Sensors and Actuators B 190 (2014) 101–110

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

# Advantages of the incorporation of 2-hydroxyl propyl beta cyclodextrin and calixarene as ionophores in potentiometric ion-selective electrodes for rivastigmine with a kinetic study of its alkaline degradation

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ARTICLE INFO

*Article history:*
Received 25 April 2013
Received in revised form 13 August 2013
Accepted 21 August 2013
Available online 30 August 2013

*Keywords:*
Rivastigmine
2-Hydroxy propyl β-cyclodextrin
4-Sulfocalix-8-arene
Ionophore
Stability-indicating methods
Kinetic study

ABSTRACT

Three selective electrodes were investigated for rivastigmine (RIV). Sensor 1 was fabricated using ammonium reineckate (RNC) as a cation exchanger without incorporation of any ionophore. Sensors 2 and 3 used 2-hydroxy propyl β-cyclodextrin and 4-sulfocalix-8-arene as ionophores respectively in addition to RNC as a cation exchanger. Linear responses of RIV within the concentration ranges of $10^{-5}$ to $10^{-2}$, $10^{-6}$ to $10^{-2}$ and $5 \times 10^{-7}$ to $10^{-2}$ M with Nernstian slopes of $51.5 \pm 0.8$, $54.6 \pm 0.7$ and $56.8 \pm 0.4$ mV/decade over the pH range of 4–7 were obtained using sensors 1, 2 and 3, respectively. The utility of ionophores had a significant influence on increasing the membrane sensitivity and selectivity of sensors 2 and 3 compared to sensor 1. The proposed sensors displayed useful analytical characteristics for the determination of RIV in pharmaceuticals, biological fluids and in the presence of its degradation product and thus could be used for stability-indicating assays. Sensor 3 was used to study the kinetics of RIV alkaline degradation that was found to follow a pseudo first-order reaction. The activation energy could be estimated from the Arrhenius plot to be 9.864 kcal $mol^{-1}$.

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## 1. Introduction

Rivastigmine [123441-03-2] (Fig. 1) Ethyl methyl carbamic acid 3-[(1*S*)-1-(dimethyl amino) ethyl phenyl ester, (*S*)-*N*-ethyl-3-[(1-dimethylamino) ethyl]-*N*-methyl phenyl carbamate], $C_{14}H_{22}N_2O_2$, mol.wt. 250.34 [1].

Rivastigmine is a carbamate type reversible acetyl-choline esterase inhibitor. It is selective for the central nervous system and is used for the symptomatic treatment of mild to moderately severe Alzheimer's disease. [2].

Several methods have been reported for the determination of RIV, these include, spectrophotometric [3–5], high performance liquid chromatographic [6–12], thin layer chromatographic [13], capillary zone electrophoresis [14,15] and electrochemical [16].

In modern analytical laboratory, there is a need for significant stability-indicating methods of analysis. From these procedures, only the spectrophotometric [5] HPLC techniques [7,8], TLC [13] and electrochemical [16] were recommended as stability indicating assays. Two ion selective electrodes have been reported for the determination of RIV [16] using a precipitation-based technique with tetrakis (4-chlorophenyl) borate as an cation exchanger with solid state graphite and platinum wire as supports without incorporation of any ionophore. Their selectivity coefficients were only tested for a few inorganic cations.

Cyclodextrins are known to accommodate a wide variety of organic, inorganic and biologic guest molecules to form stable host–guest inclusion complexes or nanostructure supramolecular assemblies in their hydrophobic cavity while exhibiting high molecular selectivity and enantioselectivity [17,18]. They have been previously applied as sensor ionophores in potentiometric ion selective electrodes for the determination of fluorinated surfactants [19], chiral molecules incorporating aryl rings [20], protonated amines [21] and quaternary ammonium drugs [22].

Calixarenes are cavity-shaped cyclic oligomers made up of phenol units linked via alkylidene groups. Their configuration includes a number of selective factors, such as cavity-size, conformation and substituents, which leads to the formation of typical host–guest complexes with numerous compounds and allow for a variety of applications in ion-selective membranes and electrodes [23–25].

The present work focused on the use of functionalized cyclodextrin derivatives and sulphonated calix-8-arene as neutral ionophores for the development of novel sensors for the

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http://dx.doi.org/10.1016/j.snb.2013.08.065

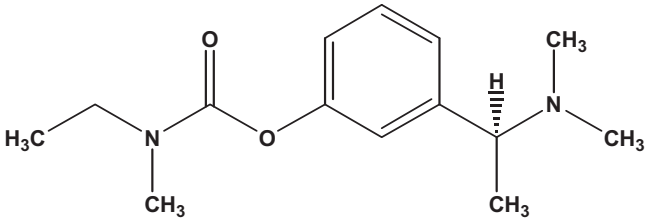


**Fig. 1.** Chemical structure of rivastigmine.

determination of RIV. These sensors were used for the determination of RIV in solution, pharmaceutical formulations, biological fluid [plasma and cerebrospinal fluid (CSF)] and in the presence of its degradation product or in the presence of other excipients without the need for preliminary extraction and separation steps. Moreover, kinetic studies and accelerated stability experiments are important to solve problems encountered in quality control and to predict the expiry dates of pharmaceutical products.

The scientific novelty of the present work is the incorporation of ionophores in potentiometric ion-selective electrodes for RIV which offers many advantages (discussed in results and discussion). Besides, it is the first kinetic study for RIV degradation to calculate the strength of this amide molecule. In addition that, this kinetic study is monitored by ion selective electrodes technique, which is more simple (require no preliminary extraction), sensitive (wider range) and rapid compared to the ordinary UV spectroscopy and HPLC methods.

## 2. Experimental

### 2.1. Apparatus

All potentiometric measurements were carried out at 25 ± 1 °C with a Hanna (Model 211) pH/mV meter with a single-junction calomel reference electrode (Model HI5412) used in conjunction with the drug sensor. A Hanna pH glass electrode part code HI 1131B, lot no. 30565 (Romania) and a Bandelin sonorox magnetic stirrer model Rx 510 S (Budapest, Hungary) were used for pH adjustments.

Precoated HPTLC plates, silica gel 60 $F_{245}$ 20 cm × 20 cm, 0.2 nm thickness, Macheray-Nagel (Germany).

### 2.2. Chemicals and reagents

Rivastigmine hydrogen tartrate (mol.wt. 400.4) (ID 3102936) reference standard was kindly supplied by Novartis Pharm Co, its purity was certified to be 99.69%. Its purity was also checked in our laboratory according to the reported spectrophotometric method [5] (2nd derivative at 262 nm) and it was found to be 99.70 ± 0.578.

Pharmaceutical formulations: Exelon® capsules batch number B 8173 and B 3003 (exp 3/2010), were purchased from the Egyptian market. Each capsule is claimed to contain 3 mg or 6 mg of rivastigmine hydrogen tartrate. Exelon® capsules are manufactured by Novartis Company (Basle, Switzerland).

All chemicals and reagents used were of analytical grade, and bi-distilled deionized water was used. Polyvinyl chloride (PVC high molecular weight), 2-hydroxy propyl β-cyclodextrin (β-CD) (mol.wt. 1460) and 4-sulfocalix-8-arene (mol.wt. 1489.48) were purchased from Fluka (Steinheim, Germany). 2-Nitrophenyl octyl ether (NPOE) was purchased from Sigma (St. Louis, MO, USA). Ammonium reineckate (RNC) (mol.wt. 354.42) was purchased from Aldrich (Steinheim, Germany), sodium hydroxide, hydrochloric acid (Prolabo).

Additives, like magnesium stearate was purchased from Aldrich (Steinheim, Germany). Tetrahydrofuran (THF) 99% was obtained from Lab scan. Sodium chloride and ammonium sulphate were obtained from Prolabo (Pennsylvania, USA). Britton–Robinson buffer (BRB) (pH 2–12) was prepared by mixing different volumes of 0.04 mol $L^{-1}$ acetic acid, 0.04 mol $L^{-1}$ phosphoric acid, 0.04 mol $L^{-1}$ boric acid and 0.2 mol $L^{-1}$ sodium hydroxide.

Plasma and cerebrospinal fluid were supplied by VACSERA (Giza, Egypt) and used within 24 h.

### 2.3. Procedures

#### 2.3.1. Preparation of the degradation product of rivastigmine [5,16]

Five hundred milligrams of RIV were dissolved in 50 mL of 0.5 M sodium hydroxide and then refluxed at 100 °C for 20 min. 1 mL was cooled to room temperature and then diluted with methanol. The degraded solution and standard solution were spotted on HPTLC plates. The plates were placed in chromatographic tanks previously saturated for 1 h with the mobile phase of methanol: butanol:$H_2O$:$NH_4OH$ (5:4:1:0.01, v/v/v/v) and then air-dried. The spots were visualized under UV light at 254 nm. The medium was rendered acidic using concentrated hydrochloric acid to precipitate the degradation product. The degradation product was filtered and then recrystallized from isopropyl alcohol.

#### 2.3.2. Fabrication of membrane sensors

For the preparation of sensor 1, 10 mL of $10^{-2}$ M RIV aqueous solution was mixed with 10 mL of a saturated aqueous solution of RNC. The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature and ground to fine powder.

In a 25 mL beaker, 0.01 g of the previously prepared ion-association complex was dissolved in 2 mL THF, mixed with 0.35 g of NPOE then added to 0.19 g of PVC already dissolved in 3 mL THF and repeat mixing. This mixture was poured in a Petri dish (5-cm diameter) and the dish was covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent forming the master membrane with 0.1-mm thickness [26].

In a Petri dish (5-cm diameter), 0.01 g (0.0282 mM) of RNC was mixed with 0.4 g NPOE and 0.041 g (0.0282 mM) of β-CD or 0.042 g (0.0282 mM) of 4-sulfocalix-8-arene (for the preparation of sensors 2 and 3, respectively), 0.19 g of PVC was added and repeated mixing then dissolved in 5 mL tetrahydrofuran. The dish was covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent forming the master membrane with 0.1-mm thickness. [26,27].

#### 2.3.3. Electrode 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 an adhesive of PVC dissolved in tetrahydrofuran. The other end of the PVC tubing was then connected to an appropriate glass outer casing and the assembly is shown in Fig. 2.

A mixture of equal volumes of $10^{-2}$ M RIV and $10^{-2}$ M sodium chloride was used as an internal reference solution. The membranes were conditioned by soaking in $10^{-2}$ M aqueous drug solution overnight and stored in the same solution when not in use.

#### 2.3.4. Sensor calibration

The prepared electrodes in conjunction with the single-junction calomel reference electrode were immersed in 50 mL aliquots of RIV aqueous solutions in the range of $10^{-7}$–$10^{-1}$ M and adding 1 mL of 2 M $(NH_4)_2SO_4$ (ionic strength adjustor) to the measured solutions. They were allowed to equilibrate while stirring and recording the e.m.f. readings within ±1 mV. The membrane sensors were washed between measurements with water. The e.m.f. values were recorded as a function of drug concentration and then calibration graphs of the recorded potentials versus −log drug concentration

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