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Research Article

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MEMBRANE SENSORS FOR THE SELECTIVE DETERMINATION OF TERAZOSIN HYDROCHLORIDE DIHYDRATE IN PRESENCE OF ITS DEGRADATION PRODUCT

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ABSTRACT

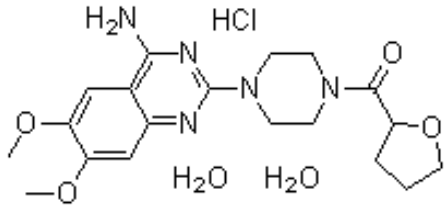
The construction and electrochemical response characteristics of polyvinyl chloride (PVC) membrane sensors for determination of terazosin hydrochloride dihydrate (THD) in presence of its degradation product are described. The sensors are based on the ion association complexes of THD cation with sodium tetraphenyl borate (THD-TPB) [sensor 1] or ammonium reineckate (THD-RNC) [sensor 2] counter anions as ion exchange sites in PVC matrix. The performance characteristics, sensitivity and selectivity of these electrodes in presence of THD alkaline degradation product were evaluated according to IUPAC recommendations. It reveals a fast, stable and linear response for THD over the concentration range 10^{-5}-10^{-2} M with cationic slopes of -30.90and -31.16 mV per concentration decade with sensors 1 and 2, respectively. These sensors exhibit fast response time (15-30sec), low quantitation limit ($5.6x10^{-6}$ and $5.2x10^{-6}$M, respectively), and good stability (30-45 days). The direct potentiometric determination of THD using the proposed sensors gave average recoveries of 100.03±1.052 and 99.97±0.927 for sensor 1 and sensor 2, respectively. The sensors are used for determination of THD, in pure form, in presence of its degradation product and in tablets. Validation of the method shows suitability of the proposed sensors for use in the quality control assessment of THD and for routine analysis as stability indicating method. The developed method was found to be simple, accurate and precise when compared with a reference HPLC method.

Keywords: Terazosin, ion selective electrodes, potentiometry, PVC membrane electrodes, sodium tetraphenyl borate. ammonium reineckate.

INTRODUCTION

Terazosin hydrochloride dihydrate (Figure **1**) is Piperazine, 1-(4-amino -6,7-dimethoxy -2-quiazolinyl)-4-[(tetrahydro-2-furanyl)-carbonyl] monohydrochloride dihydrate[1]. It is an α_1 –adrenoceptor blocker with actions similar to those of prazosin, but a longer duration of action. It is used in the management of hypertension and in benign prostatic hyperplasia[1] to relieve symptoms of urinary obstruction. It could be determined by several analytical techniques, Densitometry[1], pharmacopoeial[2] (USP), potentiometry[1], voltametry[3,4], spectrophotometry[5-8], colorimetry[6-11], flourimetriy[7,12-14], HPLC[1,15-23], LC-MS[24].

Figure 1. Structural formula of terazosin hydrochloride dihydrate



Molecular formula: $C_{19}H_{25}N_5O_4.HCl.2H_2O$
Molecular weight: 459.93 g/mol

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Additionally, most of these methods as HPLC involve time consuming procedures and use sophisticated instruments.

Tetraphenyl borate and ammonium reineckate were reported as ion exchangers[25,26] for basic drugs. They have been used in the formation of many sensors.[27,28] In this work, it was found that THD react with tetraphenyl borate or ammonium reineckate to form ion association complex. The high lipophilicity and remarkable stability of these complexes suggested their selective use as electroactive materials in PVC matrix membrane sensors for the determination of the studied drug in the presence of its degradate.

The advantages of these electrodes are the ease of construction, rapid manipulation, low cost, fast response, wide concentration range and applicability to turbid and colored solutions. Moreover, they offer highly sensitive, selective and convenient technique for the determination of THD in pure form and pharmaceutical preparation.

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals were of analytical grade and bidistilled water was used. Tetrahydrofuran (THF) 99% (Lab scan), high molecular weight (10000) polyvinylchloride (PVC) powder (Aldrich), sodium tetraphenyl borate (Na TPB) (Aldrich), ammonium reineckate (RNC) (Sigma) and phosphate buffer pH 5 and 6 were prepared.[29]

- **Pure samples:** Terazosin hydrochloride dihydrate was kindly supplied by Pharaonia Parmaceuticals, New borg El-Arab City, Alexandria, A R E. It was analyzed and found to be 100.16±0.954 by applying RP-HPLC[2].
- **Market samples:** Terazin® 2 tablets, produced by Pharaonia Pharmaceuticals, New borg El-Arab City, Alexandria, A R E Batch number: 1327101. Each tablet was labelled to contain terazosin hydrochloride dihydrate equivalent to 2mg.

Preparation of stock solutions

THD stock solution (10^{-1}M) in water or phosphate buffer pH 5 and 6 was prepared by transferring 1.148g of THD powder into three separate 25ml measuring flasks, either water in case of studying optimum parameters or phosphate buffer for calibration and determination with optimum pH were added, shaken and completed to volume with the same solvent.

Working standard solutions: THD working standard solutions (10^{-6} - 10^{-2} M) were prepared by suitable dilution from its stock solution using either water or phosphate buffer pH 5 and 6.

Instrumentation

Potentiometric measurements were made with Jenway digital ion analyser model 3330 (UK) with Ag/AgCl reference electrode no 924017-LO-Q11C in conjugation with the drug sensor, Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian). A WPA pH combined glass electrode Model CD-740 was used for pH measurements.

Preparation of pure degraded samples

100 mg of terazosin hydrochloride were accurately weighed and dissolved in 25ml water then refluxed with 100 ml 0.1 N sodium hydroxide for about three hours at 100°C.[7] Complete degradation was confirmed by diluting 0.2ml of this solution with methanol and spotted on a TLC plate next to a spot of pure THD, the plate was developed using ethyl acetate: methanol: ammonium hydroxide (9: 1: 0.01 by volume). Two different spots were obtained, one for the intact drug (R_f =0.45) and the other for its alkaline degradation product (II) (R_f =0.15).The solution was neutralized with 0.1 N HCl and concentrated to a small volume then extracted with chloroform. The chloroformic extract was evaporated under reduced pressure then transferred to a porcelain dish and left overnight. The residue was scratched and dried in an oven at 50°C overnight and left to cool in a dessicator. The degradate identity was confirmed by infra red and mass spectroscopy. 6.78mg of THD degradate were transferred into 25ml volumetric flask, and the volume was completed with either water or phosphate buffer to prepare (10^{-3} M) solution.

Laboratory-prepared mixtures

Aliquot portions of THD degradate (10^{-3}M) was transferred accurately to a series of 25-ml measuring flasks. Add to each flask aliquot portions from THD (10^{-3} M) solution to prepare mixtures containing 0.5:1, 1:0.5, 1:1, 1:2 and 4:1 THD and degradate, respectively.

Precipitation-based technique for the preparation of PVC-membrane sensors

Two membranes namely THD-tetraphenyl borate (THD-TPB) and THD-reineckate (THD-RNC) were prepared.

Preparation of THD-tetraphenyl borate membrane: Ten milliliter of 10^{-2} M THD aqueous solution was mixed with 10 ml of a saturated aqueous solution of sodium tetraphenyl borate. The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature then grounded to fine powder. Elemental analysis for carbon, hydrogen and nitrogen was carried to study the formation of the complex.

In a glass Petri dish (5 cm diameter), 10 mg of the previously prepared ion association complex was mixed thoroughly with 0.35 ml of dibutylsebacate (DBS) then 0.19 g of polyvinyl chloride was added (PVC). This mixture was dissolved in 5 ml tetrahydrofuran (THF), covered with filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature, thus a master membrane with 0.1 mm thickness was formed.

Preparation of THD-reineckate membrane: The same procedure described under previous section was followed using saturated aqueous solution of ammonium reineckate instead of tetraphenyl borate.

Electrodes assembly

A disk of an appropriate diameter (about 8 mm) was cut from the previously prepared master membranes and cemented to the flat end of PVC tubing with THF as adhesive. A mixed solution consists of equal volumes of 10^{-2} M THD and 10^{-2} M sodium chloride was used as internal reference solution (equimolar ratio of the highest concentration in linearity range of the drug added to NaCl solution). Ag/AgCl coated wire (3mm diameter) was employed as an internal reference electrode. The prepared sensors were conditioned by soaking for 24 hrs into 10^{-2} M aqueous drug solution and stored in the same solution when not in use.

Sensors calibration

The prepared electrodes were immersed in conjugation with the single junction Ag/AgCl reference electrode in phosphate buffer pH 5 and 6 solution of THD in the range of 10^{-6} to10^{-2} M. They were allowed to equilibrate whilst stirring and recording the emf readings within ±1 mV. The membrane sensors were washed between measurements with water. The mV versus concentration profiles was plotted. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown THD concentrations.

Selectivity measurements

Potentiometry selectivity coefficient (K^{Pot}_{THD}) were evaluated according to IUPAC guidelines using the separate solutions method[30] in which the potential of cell compromising the membrane electrode and a reference electrode is measured with two separate solutions, A and B where A (THD ions) and B (interfering ion) at the same activity. The emf for A and B are measured values, E_1, E2, respectively. Different interfering anions at a concentration of 1x1 0^{-3} M at a suitable pH (phosphate buffer) were utilized and the results were obtained using the equation

$$-\log\left(K_{A.B}^{pot}\right) = \frac{E_1 - E_2}{2.303\dfrac{RT}{Z_A F}} + \left(1 - \frac{Z_A}{Z_B}\right) log \propto A$$

Where, $K^{pot}_{A.B}$= the potentiometric selectivity coefficient, $2.303RT/Z_AF$= slope of the calibration plot, α_A= the activity of THD, Z_A and Z_B= charges on degradation product.

Application to laboratory prepared mixtures

The membrane sensor was immersed in conjunction with the double junction Ag/AgCl reference electrode in different laboratory mixtures containing 1x10^{-3} M THD solution mixed separately with proportions from the degradate solution in different ratios. The membrane

sensor was washed with water between measurements. The e.m.f. produced for each mixture was measured by the two proposed electrodes then the concentration of THD was determined from the corresponding regression equation.

Application to pharmaceutical preparation

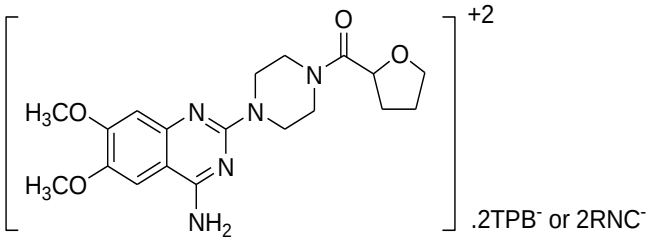
Ten tablets of terazin 2 tablets were weighed and powdered. An amount of the powdered tablets equivalent to 0.01 g THD was accurately transferred into a 25ml volumetric flask and the volume was completed to the mark with phosphate buffer to prepare a 10^{-3} M solution of THD. The e.m.f. produced by immersing the prepared electrodes in conjunction with double junction Ag/AgCl reference electrode in the prepared solution was determined then the concentration of THD was calculated from the regression equation of the corresponding electrode.

RESULTS AND DISCUSSION

Sensors for cationic and basic drugs are based on the use of the ion association complexes of these species with one of anionic compounds forming ion-association complexes embedded in PVC matrix membrane with suitable solvent and mediators.

In the present work THD[1] behave as cation in acidic medium, due to presence of amino group. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl borate and ammonium reineckate with their low solubility. The PVC was used as a polymer matrix in fabrication of membrane sensors. The drug was found to form 1:2 ion association complex (Figure **2**) with each Na TPB and ammonium reineckate as proved by elemental analysis. Calculated results were agreed with the found ones, also the Nernstian response of the suggested sensors was about 30 mV; which is the typical value for divalent drugs[30]. The suggested structural formula is shown in Figure **2**.

Figure 2. Structural formula of ion association complex of THD with TPB or RNC.



The PVC acts as a regular support matrix for the membrane but its use creates a need for a plasticizer[31]. In the present investigation, dibutylsebacate was found to be the optimum available plasticizer for the PVC membrane sensors. It plasticizes the membrane, dissolves the ion-association complexes and adjust both of the membrane permittivity and ion-exchanger sites mobility to give highest possible selectivity and sensitivity.[32,33] Other plasticizers such as nitrophenyl phenyl ether, tricresyl phosphate and castor oil failed in dissolving the ion association complexes and thus gave noisy response. Electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards.[30]

Table **1** shows the slopes of lines, response times, detection limits and intervals of linearity over a period of 2 month for three different assemblies of each sensor at optimal pH and temperature at 25±1°C using the recommendations of IUPAC.[30] The sensors displayed constant potential readings within ±1 mV from day to day and the calibration slopes did not change by more than 2 mV per decade concentration over a period of 1 month for PVC sensors.

In measurements with the investigated sensors the experimental conditions were studied to reach the optimum. The potential response displayed by each of the investigated electrodes was monitored as a function of the temperature and the drug concentration in the range of 25-40°C. Both electrodes exhibited constant slope value and gradual increase in their potentials as the temperature increased. A pH value within the range of 5-7 for THD-TPB and 4-6 for THD-RNC sensors respectively was found optimum. Figures **3**, **4** show the potential pH profiles for 10^{-3} and 10^{-4} M drug solutions using sensor 1 and 2, respectively.

Table 1. Electrochemical response characteristics of the two investigated terazosin hydrochloride dihydrate electrodes.

Parameter	THD-TPB	THD-RNC
Slope (mV / decade)	-30.90	-31.16
Intercept (mV)	167.40	158.26
LOD (M)*	5.6×10^{-6}	5.2×10^{-6}
Response Time (Sec.)	15	30
Working pH Range	5-7	4-6
Concentration Range (M)	10^{-5}-10^{-2}	10^{-5}-10^{-2}
Stability (days)	30	45
Accuracy (mean ± S.D.)	100.03±1.052	99.97±0.927
Correlation coefficient	0.9994	0.9992

Limit of Detection (measured by interception of the extrapolated arms of Figure **5.*

Figure 3. Effect of pH on the response of sensor 1 (THD-TPB).

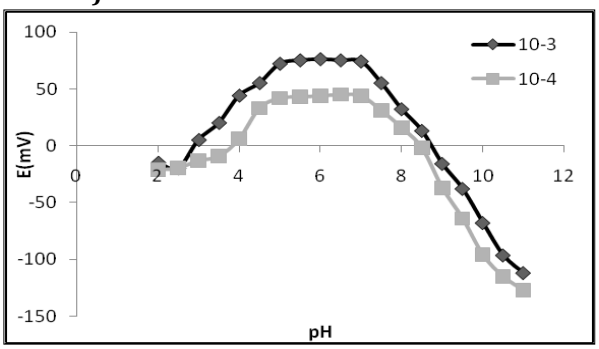
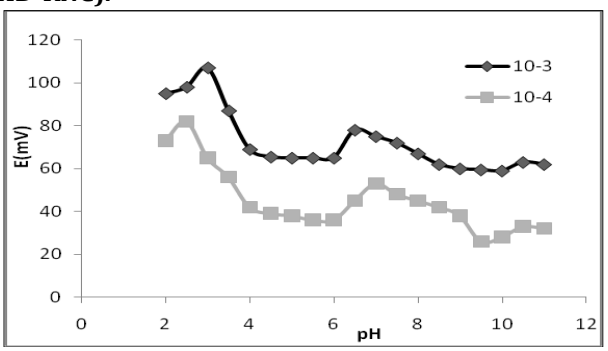


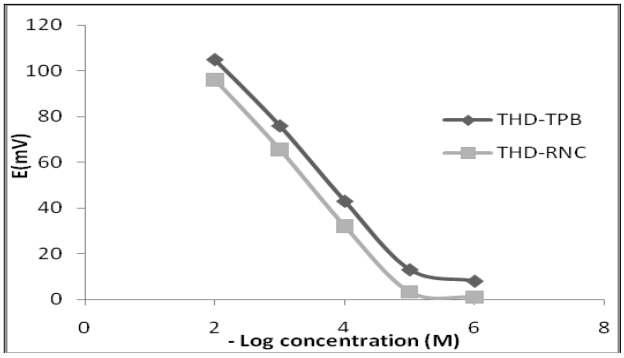
Figure 4. Effect of pH on the response of sensor 2 (THD-RNC).



The response time of the electrodes was tested for concentrations of the drug from 10^{-6} to 10^{-2} M. The measurements were characterized by a fast stable response within 15-30 seconds for electrodes 1 and 2, respectively. Long term potential stability of the proposed sensors was fairly good as it practically unchanged over a period of 4-5 weeks. The potentiometric response of the two studied electrodes at the optimum pH was linear with constant slopes over a drug concentration range 10^{-5}-10^{-2} M of THD (Figure, **5**). The results showed average

recoveries of 100.03±1.052 and 99.97+0.927 for THD-TPB and THD-RNC, respectively. Low detection limits are one of the advantages of the investigated sensors as declared in table **1**.

Figure 5. Profile of the potential in mV versus –log molar concentration of THD with TPB and RNC.



The performance of the two sensors in the presence of degradate and a number of related substances (Pharmaceutical additives, diluents and ingredients commonly used in drug formulations such as lactose, sucrose, glucose, magnesium chloride and urea), were assessed by measuring and comparing the potentiometic selectivity coefficient values (K^{Pot}_{THD}). The separate solution method[30] with a fixed concentration of the interferent (10^{-3}M) was used for evaluation of the selectivity. The results obtained by the developed sensors in Table **2** show reasonable selectivity for the two sensors for THD in presence of any of the mentioned interferents. Thus, analysis was carried out without prior treatment or extraction.

Table 2. Potentiometric selectivity coefficients ($K^{pot}_{THD,I}$) of the two proposed electrodes.

Interferent**	Selectivity coefficient* (×10^{-3})	
	THD-TPB	THD-RNC
Degradate	1.22	1.23
NaCl	2.59	2.63
KCl	2.69	2.61
NH_4 Cl	2.48	2.40
$CaCl_2$	2.42	2.35
$MgCl_2$	2.22	2.15
Glucose	2.01	1.95
Lactose	2.15	2.09
Sucrose	2.06	1.99
Urea	1.88	1.83

**Average of 3 different determinations.*
***All interferents are in the form of 1× 10^{-3} M solution.*

This fact motivated us to determine the intact drug in the presence of its degradate (table **3**) shows the results obtained upon analysis of laboratory prepared mixtures of intact drug and its degradate. It is obvious from the results that the proposed sensors (1 and 2) can be successfully used for selective determination of the intact THD in presence of its degradate.

Thus THD-TPB and THD-RNC were successfully used for the determination of THD in Terazin 2 tablets with average recoveries of 99.32±0.596 and 99.58±0.719 for THD-TPB and THD-RNC, respectively. Statistical evaluation of the results of analysis of pure THD by the proposed electrodes and the compendial HPLC method[(2)] shows that there is no significant difference between the proposed and the compendial method in term of accuracy and precision (table **4**).

Table 3. Determination of THD in laboratory prepared solutions containing different ratios of THD and its degradation product by the proposed electrodes.

** Ratio drug : degradate	Drug recovery* %	
	THD-TPB	THD-RNC
0.5:1	98.15	101.09
1:0.5	99.26	101.32
1:1	98.16	101.88
1:2	101.26	101.76
4:1	101.25	100.75
Mean S.D. R.S.D.%	99.62 1.563 1.569	101.36 0.468 0.462

**Average of 3 different determinations.*
*** 1×10^{-3} M phosphate buffer of pH 6 (THD-TPB)*
1×10^{-3} M phosphate buffer of pH 5 (THD-RNC)

Table 4. Statistical comparison for the results obtained by the proposed electrodes and the compendial method for the analysis of terazosin hydrochloride dihydrate in pure powder form.

Parameter	THD-TPB	THD-RNC	Compendial method [(2)]*
Mean	100.03	99.97	99.75
S.D.	1.052	0.927	0.652
n	4	4	4
Variance	1.107	0.859	0.425
Student's t-test	0.429 (2.447)**	0.35 (2.447)**	
F value	2.605 (9.280)**	2.021 (9.280)**	

**RP-HPLC method.*
*** The values in parenthesis are the corresponding tabulated t and F values at P= 0.05.*

Validation of the proposed potentiometric methods for determining THD was made by measuring the range, lower limit of detection (LOD), accuracy (recovery), precision (R.S.D.), linearity and sensitivity (slope) (table **1**). These data render the proposed potentiometric method applicable as stability indicating one for quality control of drug formulations.

CONCLUSION

THD-TPB and THD-RNC electrodes are sufficiently simple and selective for the quantitative determination of THD at a wide concentration range (1x10^{-5} - 1x10^{-2}M) in pure, pharmaceutical formulation. The method is a stability indicating one as the degradate is not interfering in the determination of the drug. The use of the proposed sensors offers the advantages of fast response, elimination of drug pretreatment or separation steps, low detection limit and direct determination of drug in turbid and colored solutions. They can therefore be used for routine analysis of the drug in quality control laboratories.

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