

Tioconazole-Tetraphenylboron(III)Modified Carbon Paste–and Cu Coated Wire Electrodes for the Determination of Tioconazole

Sayed S. Badawy, Marwa El badry Mohamed, Amira M. Shawky

Department of chemistry, Faculty of science, Cairo University, Giza, Egypt.

Summary: Tioconazole modified carbon paste and copper coated wire ion selective electrodes have been prepared, based on the ion pair of tioconazole **Tc** with sodium tetraphenyl boron (III) Tc-TPB dissolved in dioctyl phthalate DOP as a pasting liquid and plasticizer. The electrodes showed the linear response with mean calibration graph slopes of 57.2 and 54.1 mV/decade, respectively, at $25 \pm 1^\circ\text{C}$; at a concentration range of 1×10^{-6} - 1×10^{-2} M and 1×10^{-6} - 5×10^{-3} M, respectively and lower detection limit of 1×10^{-6} M. The change of pH of the test solution within the range 2.5 – 4.5 did not affect the electrodes performance. The electrodes showed a very good selectivity toward **Tc** with respect to a large number of organic and inorganic cations and compounds. The standard addition and potentiometric titration methods were applied for the determination of tioconazole in pure solution and in pharmaceutical preparations with an average recovery range of 98.0% – 101.3% and a mean relative standard deviation (RSD) of 0.12% - 1.35% which were of comparable accuracy and precision to pharmacopeial method.

Introduction

Tioconazole (**Tc**), 1-[(2RS)-2-[(2-chlorothiophen-3-yl) methoxy]-2-(2,4-dichlorophenyl) ethyl]-1H-imidazole⁽¹⁾ (Scheme 1), is an unusual imidazole antifungal agent, having a higher activity against vaginal yeast infection such as *candida albicans* and dermatophytes⁽²⁾ than other azole antifungals. Thus impairing the fungi activity even when yeasts are in the stationary phase⁽³⁾. **Tc** is also active against some G+ve bacteria⁽⁴⁾.

The pharmaceutical characteristics and quantitative identification of **Tc** include chromatographic techniques like: LC-MS⁽⁵⁾, UPLC-DAD⁽⁶⁾, HPLC⁽⁷⁾, HPLC-UV⁽⁶⁾, HPLC-PDA⁽⁸⁾; spectrometric techniques like: UV-visible⁽⁷⁾, charge transfer⁽⁹⁾, (LEMS)⁽¹⁰⁾ and capillary electrophoresis⁽¹¹⁾.

In this work two types of potentiometric ion-selective electrodes; the chemically modified carbon paste (CMCP) and copper coated wire (Cu-CW) electrodes were applied for the determination of **Tc** in bulk and in the pharmaceutical preparations. These methods are characterized by simplicity, accuracy, rapid response⁽¹²⁾ and cost effective.

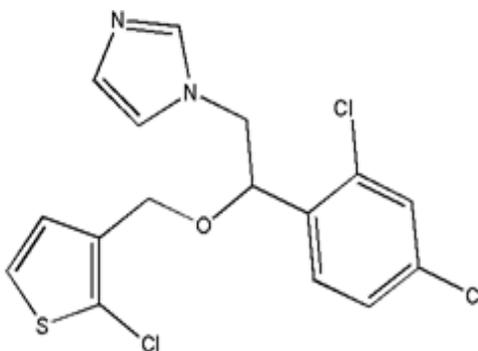
Experimental

Materials and Reagents

All materials in the present work were of a spectroscopic pure. tetrahydrofuran (THF) and sodium tetraphenylboron(III) (Na-TPB) are from (Oxford Lab., India). Graphite powder and poly(vinyl chloride) (PVC) are from (Fluka, Swiss. land). Plasticizers ⁽¹³⁾ as: Dioctyl Phthalate (DOP), diisononyl phthalate (DINP), dinonyl phthalate (DNP), dibutyl phthalate (DBP), tricresyl phosphate (TCP) and ortho-nitrophenyl octyl ether (o-NPOE) and hydrochloric acid (HCl), are all from (Aldrich, Germany). Pharmaceutical grade **Tc** was supplied by Pfizer company (Cairo, Egypt) and doubly-distilled water was used through all experiments.

Apparatus

Potentiometric and pH measurements were carried out by using HANNA pH-mV meter model 8519 with a constant stirring system, a Techne circulator thermostat model: C-100 to control the temperature of the test solution, chemically modified carbon paste electrode (CMCPE) and copper coated wire electrode (Cu-CWE) as working electrodes and Ag/AgCl in 3M KCl (Metrohm 6.0726.100) as a reference electrode. The electrochemical system of the measurements may be represented as follows: Working electrodes/test solution//reference electrode.



Scheme 1. The Structural formula of Tioconazole

Preparation of Tc Ion Exchanger

Standard solution was prepared by dissolving the exactly weighed **Tc** solid base in few milliliters of 1.0 M HCl and completed to the volume by doubly distilled water to convert it to tioconazole Hydrochloride(Tc-HCl). The ion-exchanger, tioconazole-tetraphenylboron(III) (Tc-TPB) was prepared by adding 50 mL 0.01M of Tc-HCl standard solution to 50 mL 0.01 M of Na-TPB. The formed white precipitate was filtered off, washed thoroughly with doubly-

distilled water till chloride free, dried at room temperature and ground to fine powder⁽¹⁴⁾. This Tc-TPB ion exchanger was used as a modifier for carbon paste and PVC coating solution.

Construction of the Electrodes

Carbon paste electrode was performed, by mixing the calculated amounts (in wt %) of the ion exchanger, graphite powder and DOP in an agate mortar. A small portion of the developed paste was carefully packed into the ending hole of the electrode and smoothed onto a paper till a shiny surface⁽¹⁵⁾ and it was directly used without preconditioning.

The Cu-CWE was prepared using long pure copper rods 10 cm and 1mm diameter covered by tight polyethylene tubes except 1cm at one end for connection and 2cm at the other end for coating; by quickly dipping into the coating solution consisting of the weighted amounts (in wt %) of the Tc ion exchanger, PVC, and DOP in 5 ml THF at room temperature. This step was repeated until 1.0 mm film thickness was formed⁽¹⁶⁾ (5 times). PVC coating layer was left to dry in air and were stored in the refrigerator to be preconditioned before use.

Recommended Procedures

Construction of the calibration graph

Suitable increments of standard Tc-HCl solution were added to 50 mL of doubly distilled water with few milliliters of 1.0 M HCl to cover the concentration range from (1.0×10^{-6} - 1.0×10^{-2} M) for both of electrodes. For higher concentrations, separate solution were used in this solution, the sensor and the reference electrodes were immersed and the emf was recorded after 10 seconds, at $25 \pm 1^\circ\text{C}$, after each addition, and plotted versus $-\log [\text{Tc}]$.

Effect of soaking of (Cu-CWE)

The performance of the desired electrode was studied as a function of soaking time either by continuous soaking in 1×10^{-3} M Tc-HCl solution at $25 \pm 1^\circ\text{C}$; or by non-continuous soaking and keeping the electrode dry in the refrigerator while not in use. The calibration graphs were plotted at different time intervals; and the measurements were stopped when the slopes deviated from Nernstian value ($S < 50$ mV/decade).

Effect of pH

The effect of the pH of the **Tc** test solution with different concentrations (1×10^{-3} , 1×10^{-4} and 1×10^{-5} M) on the potential values were studied at $25 \pm 1^\circ\text{C}$. Aliquots of the Tc-HCl solution (50 ml) were transferred into 100 ml beaker with the tested electrode in contact with Ag/AgCl reference electrode and a combined glass electrode were immersed in this solution. The potential and the pH readings were recorded ⁽¹²⁾. The pH of the solution was varied over range of (1.3-5.5) in CMCP electrode and (1.5-6.5) in Cu-CW electrode by addition of small volumes of 0.1-1.0 M HCl and/or NaOH solutions. The potential readings were plotted against the pH

Selectivity of the electrodes

The selectivity coefficients $K_{Tc,J^{z+}}^{\text{pot}}$ were evaluated by separate solution method (SSM) ⁽¹²⁾, for charged species applying the following equation:

$$\log K_{Tc,J^{z+}}^{\text{pot}} = (E_2 - E_1) / S + \log [Tc] - \log [J^{z+}]^{1/z}$$

E_1 and E_2 are the electrode potentials in (1.0×10^{-2} M) Tc-HCl and in (1.0×10^{-2} M) of interferent solutions J^{z+} and S is the slope of the calibration graph.

The $K_{Tc,J^{z+}}^{\text{pot}}$ was also determined by the matched potential method (MPM) ⁽¹⁷⁾ for all types of species, charged or neutral. In this method the potentiometric selectivity coefficient was defined as the concentration of primary and interfering species that gives the same potential change under identical conditions.

At first, a known concentration ($C_{Tc'}$) of the primary ion is added to a reference solution that contains a fixed concentration (C_{Tc}) of primary ions, and the corresponding potential difference was recorded and a solution of an interfering ion (C_J) was added to the reference solution until the same potential change (ΔE) was recorded. The change in potential produced at the constant background of the primary ion must be the same in both: $K_{Tc,J^{z+}}^{\text{pot}} = (C_{Tc'} - C_{Tc})/C_J$

Potentiometric determination of Tc.

The standard addition method was applied ⁽¹²⁾, in which small known increments of 0.01M standard Tc-HCl solution were added to 50 ml aliquot samples containing various amounts of pure **Tc** or the pharmaceuticals formulations. The change in potential reading was recorded for each increment and used to calculate the concentration of **Tc** in the sample solution using the following equation: $C_X = C_S (V_S/V_X + V_S) [10^{n(\Delta E/S)} - (V_X/V_S + V_X)]^{-1}$
Where: C_X and V_X are the concentrations and the volumes of the unknown, C_S and V_S are the concentrations and the volumes of the standard, S is the slope of the calibration graph, and (ΔE) is the change in the potential due to addition of the standard.

In a potentiometric titration ⁽¹²⁾, aliquots containing (1.93-19.38mg) of Tc-Hcl were transferred into volumetric flask and diluted to (50ml) with doubly-distilled water. The resulting solutions were transferred into 100 ml beacker and titrated against (1.0×10^{-2} M) of (Na-TPB) solution. The end points were determined by using S-shaped curves and the first derivative method. The same procedure was applied for the pharmaceutical preparations.

Results and Discussion

Compositions and characteristics of the electrodes

In preliminary experiments carbon paste electrodes CMCPE, in the presence of the proposed ion exchanger Tc-TPB, exhibited an appreciable response and remarkable selectivity for Tc in the solution. The influence of the plasticizer type and concentration on the characteristics of the electrode was examined by using four plasticizers with different polarities including (DOP, DBP, DINP and DNP). An electrode was modified by 2 % Tc-TPB, 70 % graphite and 28 % DOP having a slope of (57.2 mV/decade) near Nernstian slope and the concentration range of (1.0×10^{-6} – 1.0×10^{-2} M) of Tc ⁽¹⁸⁾.

Different coating layers compositions (in wt %) of Cu-CWE were prepared to cover the range from 1-5 % Tc ion exchanger with different types of plasticizers (DOP, DINP, DBP, o-NPOE and TCP) with a constant PVC percentage 70% and near Nernstian slope (54.1 mV/decade) was expressed by (4% Tc-TPB, 26% DOP and 70% PVC) in the concentration range (1.0×10^{-6} – 5.0×10^{-3}).

Effect of pH of the Test Solution

The results indicate that at pH range 2.5 - 4.5, the potential of the electrode was independent of the value of pH. At pH values lower than 2.5, the potential slightly increased, which can be related to the penetration of hydronium ion, while the decreased potential that took place at pH values higher than 4.5 is most probably attributed to the formation of the free Tc base in the test solution **Fig. (1)**.

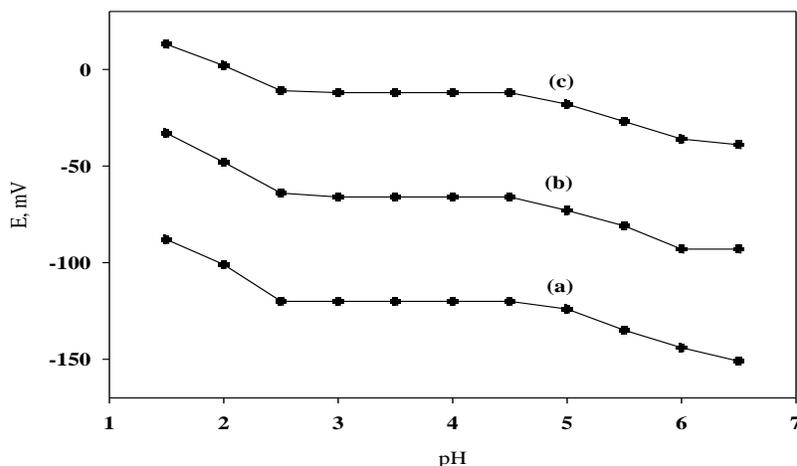


Fig. (1): Effect of pH of the test solution of concentrations 10^{-5} (a), 10^{-4} (b) and 10^{-3} M (c) on the potential response of Tc- Cu coated wire electrode.

Selectivity of The Electrodes

The determined selectivity coefficient $K_{Tc,J^{z+}}^{pot}$ **Table (1)** reflects a very high selectivity of the investigated electrodes toward Tc^{+} cations, with respect to many common inorganic cations, sugars and amino acids which are frequently present in biological fluids and pharmaceutical preparations. The inorganic cations did not interfere due to the difference in their motilities and permeabilities as compared to Tc^{+} cations.

Table (1): Selectivity coefficient $K_{Tc,J^{z+}}^{pot}$ of Tc- CMCPE and Cu-CWE electrodes.

Carbon paste electrode			Copper coated wire electrode		
Interferent			Interferent		
ion	SSM*	MPM**	ion	SSM*	MPM**

Na ⁺	2.00×10 ⁻³	4.00×10 ⁻³	Na ⁺	8.79×10 ⁻⁸	8.08×10 ⁻⁶
Ni ²⁺	3.00×10 ⁻³	5.50×10 ⁻⁴	Ni ²⁺	9.18×10 ⁻⁶	1.18×10 ⁻⁶
NH ₄ ⁺	8.50×10 ⁻³	2.30×10 ⁻³	NH ₄ ⁺	1.97×10 ⁻⁸	2.00×10 ⁻⁷
Mn ²⁺	2.40×10 ⁻³	4.03×10 ⁻³	Mn ²⁺	4.84×10 ⁻¹¹	2.20×10 ⁻⁸
Pb ²⁺	1.50×10 ⁻³	2.60×10 ⁻⁴	Pb ²⁺	5.00×10 ⁻⁴	3.13×10 ⁻⁴
Cu ²⁺	4.50×10 ⁻³	1.50×10 ⁻⁴	Cu ²⁺	1.29×10 ⁻⁴	5.00×10 ⁻⁶
Cr ³⁺	2.40×10 ⁻⁴	8.48×10 ⁻⁴	Cr ³⁺	4.60×10 ⁻⁹	1.21×10 ⁻⁸
Ca ²⁺	1.20×10 ⁻³	2.40×10 ⁻³	Ca ²⁺	1.50×10 ⁻⁷	1.00×10 ⁻⁷
Ba ²⁺	1.10×10 ⁻³	2.00×10 ⁻⁴	Ba ²⁺	2.20×10 ⁻⁹	4.18×10 ⁻⁸
Co ²⁺	6.20×10 ⁻⁴	1.80×10 ⁻³	Co ²⁺	1.00×10 ⁻⁴	6.30×10 ⁻⁹
Cd ²⁺	1.20×10 ⁻³	3.00×10 ⁻³	Cd ²⁺	1.50×10 ⁻⁴	1.91×10 ⁻⁷
Sr ²⁺	1.00×10 ⁻³	3.50×10 ⁻³	Sr ²⁺	4.80×10 ⁻¹¹	3.50×10 ⁻⁸
K ⁺	5.00×10 ⁻³	4.50×10 ⁻⁴	K ⁺	4.80×10 ⁻⁷	2.83×10 ⁻⁹
Hg ²⁺	2.50×10 ⁻⁴	3.00×10 ⁻⁴	Hg ²⁺	1.00×10 ⁻⁵	3.53×10 ⁻⁸
Ascorbic acid	--	5.10×10 ⁻⁴	Ascorbic acid	--	2.33×10 ⁻¹¹
Glucose	--	2.40×10 ⁻⁵	Glucose	--	8.00×10 ⁻⁶
Glycine	--	4.20×10 ⁻⁴	Glycine	--	6.03×10 ⁻⁸
Alanine	--	6.08×10 ⁻⁴	Theronine	--	3.00×10 ⁻³
Threonine	--	3.80×10 ⁻⁴	Alanine	--	2.28×10 ⁻⁴
Lysine	--	8.00×10 ⁻³	Lysine	--	1.00×10 ⁻⁹
Fructose	--	6.50×10 ⁻³	Fructose	--	5.40×10 ⁻⁷

*SSM: Separate solutions Method, **MPM: Matched Potential Method.

Effect of Continuous, Non-Continuous soaking and lifetime of (Cu-CWE) electrode

In continuous soaking, the slope of a calibration curve was recorded (54.1 mV/decade), the calibration slope decreased to 52.6 mV/decade after 10 days and continued to decrease reaching to (48.1 mV/decade) after 16 days.

In non-continuous soaking, The slope of the calibration curve was recorded (54.1mV/decade) and slightly decreased to 53.9 mV/decade after 30 days and continued decreasing to 51.1 mV/decade after 40 days. As a result, soaking for continuous time had a negative effect on the coating layer.

Analytical Applications

Tc was determined, in pure solutions and in pharmaceutical preparations, potentiometrically using the investigated electrode by both standard addition and potentiometric titration methods. The mean recovery and the relative standard deviation values, for a pure solution and pharmaceutical preparations, were calculated and summarized in **Table (2)**.

In pharmaceutical analysis, it is important to test the selectivity toward the excipients and fillers added to the pharmaceutical preparations. It was clear from the results obtained that these

components and excipients do not interfere as indicated by high recovery and low standard deviation values.

These results were compared with those obtained from the pharmacopeial method (based on non aqueous titration of the drug with 0.1 M perchloric acid in the presence of anhydrous acetic acid and the end point was determined potentiometrically ⁽¹⁾) by applying F and t-tests ⁽¹⁹⁾. The calculated F-values were found to be lower than the tabulated value (6.39 at 95 % confidence limit) and the t-values were found to be lower than the tabulated value (2.306 at 95 % confidence limit) which means that was no significant difference appeared, representative results were given in **Table (3)**.

Table (2): Determination of Tc in pure form and in pharmaceutical preparations by applying standard addition and potentiometric titration methods.

Standard addition method

Sample	Carbon paste electrode			Copper coated wire electrode		
	Taken*	Recovery %	RSD***%	Taken*	Recovery %	RSD***%
Pure solution	1.93 - 19.38	98.3 - 101.2	0.36 - 1.27	1.93 - 19.38	98.7 - 100.8	0.67 - 1.33
Gynotrosyd vag. tab. (100 mg/tab.)	1.93 - 19.38	98.2 - 101.3	0.29 - 1.11	1.93 - 19.38	98.4 - 101.0	0.41 - 1.07
Trosyd powder (10 mg/gm)	1.93 - 19.38	99.4 - 101.1	0.63 - 1.06	1.93 - 19.38	99.1 - 100.9	0.20 - 1.35

Potentiometric titration method

Pure solution	1.93 - 19.38	98.3 - 101.1	0.26 - 1.04	1.93 - 19.38	98.1 - 100.9	0.25 - 1.14
Gynotrosyd vag. tab. (100 mg/tab.)	1.93 - 19.38	98.5 - 101.0	0.63 - 1.30	1.93 - 19.38	99.9 - 100.9	0.17 - 1.15
Trosyd powder (10 mg/gm)	1.93 - 19.38	98.7 - 101.0	0.24 - 1.26	1.93 - 19.38	98.0 - 101.0	0.12 - 1.31

* Taken (mg per 50 ml), ***RSD, Relative standard deviation (five determinations).

Table (3): Statistical treatment of the data obtained for Tc using modified Carbon paste electrode in comparison with the pharmacopeial method.

Method	F-value (6.39)	t-value (2.306)
Standard Addition	1.90	1.11
Potentiometric Titration	2.68	0.16

Conclusion

The presented electrodes based on Tc-TPB ion exchanger can successfully offer a valuable, simple, sensitive and highly specific technique for the potentiometric determination of tioconazole over a relatively wide concentration ranges of (1.0×10^{-6} – 1.0×10^{-2} M) for CMCPEs and of (1.0×10^{-6} – 5.0×10^{-3} M) for Cu-CWEs with the same safe pH range of (2.5 – 4.5) and lifetime up to 30 days when kept dry in non-continuous soaking. The proposed electrodes has high selectivity that allows the feasibility of applying such electrodes for the determination of tioconazole in pure form and in pharmaceutical preparation with high precision and accuracy.

References

1. British Pharmacopoeia, "The Stationary Office", Volume II p. 1127, London (2019)
2. L. Brunton, B. Chabner, B. Knollman, Goodman and Gilman (Editors), "The Pharmacological Basis of Therapeutics", 12th Ed., McGraw-Hill, New York (2010)
3. W.H. Beggs, Antimicrob. Agents Chemother., **26** (5), 699 (1984).
4. S.S. Martindale, "The Complete Drug Reference", 33rd Ed., p. 595 Pharmaceutical Press, London (2017)
5. G. Castro, M. Roca, I. Rodríguez, M. Ramil and R. Cela, J. Chromatogr. A, **1476**, 69 (2016).
6. E.F. Elkady, M.H. Tammam and A.A Elmaaty, Anal. Chem. Lett., **7** (2), 153 (2017).
7. R.I. El-Bagary, E.F. Elkady, M.H. Tammam and A.A. Elmaaty, Anal. Chem. : Indian J. **14** (12), 462 (2014).
8. M. Locatelli, A. Kabir, D. Innosa, T. Lopatriello and K.G. Furton, J. Chromatogr. B, **1040**, 192 (2017).
9. M.S. Elmasry, M.S. Elazazy and H.M. El-Sayed, Spectrochim. Acta, Part A, **202**, 401 (2018).

10. P.M. Flanigan, IV, J. J. Perez, S. Karki and R. J. Levis, *J. Anal. Chem.*, **85** (7), 3629 (2013).
11. G. S. Singh, D.A. Brown, F.S. Pullen and A.G. Wright, *J. Chromatogr. A*, **888**, 219 (2000).
12. S.S. Badawy, A.F. Shoukry and Y.M. Issa, *Analyst*, **111** (1986).
13. H. Reinecke, R. Navarro, M. Pe`rez, B.L. Wadey and Basf (Editors), " Encyclopedia of Polymer Science and Technology", 3 rd Ed., Volume 3 p. 498, John Wiley & Sons, Inc., New York (2011)
14. Y.M. Issa, S.S. Badawy, W.F. El-Hawary and M.S. Ashour, *Electroanalysis*, **11** (14), 1063 (1999).
15. M. Ghaedi, S.Y.S. Jaber, S. Hajati, M. Montazerzohori, A. Asfaram and M. Zare, *IEEE Sensors J.*, **15** (5), 2974 (2015).
16. A.F. Shoukry, S.S. Badawy and Y.M. Issa, *J. Electroanal. Chem.*, **233**, 29 (1987).
17. Y. Umezawa, P. Buhlmann, K. Umezawa, K. Tohda and S. Amemiya, *Int. J. Pure Appl. Chem.*, **72** (10), 1851 (2000).
18. C.C. Rundle, "A Beginners guide to ion selective electrode measurements", Nico 2000 Ltd, London (2000)
19. A.I. Vogel, "A text book of Quantitative Inorganic Analysis", 4 th Ed., p. 139, Longman, London and New York (1978)