Miniaturized Membrane Sensors for the Determination of Rivastigmine Hydrogen Tartrate

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Novel miniaturized polyvinyl chloride (PVC) membrane sensors in all-solid state graphite and platinum wire supports were developed, electrochemically evaluated and used for the assay of rivastigmine hydrogen tartrate drug (RIV). The RIV sensors are based on the formation of an ion-association complex between the drug cation and tetrakis(4-chlorophenyl)borate (TpClPB) anionic exchanger as electroactive material dispersed in a PVC matrix. Linear responses of 10^{-2}—10^{-5} M and 10^{-2}—10^{-4} M with cationic slopes of 56.4 mV and 53.6 mV over the pH range 4—7 were obtained by using the RIV-coated graphite (sensor 1) and platinum wire (sensor 2) membrane sensors, respectively. The proposed method displays useful analytical characteristics for the determination of RIV in Exelon® capsules with average recoveries of 100.01±0.835, 100.09±0.896, and in plasma with average recoveries of 99.47±0.97, 99.58±0.82, and in rat brain homogenate with average recoveries of 98.16±1.62, 99.02±1.57, for sensors 1 and 2, respectively. The methods were also used to determine the intact drug in the presence of its degradation product and thus could be used as stability indicating methods. The results obtained by the proposed procedures were statistically analyzed and compared with those obtained by using a reported method. No significant difference for both accuracy and precision was observed.

Key words rivastigmine hydrogen tartrate; potentiometry; poly(vinyl chloride); tetrakis(4-chlorophenyl)borate; plasma; rat brain homogenate

Alzheimer's disease is a progressive neuro-degenerative disorder characterized by loss of short-term memory and immediate recall and decline in other cognitive functions such as attention. Memory loss eventually becomes so severe that patients with Alzheimer's disease lose the ability to care for themselves. Alzheimer's disease is recognized as being one of the most important challenges facing medicine in the 21st century due to aging population and high cost of managing the disease.[1)]

Rivastigmine hydrogen tartrate (Exelon), (−) *S*-*N*-ethyl-3-[(1-dimethyl-amino)ethyl]-*N*-methylphenyl-carbamate hydrogen tartrate, a carbamate inhibitor of acetylcholinesterase. Exelon helps to slow down the mental decline that happens in people with Alzheimer's disease and it helps to improve the ability to cope with everyday activities.[2)]

Few analytical techniques have been reported in the literature for the quantitative determination of rivastigmine hydrogen tartrate (RIV); most of them determine RIV in biological fluids. These are gas chromatography,[3,4)] HPLC,[5,6)] and capillary electrophoresis.[7)]

No ion selective electrode (ISEs), have been recommended/used for its determination as the pure drug, in pharmaceutical dosage forms, or in the presence of its degradation products.

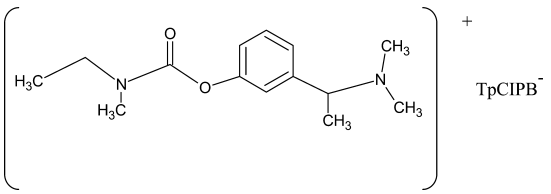

Fig. 1. Suggested Structural Formula of Ion Association Complex of RIV with TpCIPB

Tetrakis(4-chlorophenyl)borate (TpClPB) was reported as famous ion exchanger.[8—10)] It has been used in the formation of many sensors.[11—13)] In this work, it has been found that RIV reacts with (TpClPB) to form water insoluble ion association complexes. 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 drug studied, in the presence of its degradation product and related substances.

The advantages of potentiometric sensors is their simplicity, low cost, fast response, wide pH range and applicability to turbid, viscous and colored solutions, combined with the wide medical use of microsized drug-coated sensors, to form the two investigated potentiometric sensors that offer highly sensitive, selective and a convenient technique for the determination of RIV as the pure drug, in pharmaceutical dosage forms, or in the presence of its degradation products and related substances.

Experimental

Instruments Jenway digital ion analyzer model 3330 (U.K.) with Ag/AgCl double junction reference electrode no 924017-LO-Q11C.

Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian).

PH glass electrode jenway (U.K.) no 924005-BO3-Q11C.

Materials a) Rivastigmine hydrogen tartrate reference standard was kindly supplied by Novartis Pharm Co. Its purity was certified to be 100.13±0.666.

b) Pharmaceutical formulations: Exelon® capsules batch number 3003, 3966 and 4074 were purchased from the Egyptian market. Each capsule is claimed to contain 6 mg of rivastigmine hydrogen tartarte. Exelon capsules are manufactured by Novartis Company (Basle, Switzerland).

Reagents All chemicals and reagents used throughout this work were of analytical grade (water used was double distilled).

Tetrakis (4-chlorophenyl)borate (TpClPB) freshly prepared, saturated aqueous solution; Aldrich.

Poly vinyl chloride (PVC) of high molecular weight; Fluka chemie GmbH Germany.

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Dioctyl phthalate (DOP); Sigma.

Tetrahydrofuran (THF); BDH.

Sodium hydroxide, 0.5 M aqueous solution; Prolabo.

Hydrochloric acid, 0.5 M aqueous solution; Prolabo.

Britton-Robinson buffer (BRB) (pH 2—12); prepared by mixing different volumes of 0.04 M acetic acid, 0.04 M phosphoric acid, 0.04 M boric acid and 0.2 M sodium hydroxide.

Fresh human plasma, obtained from blood (VACSERA) and was used within 24 h.

Procedures. 1) Preparation of Electroactive Coating Membrane: (RIV/TpClPB/PVC) 5 ml 10^{-2} M aqueous drug solution was acidified with two drops of 1 M hydrochloric acid and mixed with about 10 ml saturated aqueous solution of TpClPB. The resultant precipitate was filtered, washed with cold water, dried at room temperature (about 20 °C) and grounded to fine powder, forming the ion-pair complex. Elemental analysis was carried out 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 DOP and 0.19 g PVC. The mixture was dissolved in 5 ml THF, and then the petri dish was covered with a filter paper and left to stand for one hour to allow slow evaporation of the solvent, producing a thick homogeneous master coating PVC solution.

A) Sensor 1 Fabrication (RIV-Coated Graphite Electrode): A rod of spectrographic graphite (5 mm in diameter and 15 mm in length) was inserted in a polyethylene sleeve, and about 3 mm of the other end of the protruded rod served as a measuring surface. This end of the rod was washed with acetone, dried in air for 3 h, and dipped rapidly into the previously prepared PVC solution. The solvent was allowed to evaporate in air after each dipping, and the dipping process was repeated 6—8 times to produce a uniform membrane on the surface of the graphite rod. One drop of mercury was added in the polyethylene sleeve to ensure electrical contact with the connection cable. The coated graphite rod was conditioned by soaking in a 10^{-2} M RIV solution for 5 h, and stored in the same solution when not in use.

B) Sensor 2 Fabrication (RIV-Coated Platinum Wire Electrode): The cover of an insulated platinum wire (1 mm in diameter and 10 mm in length) was removed for a length of about 1 cm at both ends. One end of the wire was immersed in the previously prepared PVC solution and was left to stand for 10 min to allow complete air drying, forming a thin membrane around the wire end. The resultant coated wire membrane sensor was conditioned in 10^{-2} M drug solution for 3 h and was stored in the same solution when not in use.

2) Conditioning of the Sensors The conditioned sensors were calibrated by separately transferring 50 ml aliquots of solution covering the concentration range of 1×10^{-6} to 1×10^{-2} M drug into a series of 100-ml beakers the electrode system was immersed in each solution in conjunction with an Ag/AgCl reference electrode. Allow to equilibrate while stirring and recording the emf reading within ±1 mV. Store the membrane sensor in deionized bidistilled water between measurements, the electrode potential was plotted versus each negative logarithmic concentration of drug, the calibration plot obtained was used for subsequent measurements of unknown samples of RIV.

3) Application to Pharmaceutical Formulations (Exelon® Capsules) The contents of 10 capsules were mixed and weighed. A suitable portion of powder equivalent to 0.4004 g RIV was transferred into a 100 ml volumetric flask and filled to the mark with bidistilled water to prepare a 10^{-3} aqueous solution of RIV. Suitable dilutions were performed using distilled water to obtain serial of 10^{-5} to 10^{-4} M RIV. Complete the procedure as described under 2) sensors conditioning.

4) Application to Synthetic Mixtures Containing Different Amounts of Its Alkaline Degradation Product Degraded sample of 10^{-3} M RIV solution was prepared by adding 5 ml of 0.5 M NaOH to 10 ml 10^{-2} M drug solution and heated on water bath for 20 min; the resulting solution was tested for complete degradation by TLC, then neutralized and transferred quantitatively into 100 ml volumetric flask and completed to volume with deionized water. Aliquots of standard drug solution (10^{-3} M) were mixed with its degraded sample (10^{-3} M) in different ratios. The emf of these laboratory prepared mixtures was recorded. Results were compared with the calibration plot.

5) Application to Plasma 1 ml of 10^{-2}, 10^{-3} and 10^{-4} M standard drug solution was added separately into three stoppered shaking tubes (20 ml), each contain 9 ml of plasma and the tubes were shaken for 1 min. The membrane sensors were immersed in conjunction with the reference electrode in these solutions, and then washed with water between measurements. The emf produced for each solution was measured by the proposed electrode then the concentration of RIV was determined from the corresponding regression equation.

6) Application to Rat Brain Homogenate A rat brain tissue was homogenized in 0.1 M hydrochloric acid. Homogenate solutions were centrifuged, filtered to remove the precipitated protein and cell debris. One milliliter of 10^{-2} and 10^{-3} M RIV solution was added separately into two 25-ml beakers, each contained 9 ml of the brain tissue homogenate and the tubes were shaken for 1 min. The membrane sensors were immersed in conjunction with the reference electrode in these solutions, and then washed with water between measurements. The emf produced for each solution was measured by the proposed electrode then the concentration of RIV was determined from the corresponding regression equation.

Results and Discussion

Microelectrodes have been the subject of much research in recent years.[14] The advantages they offer over conventional electrodes are well known.[15] Their small physical size allows exploration of microscopic domains, such as biological systems. Their fast response time, due to the reduced diffusion layer, allows rapid scan rates to be used. Their low susceptibility to ohmic loss, due to the small currents produced, enables their uses in highly resistive biological media. Metallic and graphite-based conductors of many geometric shapes have been suggested, such as wire, disc and cylinders.[16,17] These electrodes behave as two interface devices, membrane/electrolyte interface and membrane/metal interface.[18] Coated wire electrodes (CWEs) for some antispasmodic drugs,[19] quaternary ammonium cleaning agents,[20] some cations (silver,[21] palladium[22]) and some anions[23] (chloride, bromide, iodide, thiocyanate) have been described. Also coated graphite rods have been used as sensors for the determination of some drugs such as atenolol,[24] tizanidine[25] and thiopental.[26]

It was found that RIV which contains a tertiary amino group; behaves as cation in acidic media. This fact suggests the use of anionic type of ion exchangers. TpCIB with its low solubility product and suitable grain size was found to be optimum for the formation of 1 : 1 hydrophobic ion association complex with the studied drug, as proved by elemental analysis, Table 1.

Sensors Fabrication In the present work, the microsized graphite and platinum wire coated with thin films of PVC-RIV-TpClPB were prepared and used as potentiometric sensors for rivastigmine drug. Upon soaking these sensors in the drug test solutions, an acid-base reaction between the cationic site of the drug and the anionic site of TpClPB in the test solution took place. The formation of a homogenous electroactive polymer-RIV site induced a potentiometic response for the RIV cation through an ion-exchange mechanism.

It has been reported that PVC act as a regular support matrix for the membrane and reproducible trap for the ions sensed,[27,29] but its use creates a need for a mediator.[30] In the

Table 1. Elemental Analysis of RIV–TpClPB Complex

Parameters	Analysis % RIV–TpClPB		
	C	H	N
Calculated %[a]	74.13	7.83	6.31
Found %	73.72	7.06	6.91

a) Calculated according to 1 : 1 ratio.

present investigation, DOP (a non polar plasticizer) was found to be the optimum available mediator for the PVC membrane sensors. It plasticizes the membrane, dissolves the ion association complexes and adjusts both of the membrane permittivity and ion exchanger sites mobility to give the highest possible selectivity and sensitivity. Except for dibutylsebacate which had the same effect as DOP, other mediators such as, tricresylphosphate and castor oil failed in dissolving the ion association complexes and thus gave noisy responses. The membrane constituents were dissolved in THF that was slowly evaporated at room temperature leading to formation of thick homogeneous PVC-RIV-TpClPB solution for coating of both the graphite rod and platinum wire.

Sensors Calibration and Response Time Electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards.[31)]

Table 2 shows the results obtained over a period of one month for two different assemblies of each sensor. Typical calibration plots are shown in Figs. 2 and 3. The sensors displayed constant potential readings within ±2 mV from day to day and the calibration slopes did not change by more than ±2 mV per decade over a period of 26 and 14 d for the coated graphite and platinum wire sensors, respectively.

The required time for the sensors to reach values within ±1 mV of the final equilibrium potential after increasing drug concentration 10 folds was found to be 5 and 7 s, for sensors 1 and 2, respectively. The slopes of the calibration plot were 56.4 and 53.6 mV/concentration decade, for the coated graphite and platinum wire sensors, respectively. The typical value of monovalent substance as RIV behaves as monovalent cation *via* its tertiary amino group. Figures 2 and 3 show an increase in potential as the concentration increases due to the decrease in negative charge on the membrane. Deviation from the ideal nerenstian slope (60 mV) stems from the fact that electrode responds to the activity of drug cation rather than its concentration.

Effects of pH and Temperature on the Response of the Sensors In measurements with the two investigated sensors, the experimental conditions were studied to reach the optimum. A pH value within the range 4—7 was found optimum from the point of view of both sensor function and the chemical form of the test solution; RIV being in the cationic form in acidic media. Figures 4 and 5 show the potential pH profile for 10^{-3} and 10^{-4} M drug solutions. Above pH 8, the potentials displayed by the sensors sharply decreases due to formation of non-protonated RIV. Below pH 4, the potentials displayed by the sensors were noisy and unbalanced due to sensor shocking. It is apparent that the sensors responses are fairly constant in BRB solutions of pH 4—7.

Upon studying the effect of temperature the suggested sensors exhibit slight gradual increase in their potentials as the temperature increases in the range of 20—45 °C however the calibration graphs obtained at different temperature were parallel, the limit of detection, slope and response time did not significantly vary with variation of temperature indicating reasonable thermal stability of PVC membrane up to 35 °C.

Table 2. Electrochemical Response Characteristics of the Two Investigated RIV Electrodes

Parameter	RIV-coated graphite	RIV-coated platinum wire
Slope (mV/decade)[a)]	56.4	53.6
Intercept (mV)	460.3	144.1
LOD (M)[b)]	8.3×10^{-6}	5.1×10^{-5}
Response time (s)	5	7
Working pH range	4—7	4—7
Concentration range (M)	10^{-5}—10^{-2}	10^{-4}—10^{-2}
Stability (d)	26	14
Average recovery (%)±S.D.[a)]	99.97±0.659	99.94±0.758
Correlation coefficient	0.9999	0.9998
Ruggedness[c)]	99.67	99.35

a) Average of five determinations. *b*) Limit of detection (measured by interception of the extrapolated arms of Figs. 2 and 3). *c*) Average recovery percent of determining 10^{-3} , 10^{-4} M RIV for the studied electrodes using Jenway 3510 digital ion analyzer instead of 3310 model.

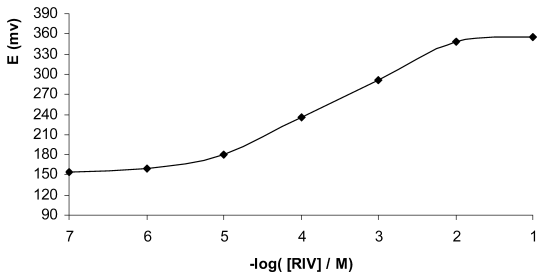

Fig. 2. Profile of the Potential in mV *versus* −log Concentrations of RIV in M Obtained by Using the Sensor 1

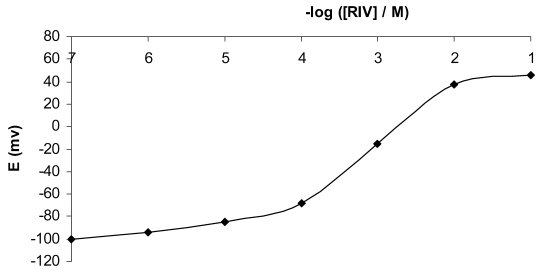

Fig. 3. Profile of the Potential in mV *versus* −log Concentrations of RIV in M Obtained by Using the Sensor 2

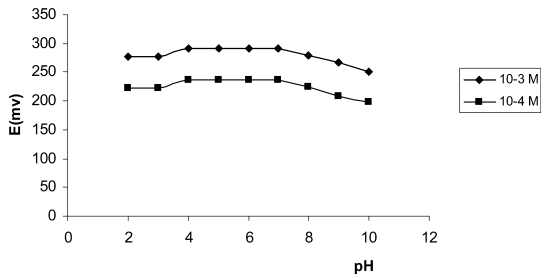

Fig. 4. Effect of pH on the Response of Sensor 1

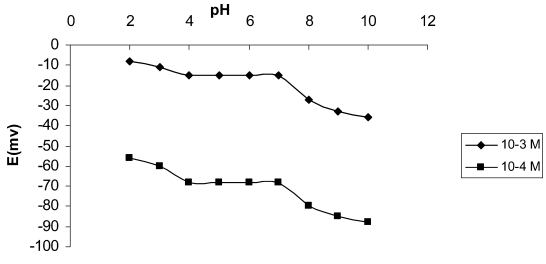

Fig. 5. Effect of pH on the Response of Sensor 2

Although, the investigated coated wire sensor (sensor 2) consists of membrane of PVC/sensing system/mediator in ratios 34 : 2 : 64, without an internal reference system, there is a confident view that the coated wire sensors have an inbuilt reference system which is attributed to the permeability of PVC to both water and oxygen and, thus, setting up an oxygen electrode at the wire membrane interface to function as an internal reference system.[15)]

Sensors Selectivity The effect of interfering substances upon the performance of the sensors was studied by separate solution method by using the following equation[31)]:

$$-\log(K^{\text{pot}}_{\text{A,B}}) = \frac{E_1 - E_2}{2.303RT/Z_{\text{A}}F} + \left(1 - \frac{Z_{\text{A}}}{Z_{\text{B}}}\right)\log a_{\text{A}}$$

Where E_1 is the potential measured in 10^{-3} M RIV solution, E_2 the potential measured in 10^{-3} M interferent solution, Z_{A} and Z_{B} are the charges of rivastigmine and interfering ion, respectively, a_{A} is the activity of drug and $2.303RT/Z_{\text{A}}F$ represents the slope of the investigated sensors (mV/concentration decade).

Table 3 shows the potentiometric selectivity coefficients of the proposed sensors in the presence of capsules excipients (propylene glycol, mannitol), degradation product ((*S*)-3-(1-dimethylaminoethyl) phenol), amino acids (β-alanine, glycine), electrolytes normally present in plasma (NaCl, KCl) and also some anticholinesterase drugs (neostigmine bromide, pyridostigmine bromide, distigmine bromide, physostigmine salicylate), the results revealed that the proposed membrane sensors displayed high selectivity, and that no significant interference was observed from interfering species. Also, they revealed that sensor 1 displayed greater selectivity of potential for ionic interfering species such as NaCl, KCl, and $CaCl_2$ than did sensor 2.

Table 4 shows the results obtained for the determination of RIV in pharmaceutical formulations (Exelon® capsules) that proves the applicability of the method, as demonstrated by the accurate and precise percentage recovery, the results obtained were also compared with those obtained by using reported method[6)] (HPLC method using aqueous 0.01 M sodium-1-heptane sulphonate, pH: 3.0–acetonitrile (72 : 28, v/v). No significant difference in results was found. Placebo experiments contain all additives in the same ratio as that used in capsules were investigated. The excipients present in Exelon® capsules are gelatin, Iron oxide, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose and titanium dioxide did not show any interference. Thus, analysis was carried out without prior treatment or extraction.

Table 5 shows the results obtained for the determination of RIV in spiked human plasma it is clear from the results that a wide concentration range of the drug could be determined by the investigated sensors and they gave stable results in slopes and mV readings as revealed by high precision and accuracy of recovery results of spiked plasma samples. It is also clear from the results shown in Table 4 that sensor 1 is more sensitive than sensor 2 because wider concentration ranges of the drug could be determined.

On application to rat brain homogenate, it has been found that the two sensors gave stable results in slopes and mV readings as revealed by high precision and accuracy of recovery results of spiked brain tissue homogenates, Table 6. As the response time of the proposed sensors are instantly

Table 3. Potentiometric Selectivity Coefficients ($K^{\text{pot}}_{\text{rivastigmine,I}}$) of the Two Proposed Electrodes by Using the Separate Solutions Method (SSM)[11)]

Interferent[b)]	Selectivity coefficient[a)]	
	RIV-coated graphite	RIV-coated platinum wire
Degradate[c)]	2.1×10^{-3}	2.2×10^{-3}
Neostigmine bromide	3.2×10^{-2}	5.2×10^{-2}
Pyridostigmine bromide	5.6×10^{-2}	3.3×10^{-2}
Distigmine bromide	2.3×10^{-2}	6.2×10^{-2}
Physostigmine salicylate	3.0×10^{-3}	3.1×10^{-3}
Glycine	5.2×10^{-3}	5.1×10^{-3}
NaCl	3.2×10^{-3}	3.9×10^{-2}
KCl	4.6×10^{-3}	4.2×10^{-2}
$CaCl_2$	3.8×10^{-3}	3.1×10^{-3}
Propylene glycol	6.4×10^{-3}	4.0×10^{-2}
Mannitol	3.2×10^{-3}	5.2×10^{-3}
β-Alanine	5.3×10^{-3}	3.1×10^{-3}

a) Each value is the average of three determinations. *b*) All interferents are in the form of 1×10^{-3} M solution that is equimolar with the 1^{ry} ion (RIV). *c*) (*S*)-3-(1-dimethylaminoethyl) phenol.

Table 4. Determination of RIV in Exelon® Capsules by the 2 Proposed Electrodes and by the Reported Method[6)]

Exelon® capsules (6 mg)	Recovery %±S.D.[a)] of rivastigmine		
	RIV-coated graphite	RIV-coated platinum wire	Reported method[b)]
Batch no. 3003	99.53±0.877	100.48±0.811	99.36±0.956
t-test[c)]	0.293 (2.306)	2.000 (2.306)	
F[c)]	1.187 (6.39)	1.389 (6.39)	
Batch no. 4074	100.49±0.793	99.71±0.981	99.87±0.917
t-test[c)]	1.144 (2.306)	0.266 (2.306)	
F[c)]	1.338 (6.39)	1.145 (6.39)	
Mean	100.01±0.835	100.09±0.896	

a) Average of five determinations. *b*) HPLC method using aqueous 0.01 M sodium-1-heptane sulphonate, pH: 3.0–acetonitrile (72 : 28, v/v). *c*) The values in parentheses are the corresponding theoretical values for *t* and *F* at $p=0.05$.

Table 5. Determination of RIV in Spiked Human Plasma by the Proposed Sensors

Added,[b)] μg/ml	Recovery (%)±S.D.[a)]	
	RIV-coated graphite	RIV-coated platinum wire
10^{-3} (400.4)	99.70±0.39	99.7±0.72
10^{-4} (40.04)	99.40±0.97	99.3±0.93
10^{-5} (4.004)	98.21±1.56	—

a) Average of three determinations. *b*) Within the concentration range in which the sensors give nernestian response.

Table 6. Determination of RIV in Spiked Rat Brain Homogenate by the Proposed Sensors

Added,[b)] μg/ml	Recovery(%)±S.D.[a)]	
	RIV-coated graphite	RIV-coated platinum wire
10^{-3} (400.4)	98.12±1.58	98.73±1.63
10^{-4} (40.04)	98.21±1.67	99.32±1.52

a) Average of three determinations. *b*) Within the concentration range in which the sensors give nernestian response.

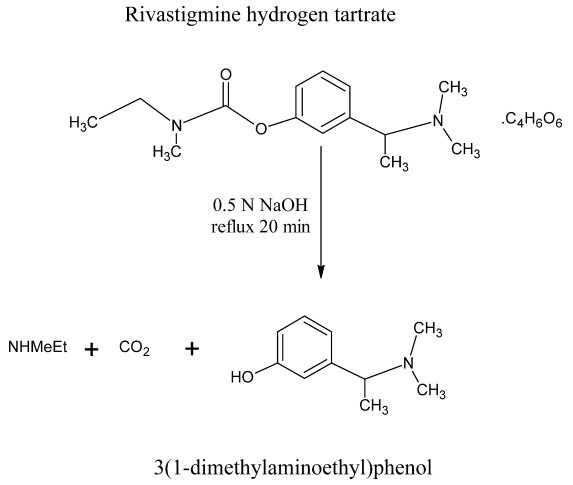

Fig. 6. Alkaline Degradation of Rivastigmine Hydrogen Tartrate[6)]

Table 7. Determination of RIV in Laboratory Prepared Mixtures Containing Different Ratios of RIV and Its Induced Alkaline Degradation Products by the Proposed Electrodes

Ratio %[b)] drug : degradate	Drug recovery[a)] %±S.D.[a)]	
	RIV-coated graphite	RIV-coated platinum wire
100 : 0	99.31±0.49	99.29±0.37
90 : 10	99.11±0.67	99.26±0.69
80 : 20	99.49±0.83	98.79±0.83
70 : 30	101.81±0.73	100.31±0.79
60 : 40	102.31±1.21	101.71±0.73
50 : 50	101.53±0.89	99.39±0.39
40 : 60	99.23±0.63	98.59±0.63
30 : 70	99.18±1.03	98.03±1.09
20 : 80	98.73±0.68	98.13±0.63
10 : 90	98.91±0.83	98.73±0.83

a) Average of three determinations. *b*) 1×10^{-3} M in BRB of pH 5.5.

(within 10 s), the sensors are rapidly transferred back and forth between the biological samples and the deionized bidistilled water between measurements for protecting the sensing part from the surface adhesion of some matrix components.

Degradation of RIV was induced by boiling with 0.5 M NaOH. Figure 6 shows the reported alkaline degradation of the drug,[6)] the degradation products are (*S*)-3-(1-dimethylaminoethyl)phenol which is also the reported metabolite of RIV[5)] and the gases carbon dioxide and ethylmethylamine. The induced alkaline degradation was tested by TLC plates and (butanol : methanol : H_2O : NH_3 (5 : 4 : 1 : 0.01 by volume) as the mobile phase); complete separation with *Rf* values of 0.70 for RIV and 0.27 for its degradation product were obtained. The spots were detected by using a UV lamp at a short wavelength of 254 nm. The intact drug was entirely degraded after boiling with 0.5 M NaOH for 20 min.

Table 7 shows the results obtained upon analysis of synthetic mixtures containing different ratios of intact drug to degraded sample, varying from 100 : 0 to 10 : 90. The results show that the proposed sensor can be successfully used for determination of intact drug in the presence of >90% of its degradate. Thus the proposed sensors are recommended for use in stability-indicating methods.

Conclusion

The studied electrodes are sufficiently simple and selective for the quantitative determination of RIV in drug bulk powder, pharmaceutical formulations, plasma and in the presence of its degradate. The use of the proposed sensors offers the advantage of fast response, elimination of drug pre-treatment or separation steps, wide pH and concentration range. They can therefore be used for the routine analysis of the drug in quality control laboratories. Moreover the proposed method can be used for the determination of the RIV in rat brain tissue homogenates.

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