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ORIGINAL ARTICLE

Ion selective PVC membrane electrodes for the determination of trazodone hydrochloride in pharmaceutical formulation

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Abstract The electrochemical response characteristics of poly(vinyl)chloride (PVC) based membrane electrodes for determination of trazodone hydrochloride (TZH) is described. The membranes of these electrodes consist of trazodone-phosphomolybdate (TZH-PMA) ion pair in a PVC matrix with di-butyl phosphate (DBP) or dioctyl pthalate (DOP) as a plasticizers. The influences of membranes composition, response time, pH of the test solution, and foreign ions on the electrodes performance were investigated. The electrodes exhibited mean slopes of calibration graphs of 56.25 and 58.55 mV per decade of trazodone concentration at 25.0 °C for the optimum electrode 6.0% with DBP (electrode I) and 10.0% with DOP (electrode II) plasticizers respectively. The electrodes were successfully applied to the determination of trazodone hydrochloride and its pharmaceutical preparation with good precision and accuracy.

Keywords Ion-selective electrode · Potentiometry · Pharmaceutical analysis · Trazodone hydrochloride

Abbreviations

DOP	Dioctylpthalate
DBP	Dibutylpthalate
PMA	Phosphomolybdic acid
ISEs	Ion-selective electrodes
PVC	Poly(vinyl)chloride
THF	Tetrahydrofuran
TZH	Trazodone hydrochloride

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Introduction

Trazodone hydrochloride (TZH), chemically 2-[3-[4-(3-chlorophenyl)-1-iperazinyl] propyl]-1,2,4-triazolo[4,3-a] pyridin-3(2H)-one hydrochloride, is an antidepressant drug indicated in symptomatic treatment of moderate to severe depression. Its major advantages include a low incidence of anticholinergic and cardiovascular side effects along with minimal stimulatory effects upon dopamine and nor epinephrine receptors and considered particularly useful in geriatric population. The chemical structure of trazodone hydrochloride was depicted in Fig. 1. 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. In this work, trazodone hydrochloride electrodes were constructed based on phosphomolybdic acid as ion pair with different plasticizers. The properties of the prepared electrodes, pH effect, and selectivity coefficient measurements were evaluated.

Experimental

Reagents and solutions

All chemicals were of analytical grade, and double distilled water was used throughout the experiments. Pure grade trazodone HCl (TZH) was purchased from Sigma. The pharmaceutical preparations containing trazodone hydrochloride (trittico® 50 mg/tablet and trazodone® 50 mg/

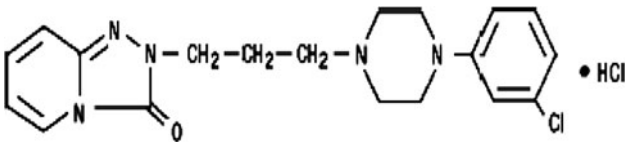

Fig. 1 Chemical structure of trazodone hydrochloride

tablet) were purchased from local drug stores. Phosphomolybdic acid (PMA) (Sigma), tetrahydrofuran (THF) (Fluka), Dioctylphthalate (DOP) (Fuka), poly (vinyl chloride) (PVC) of high relative molecular weight (Sigma) and Dibutyl phthalate (DBP) (Supelco) were used. Stock trazodone hydrochloride solution (1.0×10^{-2} M) was prepared daily by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by appropriate dilution. All trazodone hydrochloride solutions were kept in dark brown bottles.

Apparatus

Potentiometric measurements were carried out using a digital pH/millivoltmeter (Jenway, Model 3305). A WTW packed saturated calomel electrode (SCE) was used as an external reference electrode. Jenway 4330 conductivity meter was used for conductance measurements.

Preparation of trazodone-phosphomolybdate ion-pair

The ion-pair associate, trazodone-phosphomolybdate [TZH-PMA] was prepared by mixing 100.0 mL aliquots of 1.0×10^{-2} M trazodone HCl and phosphomolybdic acid. The resulting precipitate was left in contact with their mother liquor over night to assure complete coagulation, was filtered, washed thoroughly with distilled water until chloride free, dried at room temperature and ground to fine powders. The chemical composition of associate complex has a molar ratio of 3:1 for TZH-PMA and was ascertained by elemental analysis. Elemental analysis: TZH-PMA observed (%) was C = 23.26; H = 2.34; O = 1.63; Cl = 3.58; N = 7.13 and calculated (%) was C = 23.28; H = 2.35; O = 1.66; Cl = 3.62; N = 7.14. The calculated and observed elemental analysis data for the ion-associate complex are in good agreement with its structure.

Composition of the membranes

The membranes were prepared by dissolving the required amount of PVC, DOP or DBP and ion- pair of total weight 0.2 g in 6.0 mL (THF). The solution was poured into a petri dish (5.0 cm in diameter), covered with a filter paper and the solvent was allowed to evaporate slowly at room temperature.

Construction of electrodes

A punched circular membrane was attached to a Pyrex tube (5.0 diameter) in an electrode configuration by means of PVC-THF solution. A mixture containing equal volumes of 1.0×10^{-3} M trazodone HCl and 1.0×10^{-1} M NaCl was used as internal reference solution in which the Ag/AgCl reference electrode was dipped. The constructed electrodes were pre-conditioned after preparation by soaking for at 1.5 h 1.0×10^{-3} M TZH solution daily. The electrochemical system may be represented as follows:

Ag/AgCl/internal solution/PVC membrane/test solution//KCl salt bridge//SCE.

Electrodes calibration

Suitable increments of standard drug solution were add to 50.0 mL doubly distilled water so as to cover the concentration range from 1.0×10^{-6} to 1.0×10^{-2} M. In this solution the sensor and reference electrode were immersed and the e.m.f. values were recorded after each addition. The values were plotted against the negative logarithm of drug concentration (P_{drug}). The electrode was washed with double distilled water and dried between measurements.

Selectivity of the electrodes

The selectivity coefficient values for the proposed electrodes were evaluated by the modified form of the Fixed Interference Method [11] as well as by the Matched Potential Method [12] at 1.0×10^{-2} M concentration of TZH solution and interfering ions (B).

Response time

The dynamic response time is an important factor with selective electrodes.

For the proposed ISEs, the response time were obtained from the dynamic potential response corresponding to trazodone concentration steps between 1.0×10^{-5} and 1.0×10^{-3} M.

Conductometric determination of the solubility product of the ion pair

A series of solutions of different concentrations (c) was prepared for TZH and PMA. The conductances of these solutions were measured at 25.0 °C, and the specific conductances (corrected for the effect of solvent) were calculated and used to obtain the equivalent conductances (λ) of the solutions. Straight-line plots of λ versus $\sqrt{c}$ were constructed, and λ for TZH and PMA were determined from the intercept of the respective line with the λ axis. The

activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute (1.0×10^{-5}–1.0×10^{-2} M). The values of $\lambda_{\text{TZH-.PMA}}$, was calculated using Kohlrausch's law of independent migration of ions [13]. The solubility (S) and solubility product (K_{sp}) of a particular ion associate were calculated using the following equations:

$$S = K_s \times 1000/\lambda\,(\text{TZH} - \text{PMA}) \quad (1)$$

$$K_{sp} = 27S^4 \text{ for } 1:3\,(\text{TZH} - \text{PMA}) \quad (2)$$

where K_s is the specific conductance of the saturated solution of the ion associate, determined at 25.0 °C. The saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 2.0 h at 25.0 °C.

Potentiometric determination of TZH

TZH was determined potentiometrically using the investigated electrodes by the standard addition method [14]. In the standard addition method, known small increments of 1.0×10^{-2} M standard TZH solution were added to 50.0 mL aliquot samples of various concentrations (1.0×10^{-4}–1.0×10^{-5} M) of pure drug and pharmaceutical preparations. The change in potentials was recorded for each increment and used to calculate the concentration of TZH sample solution using the following equation:

$$C_x = C_s\left(\frac{V_s}{V_s + V_x}\right)\left(10^{n(\Delta E/S)} - \frac{V_x}{V_s + V_x}\right)^{-1} \quad (3)$$

where C_x and V_x are the concentration and volume of the unknown, respectively, C_s and V_s are the concentration and volume of the standard, respectively, n is the number of halogen, S is the slope of the calibration graph, and ΔE is the change in potential due to the addition of the standards.

Determination of TZH in pharmaceutical preparations

The contents of ten tablets were accurately weighed and powdered in a mortar; then, the required amount from the tablet powder was dissolved in about 30.0 mL distilled water and filtered in a 50.0 mL measuring flask. The residue was washed three times with double distilled water, and the volume was completed to the mark with distilled water. The contents of the measuring flask were transferred into a 100.0 mL beaker and subjected to potentiometric determination of TZH.

Potentiometric titration of TZH

An aliquot of TZH (1.0×10^{-4}–1.50×10^{-4} M) was transferred into a 100.0 mL beaker, then titrated against a standard solution of PMA using the investigated electrodes as indicator electrodes. The same method was applied for the determination of TZH in the pharmaceutical preparations.

Results and discussion

Optimization of the electrodes

Composition of the membranes

Four membranes of the different compositions were investigated with the DBP (electrode I) plastizer as given in Table 1, and five compositions with the DOP (electrode II) plastizer Table 2. The results showed that on using membranes of optimum compositions (assigned by ** in the tables), slopes of 56.25 and 58.33 mV/concentration decade were obtained for electrode I and electrode II, respectively. A typical calibration plot for electrodes I and II is shown in Fig. 2.

Effect of socking

Freshly prepared electrodes must be soaked in their respective drug solution to activate the surface of the membrane to form an infinitesimal thin gel layer at which ion-pair process occurs. The preconditioning process requires different soaking intervals depending on diffusion and equilibration at the interface, fast establishment of equilibrium is certainly a sufficient condition for fast potential response [15]. The performance characteristics of the electrodes were studied as a function of soaking time. For this purpose the electrodes were soaked in a 10^{-2} M drug solution for 24.0 h at 25.0 °C, Table 3. The optimum

Table 1 Composition of different TZH-PMA membranes and slopes of the corresponding calibration graphs (electrode I) at 25.0 °C

Composition % (w/w)			Slope (mV/decade)	SD*	Correlation coefficient
Ion pair (%)	DBP (%)	PVC (%)			
6.0**	47.0	47.0	56.25	5.36×10^{-6}	0.969
7.0	46.5	46.5	51.85	4.43×10^{-6}	0.989
8.0	46.0	46.0	46.87	4.07×10^{-6}	0.991
9.0	45.5	45.5	60.00	5.77×10^{-6}	0.998

* Standard deviation (four determination)

** Optimum composition

Table 2 Composition of different TZH-PMA membranes and slopes of the corresponding calibration graphs (electrode II) at 25.0 °C

Composition % (w/w)			Slope (mV/decade)	SD*	Correlation coefficient
Ion pair (%)	DOP (%)	PVC (%)			
1.0	49.50	49.5	65.00	1.63×10^{-5}	0.998
2.0	48.0	48.0	48.39	8.93×10^{-6}	0.992
3.0	48.5	48.5	68.18	5.47×10^{-6}	0.989
5.0	47.5	47.5	52.98	7.89×10^{-6}	0.998
10.0**	45.0	45.0	58.33	6.05×10^{-6}	0.989

* Standard deviation (four determination)

** Optimum composition

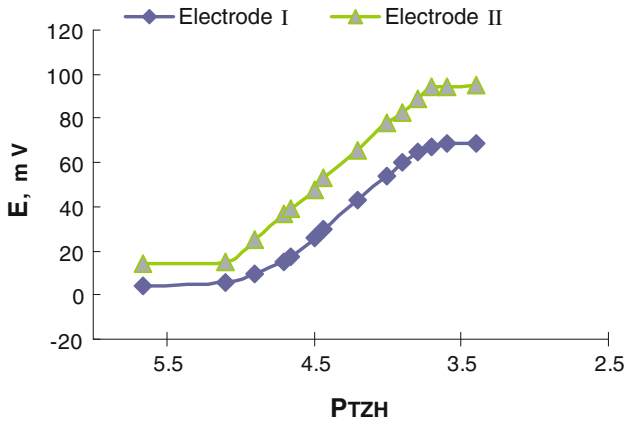

Fig. 2 Calibration curves for TZH-PMA electrodes

Table 3 Effect of socking on the two proposed electrodes at 25.0 °C

Electrodes	Soaking time	Slope (mV/decade)
Electrode I	5.0 min	56.20
	30.0 min	55.55
	1.0 h	53.12
	1.5 h	52.63
	3.0 h	48.3
Electrode II	5.0 min	58.12
	30.0 min	57.11
	1.0 h	56.25
	1.5 h	54.44
	2.0 h	45.80

soaking time was found to be 5.0 and 30.0 min, at which the slopes of the calibration curves were 56.20 and 58.12 mV per pTZH decade, at 25.0 °C for (electrode I) and (electrode II), respectively. Soaking for longer than 24.0 h is not recommended to avoid leaching, though very little, of the electroactive species into the bathing solution. The electrodes should be kept dry in an opaque closed vessel and stored in a refrigerator while not in use.

Effect of pH

The effect of pH of the trazodone HCl solutions (1.0×10^{-3}, 1.0×10^{-4} and 1.0×10^{-5} M TZH) on the

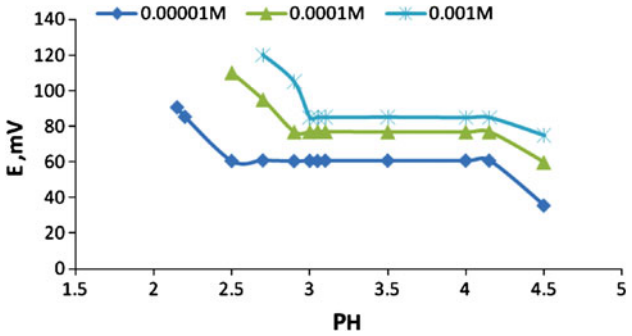

Fig. 3 Effect of pH on the potential response of TZH-selective (electrode I) for different concentrations of drug

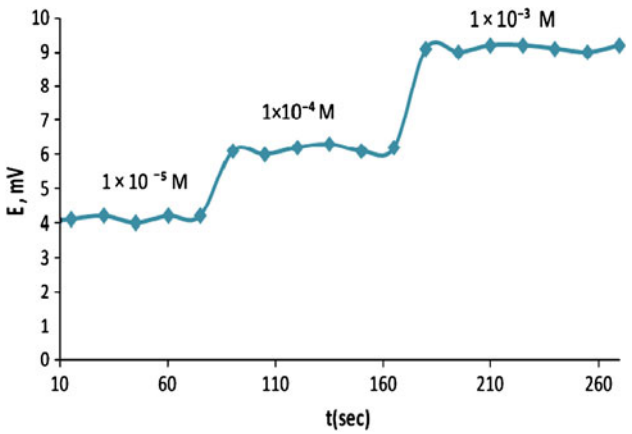

Fig. 4 The potentiometric dynamic response time of the electrode II

electrode potential was investigated. The solutions were acidified by the addition of very small volumes of 0.1 N HCl acid then the pH value was increased gradually using NaOH (0.1 or 1.0 M) for each pH value, the potential was recorded and thus the potential-pH curves for three trazodone HCl concentrations were constructed as shown in Fig. 3 for electrodes I, taken as a representative. The change in pH had a negligible effect in the pH range 2.70–4.13 and thus in this range the electrode can safely be used for trazodone HCl determination. The decrease in the potential reading with pH above the mentioned range can be attributed to the formation of the free base of the drug and disappearance of the protonated species [16].

Table 4 Selectivity coefficients ($K^{pot}_{TZH^+,B}$) for the two proposed electrodes at 25.0 °C

Interfering ions (B)	Selectivity coefficient $K^{pot}_{TZH^+,B}$	
	Electrode I	Electrode II
K^+ [a]	1.62×10^{-3}	1.68×10^{-3}
Na^+	1.68×10^{-3}	1.85×10^{-3}
Co^{2+}	3.25×10^{-5}	3.32×10^{-5}
Zn^{2+}	3.30×10^{-5}	3.37×10^{-5}
Fe^{3+}	1.31×10^{-5}	3.43×10^{-5}
Al^{3+}	1.29×10^{-5}	1.30×10^{-5}
Glycine[b]	–	–
Valine	–	–
Glucose[b]	1.25×10^{-3}	1.37×10^{-3}
Lactose	2.18×10^{-3}	2.09×10^{-3}

[a] Inorganic cations were studied by fixed interference method

[b] Amino acids and sugar were studied by matched potential method

Response time

To investigate the dynamic response time of the proposed TZH electrodes, the practical response time was recorded by changing solution with different TZH ion concentration from 1.0×10^{-5} to 1.0×10^{-3} M. The actual potential versus time traces is shown in Fig. 4 for electrode II, taken as a representative. As can be seen, the electrode reaches the equilibrium response in a very short time of about 15.0 s over the linear concentration range.

Selectivity of the electrodes

The selectivity coefficients $K^{pot}_{TZH^+,B}$ presented in Table 4 clearly showed that the proposed PVC membrane electrodes are very selective toward TZH^+ with respect to many common inorganic cations, sugars, and amino acids which are frequently present in biological fluids and pharmaceutical preparations. The selectivity coefficients revealed that the proposed electrodes are highly selective. The inorganic cations did not interfere due to the differences in their ionic size, mobility and permeability. Also, the smaller the energy of hydration of the cation facilitated a greater response of the membrane. In the case of sugar and amino acid, the high selectivity is mainly attributed to the difference in polarity and lipophilic nature of their molecules relative to trazodone hydrochloride.

Conductometric determination of the solubility product of TZH-PMA ion-pair

The determination of the solubility product of a precipitate is important since its reciprocal is approximately equal to the equilibrium constant of the precipitation reaction leading to the ion-pair formation. This is related to the degree of hydrophobicity of the ion pair, so the leaching

Table 5 Determination of TZH in pure form and in pharmaceutical preparations

	Pure solution		Pharmaceutical preparations			
			Trazodone tablets		Trittico tablets	
	Standard addition	Potentiometric titration	Standard addition	Potentiometric titration	Standard addition	Potentiometric titration
Taken (M)	1.0×10^{-5}	1.0×10^{-4}	1.0×10^{-5}	1.0×10^{-4}	1.0×10^{-5}	1.0×10^{-4}
	1.5×10^{-4}	1.3×10^{-4}	1.5×10^{-4}	1.3×10^{-4}	1.5×10^{-4}	1.3×10^{-4}
	1.0×10^{-4}	1.5×10^{-4}	1.0×10^{-4}	1.5×10^{-4}	1.0×10^{-4}	1.5×10^{-4}
(Electrode I)	99.90	105.04	99.90	104.60	103.80	102.80
Recovery (%)	104.98	103.39	98.00	102.29	97.22	98.11
	106.80	98.03	99.00	104.16	102.92	97.46
R.S.D. (%)[a]	0.82	0.18	0.57	0.19	0.33	0.12
	0.10	0.15	0.33	0.09	0.16	0.14
	0.05	0.04	0.39	0.05	0.35	0.10
(Electrode II)	99.80	104.16	99.89	103.30	99.99	105.48
Recovery (%)	97.20	101.21	102.90	100.16	104.98	102.83
	102.90	96.89	107.50	102.80	95.08	102.24
	0.03	0.15	0.66	0.12	0.36	0.11
R.S.D. (%)	0.33	0.15	0.59	0.13	0.30	0.12
	0.32	0.23	0.18	0.15	0.13	0.08

[a] RSD (three determination)

Table 6 Statistical treatment of the data obtained for the TZH-PMA electrodes employing the standard additions method and potentiometric titration in comparison with the reference method

	Reference method	Electrode I	Electrode II
Pure solution			
Mean ± SD	100.25 ± 2.03	100.60 ± 1.16[a]	100.76 ± 1.57[a]
		102.00 ± 3.61[b]	100.23 ± 4.02[b]
% RSD		0.01[a]	0.02[a]
		0.03[b]	0.04[b]
% Error		6.63×10^{-3} [a]	8.94×10^{-3} [a]
		0.02[b]	0.02[b]
Student *t* test (2.36)[c]		0.27[a]	0.37[a]
		0.90[b]	0.61[b]
F value (6.94)[d]		3.07[a]	1.69[a]
		3.15[b]	3.91[b]
Tirittico tablets			
Mean ± SD	100.54 ± 0.64	102.30 ± 0.58[a]	101.46 ± 2.71[a]
		98.96 ± 2.63[b]	103.10 ± 1.65[b]
% RSD		5.65×10^{-3} [a]	0.03[a]
		0.03[b]	0.02[b]
% Error		3.26×10^{-3} [a]	0.02[a]
		0.02[b]	9.25×10^{-3} [b]
Student *t* test (2.36)[c]		0.54[a]	0.57[a]
		1.01[b]	1.50[b]
F value (6.94)[d]		1.22[a]	3.92[a]
		3.92[b]	4.67[b]

[a] Standard addition method
[b] Potentiometric titration method
[c] Theoretical value of *t*-test
[d] Theoretical value of *F*-value

process of it, which is the main controlling factor of the electrode life time, is very slow. The solubility product of the ion pair was found to be 2.39×10^{-7}. This value indicate that the solubility of the ion pair is very low (9.70×10^{-3} M). Consequently, the equilibrium constants of the reactions,

$$3TZH + H_3PMA = TZH_3 - PM + 3HCl$$

are 2.45×10^{6}, which reflects that the reaction is more than 99.9% complete. In the above equilibria, the solubilities of the undissociated ion pair in water (i.e. the intrinsic solubility) were omitted as they only have a negligible contribution to the total solubility.

Analytical applications

The investigated electrodes were found to be useful in the potentiometric determination of TZH in pure solutions and in the pharmaceutical preparations Trazodone and Trittic (tablets).The recovery and the relative standard deviation values are summarized in Table 5. The present method is not applicable to cream products since the presence of greasy material poisons the membrane surface. The results of the pure solutions and the pharmaceutical preparations (Trittico tablets) were compared (Table 6) with the reference method [17]. The results are in good agreement with those obtained from the reference method. Student's *t* test and *F* test were applied [18]. The results showed that the calculated *t*- and *F* values did not exceed the theoretical values.

Conclusion

The new trazodone HCl ion-selective electrodes based on PVC membrane was constructed and used for determining trazodone HCl in pure form, and pharmaceutical preparations. This electrodes is sensitive and accurate to be a privilege for applications in trazodone HCl determination and its quality control.

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