Hg.

Construction of the calibration graphs

Suitable increments of standard TZHCl solution were added to 50 ml of 1×10^{-6} M TZHCl solution so as to cover the concentration range from 1×10^{-6} to 3.2×10^{-2} M. In this solution the sensor and the reference electrode were immersed and the emf was recorded after 10 s, at 25 °C, for each addition.

The electrode potentials, E_{elec}, were calculated from the emf values and plotted *versus* pTZH (−log[TZH]). The process was repeated at 25, 30, 35, 40 and 45 °C. To determine the linearity range in the case of the pharmaceutical samples, calibration graphs were constructed by using standardized drug solutions, at 25 °C, by measuring the electrode potential in solutions containing varying amounts of the respective drug. The electrode was repeatedly calibrated over a period of four months.

Selectivity of the electrode

The selectivity coefficients, $K^{pot}_{TZH,\ J^{z+}}$, were evaluated by the separate solution method described by Badawy *et al.*[14]

Potentiometric determination of trazodone

The standard addition method was applied in which small increments of standard trazodone hydrochloride solution (1×10^{-2} M) were added to 50 ml aliquot samples of various concentrations (3.0×10^{-4} to 1.5×10^{-3} M). The change in the potential reading (at constant temperature of 25 °C) was recorded for each increment and used to calculate the concentration of TZHCl sample solution.

For analysis of trazodone formulations 8.50–32.65, 9.65–28.16 or 7.35–34.25 mg of Deprax (16 tablets), Trazolan (12 tablets) or Trittico (20 tablets), respectively, were dissolved in 50 ml of distilled water and the standard addition technique was applied as described above.

Results and discussion

Composition of the coating membrane

Four coating membrane compositions were investigated as given in Table 1. CWE made by using coating solution (d) exhibited a calibration plot of very good Nernstian slope (59.0 mV per concentration decade, at 25 °C, Table 1) over a relatively wide range of TZH^+ concentration (1.41×10^{-5} to 0.89×10^{-2} M) with a response time < 10 s. Consequently, the electrode made by using coating solution (d) was selected for carrying out all the following studies.

Effect of soaking

The performance characteristics of the TZH^+ CWE were studied as a function of soaking time. For this purpose the electrode was soaked in a 1×10^{-3} M solution of TZHCl and the calibration graphs (pTZH *vs.* E_{elec}, mV) were plotted after 5 min and 0.5, 1.0, 1.5, 2, 3, 4, 8, 24, and 48 h. The optimum soaking time was found to be 1.5–2.0 h, at which the slopes of the calibration curves were 57.0–59.0 mV per pTZH decade, at 25 °C. Soaking for longer than 24 h is not recommended to avoid leaching, though very little, of the electroactive species into the bathing solution. The electrode should be kept dry in an opaque closed vessel and stored in a refrigerator while not in use. The reproducibility of repeated measurements on the same solutions was ±1 mV.

Effect of temperature of the test solution

Calibration graphs constructed, as previously described, at test solution temperatures of 20, 25, 30, 35, 40, 45, and 50 °C are represented in Fig. 1 (a–g, respectively). The slope, usable concentration range, and response time of the electrode corresponding to each temperature are reported in Table 2. From the table it is clear that the electrode gave a good Nernstian response in the temperature range 20–45 °C. From Fig. 1, the standard electrode potentials ($E°$) were determined, as the intercepts of the calibration graphs at pTZH = 0, and used to obtain the isothermal temperature coefficient ($dE°/dT$) of the electrode by aid of the following equation:[15]

$$E° = E°_{25} + (dE°/dT)\ (t - 25)$$

A plot of E^o *vs.* $(t - 25)$ gave a straight line, the slope of which was taken as the isothermal temperature coefficient. It amounts to −0.0009 V per °C, revealing a fairly good thermal stability of the electrode.

Effect of pH

The effect of pH of the TZHCl test solution on the electrode potential is graphically represented in Fig. 2. The pH of the initial solution is altered by the addition of very small volumes of HCl and/or NaOH (0.1–1.0 M each). Fig. 2 indicates that the pH has a negligible effect within the pH range of 2.3–9.0. In this range the electrode can be safely used for trazodone determination.

During the operative life of the electrode (four months), no significant change in the potential–pH behaviour was observed.

Table 1 Composition of the coating membranes and slopes of the corresponding calibration graphs at 25 °C

	Coating solution/mg[a]			Membrane composition (%, m/m)			Slope/ mV decade^{-1}	RSD
Membrane	PVC	DOP	Ion pair	PVC	DOP	Ion pair	1.5 h Presoak	(%)[b]
(a)	120.0	112.5	17.5	48	45	7	48.0	1.3
(b)	115.0	112.5	22.5	46	45	9	51.5	1.1
(c)	112.5	100.0	37.5	45	40	15	54.0	1.2
(d)	120.0	100.0	30.0	48	40	12	59.0	1.1

[a] Dissolved in the least amount of tetrahydrofuran possible (3–4 ml). [b] Relative standard deviation values of slopes (six determinations).

The decrease in potential readings at pH < 2.3 and pH > 9.0 until pH ≃ 10.3 may be attributed to penetration of Cl^- and OH^- ions, respectively. At pH 10.3, a turbidity due to precipitation of trazodone base was first detected and associated with a concurrent increase in the electrode potential up to pH 11.0. This increase is most probably due to a corresponding decrease in the penetration of the OH^- ions as a result of their reaction with the protonated trazodone species. Beyond pH 11.0, the sharp decrease in potential may be attributed to two reasons. The first is the disappearance of the TZH^+ species from the medium as a result of precipitation. The second reason is the penetration of the OH^- ions into the gel layer of the membrane replacing, partially, the TPB^- anions of the ion pair. Thus the electrode works as a sensor for the OH^- ions in highly alkaline media, exhibiting a decrease in potential as the pH value increases.

Selectivity of the electrode

The selectivity coefficients $K^{pot}_{TZH,\,J^{z+}}$ presented in Table 3 clearly showed that the proposed CWE is very selective toward TZH^+ with respect to many common inorganic and organic cations, sugars, and amino acids which are frequently present in biological fluids and pharmaceutical preparations.

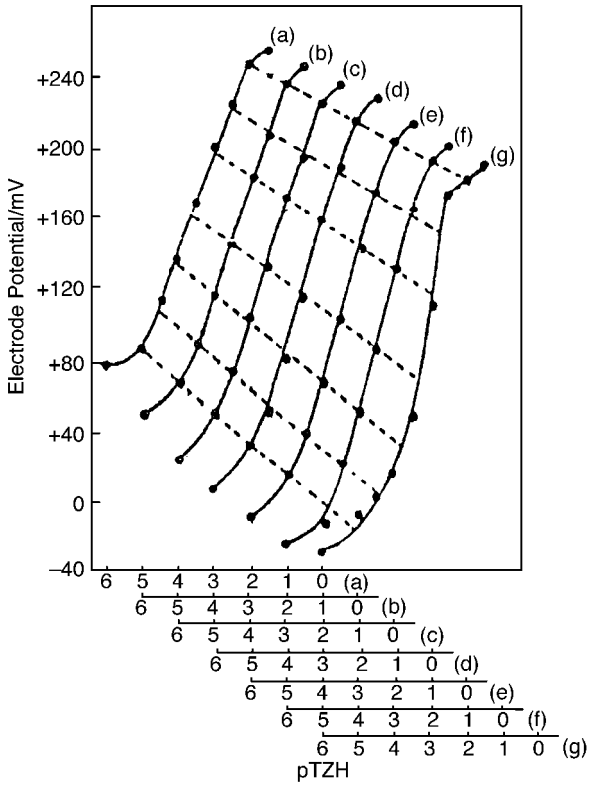

Fig. 1 Calibration graphs at 20 (a), 25 (b), 30 (c), 35 (d), 40 (e), 45 (f), and 50 °C (g) using a trazodone-coated wire electrode [membrane (d)] soaked for 1.5 h.

Analytical applications

The present CWE has been successfully used for the determination of trazodone in aqueous solution and in the pharmaceutical preparations Deprax, Trazolan, and Trittico (tablets) by using the standard addition method described above.

The recovery and standard deviation values given in Table 4 were calculated from ten determinations in the case of pure TZHCl solution and from six determinations in the case of pharmaceutical preparations. The present method is not applicable to cream products since the presence of greasy material poisons the membrane surface.

In pharmaceutical analysis it is important to test the selectivity toward excipients and fillers added to the pharmaceutical preparations. Fortunately, such materials mostly do not interfere. It is clear from the results obtained for the pharmaceutical preparations (Table 4) that these excipients do not interfere.

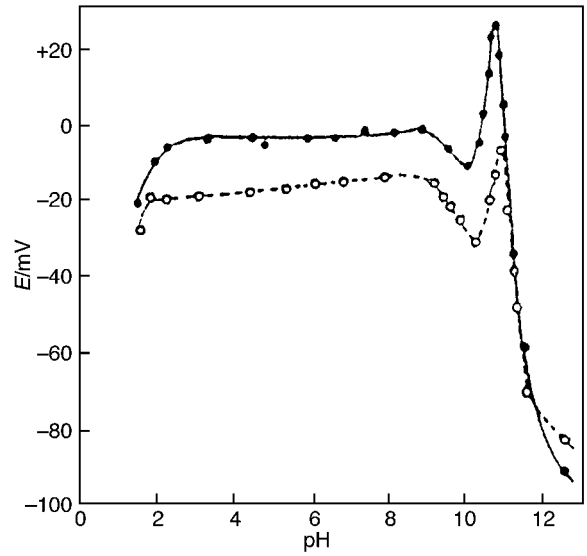

Fig. 2 Effect of pH of the test solution on the potential reading: (●) 4.5×10^{-3} M TZHCl, (○) 2.8×10^{-3} M TZHCl solution at 25 °C, using electrode (d).

Table 3 Selectivity coefficients of the TZH^+ CWE calculated by the separate solution method (1×10^{-3} M of both TZH^+ and the interferent) at 25 °C

Interferent	$K^{pot}_{TZH,\,J^{z+}}$	Interferent	$K^{pot}_{TZH,\,J^{z+}}$
Na^+	1.35×10^{-3}	Lactose	2.54×10^{-3}
K^+	1.31×10^{-3}	Sucrose	1.58×10^{-3}
NH_4^+	1.41×10^{-3}	Glycine	1.10×10^{-3}
Mg^{2+}	3.65×10^{-4}	Alanine	9.44×10^{-4}
Ca^{2+}	1.24×10^{-4}	Phenylalanine	1.08×10^{-3}
Fe^{2+}	1.44×10^{-4}	$(Me)_2NH^+$	1.55×10^{-3}
Fe^{3+}	1.01×10^{-4}	$(Et)_2NH_2^+$	2.17×10^{-3}
Glucose	2.42×10^{-3}	$(Et)_3NH^+$	1.11×10^{-3}
Maltose	1.99×10^{-3}	$(Et)_4N^+$	2.58×10^{-3}

Table 2 Performance characteristics of trazodone CWE[a] at different temperatures as determined in aqueous solutions

Temp/°C	Slope (expt)/ mV decade^{-1}	Usable range/M	Response times/s	Intercept at pTZH = 0 $E°_{elec}$
20	56.0	1.12×10^{-5}–2.81×10^{-2}	≤10	368.0
25	59.0	1.41×10^{-5}–0.89×10^{-2}	≤10	362.5
30	62.5	1.58×10^{-5}–0.61×10^{-2}	≤10	356.6
35	66.0	1.51×10^{-5}–0.61×10^{-2}	≤10	352.0
40	68.0	1.62×10^{-5}–0.60×10^{-2}	≤10	347.0
45	71.0	1.54×10^{-5}–0.49×10^{-2}	≤10	343.5

[a] Preconditioned by soaking for 1.5 h, approximate film thickness is 1.0 mm.

Table 4 Potentiometric determination of trazodone in aqueous solution and in pharmaceutical preparations with a TZH electrode by the standard addition method, at 25 °C

Sample	Amount taken/mg	Recovery (%)	RSD (%)
Pure TZH^+ solution	5.75–36.30	100.15	0.85
Deprax tablets[a]	8.50–32.65	99.70	1.13
Trazolan tablets[b]	9.65–28.16	99.10	0.80
Trittico tablets[c]	7.35–34.25	98.70	1.20

[a] Farma Lepori, Spain. [b] Searle, Netherlands. [c] Egyptian International Pharmaceutical Industries Co., Tenth of Ramadan City A.R.E.

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