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Highly Selective Sensors for Assay of Donepezil Hydrochloride by Potentiometry: Green Approaches

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Abstract- Donepezil hydrochloride (DPH), an indan and piperidine derivative, is a selective medicament of Alzheimer's disease. Two highly selective and eco-friendly membrane based sensors have been designed to determine DPH. Sodium tetraphenyl boron (STPB) and sodium phosphotungestate (SPT) have been used as ion-exchangers, for construction of Sensors 1 and 2, respectively, with β-cyclodextrin (β-CD) as ionophore and nitrophenyl octyl ether (NPOE) as a plasticizer. The sensors are highly capable to determine DPH of linear concentration range 1.0×10^{-6} to 8.0×10^{-3} M at the pH ranged between 5 and 8. The regression coefficient values for the resulted calibration lines were 0.9992 and 0.9984 with Sensor 1 (DPH-STPB sensor) and Sensor 2 (DPH-SPT sensor), respectively. The Nernstian slopes of 58.51±0.80 and 57.24±0.67, for Sensor 1 and 2, respectively, reflected the appropriate functioning of sensors in relative to concentration of DPH. The limits of detections (LOD) values were calculated to be 6.3×10^{-7} and 7.14×10^{-7} M for Sensor 1 (DPH-STPB sensor) and Sensor 2 (DPH-SPT sensor), respectively. The results from validation of both the sensors reflected high selectivity for measuring potential of DPH solutions. Sensors have been subjected to validity check through accuracy, precision, robustness and ruggedness. Specific functioning of Sensor 1 and 2 permitted to achieve 99.26% as mean recovery of DPH from tablets analyses. The outcome of statistical tests between the results from sensors 1 and 2 with reference method pronounced the extraordinary applicability of the proposed new methods to determine DPH in pharmaceuticals. These methods are greener approaches due to the non-usage of any organic toxic solvent and pre-treatment and extraction steps' absence.

Keywords- Donepezil; Sensors; Potentiometry; Determination; Pharmaceuticals

1. INTRODUCTION

Donepezil hydrochloride (DPH) with the IUPAC name of (±)-2-[(1-Benzyl-4-piperidyl) methyl]-5, 6-dimethoxy-1-indanone hydrochloride (Fig**.** 1) has the ability to increase cortical acetylcholine and hence is a major therapeutic candidate to treat Alzheimer's disease. The reversible inhibition of hydrolysis of DPH by acetyl cholinesterase is held responsible to increase the acetyl choline concentration and as a result the therapeutic property is exerted [1-3].

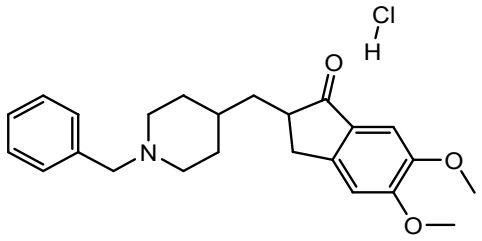


Fig. **1.** Chemical structure of DPH

The official Pharmacopeia of United States monographed a HPLC assay procedure [4] for DPH in tablets. The survey of literature for analytical methods for DPH is scanty. The chromatographic, namely, ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) [5] and high-performance liquid chromatography with ultraviolet absorbance (HPLC-UV) [6,7], diode-array (HPLC-DAD) [8], mass spectrometric (HPLC-MS) [9,10], tandem mass spectrometric (HPLC-MS/MS) [11-14] and fluorescent detections [15,16], spectrofluorimetric [17,18] and voltammetric techniques [19,20] have been used before for assay of DPH in biological materials.

To determine DPH in pharmaceuticals few articles describing chromatographic techniques such as UPLC with UV detection (UPLC-UV) [21], HPLC-UV [22-25], HPLC-MS [26], and HPLC-photo-diode array (HPLC-PDA) detection [26,27-29], HPLC with fluorescent detection [16] and high-performance thin layer chromatography (HPTLC) [30,31] are set-up by different analysts. The other articles describing spectrofluorimetric [18] and spectrophotometric procedures [18,32-36] have also been published.

From the literature reference of analytical methods reported for DPH in pharmaceuticals, it is envisaged that potentiometry has not been employed so far. However, in the voltammetric method reported by Golcu and Ozkan [19], DPH has been determined by cyclic (CV), linear sweep (LS), differential pulse (DPV) and square-wave (SWV) voltammetric techniques using glassy carbon working electrode. The procedures are able to determine DPH in the concentration range from 1×10^{-6} to 1×10^{-4} M. Rao et al. [20], reported the study of electrochemical behaviour of DPH by extending the application of CV and DPV techniques using β-cyclodextrin modified carbon paste working electrode (β-CDCPE). The performances in both CV and DPV techniques have been compared with that of β-CDCPE. The analytical

results showed the linear correlation between peak currents and applied potential in the concentration ranges from 4.2×10^{-8} to 5.6×10^{-7} M and 3.2×10^{-9} to 4.2×10^{-8} M DPH using CPE and β-CDCPE, respectively. The reported electro-analytical procedures have narrow linear range of DPH concentration and moreover they are in need to maintain unusual and complex experimental set-up and conditions such as requirement of potentiostat, electronic integrators, and maintenance of oxygen-free atmosphere etc.

Therefore, for the first time for DPH, potentiometric methods with the simple, cost-effective and non-hazardous membrane sensors using sodium tetraphenyl boron (STPB) and sodium phosphotungstate (SPT) as ion-exchangers, β-cyclodextrin (β-CD) as ionophore and nitrophenyl octyl ether (NPOE) as a plasticizer, are proposed to determine DPH in pharmaceuticals. The sensors' fabrication procedures are pretty simple using innocuous materials. After validation the sensors have been used to determine DPH in pharmaceuticals.

2. EXPERIMENTAL

2.1. Instrument

Potentiometric measurements were carried out using a PICO digital model (Chennai-32, India) potentiometer with Ag/AgCl double junction reference electrode (Elico, India) (3 mol/L KCl saturated with AgCl as an inner filling solution and 10% KNO_3 as an electrolyte). The pH measurements were made using glass electrode and Labtronics model (Bengaluru, India) pH meter. A Magnetic stirrer from Remi (Bengaluru, India) was used for stirring purpose.

2.2. Materials and reagents

The pure DPH (99.8% purity) was received from Ranbaxy Laboratories Ltd, Sirmur, Himachal Pradesh, India. Aricept-10 tablets (10 mg DPH/tablet) (Eisai Pharmaceuticals Ltd., India) were obtained from Medicine shops.

Analytical graded chemicals, reagents and solvents were used. The solutions were prepared with bi-distilled water. Sodium tetraphenyl boron (STPB), sodium phosphotungestate (SPT), β-cyclodextrin (β-CD), polyvinyl chloride (PVC) of high molecular mass, o-nitrophenyl octylether (NPOE), tetrahydrofuran (THF), dibutyl phthalate (DBP), di-octyl phthalate (DOP), di-butyl sebacate (DBS), concentrated sulphuric (H_2SO_4) (98% v/v, Sp. gr. 1.84) and hydrochloric (HCl) (36% v/v, Sp. gr. 1.19) acids, ammonia (NH_3), sodium acetate (NaOAc) and sodium hydroxide (NaOH) were purchased from Merck (Mumbai, India) distributors.

Aqueous solutions of 0.1 M each of H_2SO_4 or HCl, 1 M each of NaOAc, Na_2CO_3, $NaHCO_3$, NaOH, CH_3COOH, KCl, $AgNO_3$, KOH, KNO_3, KH_2PO_4, H_3PO_4, $NaNO_2$, $CdCl_2$, $CoCl_2$, glycine, talc, arginine, glucose, oxalic acid, sucrose, talc and urea (all from S.D. Fine Chem Ltd., Mumbai, India) were prepared in bi-distilled water.

2.3. Procedures

2.3.1. Preparation of standard DPH solution

The standard 0.01 M solution was prepared by dissolving in 416 mg of pure DPH and bringing the volume to 100 mL in a calibrated flask with water. The solution prepared was found stable for 24 h when stored at 25^{O} C.

2.3.2. Preparation of tablet extract

Pre-weighed 20 Aricept tablets were powdered in a mortar. Tablet powder having 416 mg of DPH was transferred in to a 100 mL volumetric flask and shaken with 70 ml of water for 20 minutes. After dilution to the mark with water it was mixed thoroughly. The extract was obtained by filtering through Whatmann No. 41 filter paper and used for assay of DPH.

2.3.3. Preparation of membranes

A mixture containing 15 mg of ion-exchanger (STPB for Sensor 1; SPT for Sensor 2), 350 mg of NPOE, 220 mg of PVC and 15 mg of β-CD were placed into Petri dish of 5.0 cm diameter. After thorough mixing, the content was dissolved in 10 mL of THF, the Petri dish was closed with a filter paper and kept ahead for 24 h under room temperature for solvent evaporation. The resulted membranes obtained with ~0.15 mm thickness were then used to device the Sensor 1 and 2.

2.3.4. Preparation of Sensor 1 and 2 assemblies

The thin layer of dried membrane of about 10 mm diameter was removed by Cork borer and fused at one tip of interchangeable Pyrex glass tube with the help of THF. After drying, the tube was filled by 3-5 mL of mixture containing 2 mM each of DPH and KCl solution as internal reference. A reference Ag-AgCl wire was immersed and the terminal of electrode was fixed to the potentiometer. The constructed DPH-STPB (Sensor 1) and DPH-SPT (Sensor 2) sensors were then soaked in a standard 2 mM DPH solution for a minimum period of 4 h and were used for measurement of potential as the function of reference Ag-AgCl electrode. Systematically, the overall potentiometric cell design is showed below:

$Ag\text{-}AgCl_{IR} \,\|\, DPH_I$, (2 mM), KCl (2 mM) $|$ Membrane $|$ $[DPH]_{Sample} \,\|\, AgCl\text{-}Ag_{SR}$

where '$Ag\text{-}AgCl_{IR}$' and '$Ag\text{-}AgCl_{SR}$' are reference Ag-AgCl electrodes immersed into internal reference DPH (DPH_I) and sample solutions, respectively, and 'Membrane' of the sensor devised with STPB and SPT as ion-exchangers for Sensor 1 and 2, respectively, using β-CD as ionophore, NPOE as plasticizer and PVC as matrix.

The relation of E_{Cell} (potential) with [DPH] in the sample, $[DPH]_{Sample}$, is given as explained in Nernst equation [37]:

$$E_{Cell} = K + 0.05916 \log[DPH]_{Sample}$$

where K accounts for the reference electrode's potential, LJP, the asymmetry potential, the activity coefficient of DPH and $[DPH]_I$.

2.3.5. Checking the linearity using sensors

Different volumes of 0.01 M standard DPH solutions to cover the concentration from 1.0×10^{-6} to 8.0×10^{-3} M were placed into the sequence of 25 mL calibrated flasks. The volumes in each were adjusted to 20 mL by introducing water and pH adjusted in between 5 and 8 with dilute NH_3 or 1 M NaOAc solution. The contents of flasks were brought up to the mark with water, mixed well and poured into sequence of 50 mL beakers. The designed sensors were then used as working electrodes separately to record the potential of each solution using the calibrated potentiometer *against* reference Ag-AgCl electrode.

The plots of E_{Cell} *versus* log [DPH] were prepared for DPH-STPB sensor (Sensor 1) and DPH-SPT sensor (Sensor 2) separately. The [DPH] (concentration of DPH) in samples containing unknown [DPH] was estimated with the help of calibration graph or regression data of E_{Cell} *versus* log [DPH] with each sensor.

2.3.6. Tablets analysis

An appropriate volume of tablet extract of 0.01 M in DPH was quantitatively diluted to obtain a solution of DPH of fixed concentration. The general procedure was strictly adhered and measured the potential separately using each sensor. The [DPH] was then calculated for the resulted potentials by graphically or relating to regression data.

2.3.7. Interference study

Into an array of 50 mL beakers, 10.0 ml of 0.01 M pure DPH solution, 10 ml of water and 1 mL of 1 M solution of interferent were taken. After pH adjusted in between 5 and 8, they were diluted to 25 mL with water, mixed for homogenous solution and measured their potentials using Sensor 1 and 2, separately in respect to Ag-AgCl reference electrode.

2.3.8. Determination of selectivity coefficient ($K_{DPH.I}$) of sensors

In a group of 50 mL beakers 1 to 10 mL of 0.01 M solution of DPH were taken and mixed with 1.0 mL of 1.0 M interferent. The pHs were manipulated to 5-8, the volumes were raised to 25 mL with water and homogenised. Different sets of solutions were obtained for different interferents. The potentials were recorded using DPH-STPB and DPH-SPT sensors, separately.

The graphs of E_{Cell} *versus* log[DPH] was prepared. The point of intersection was located and the values of $K_{DPH.I}$ for each interferent were calculated using the formula [37]:

$$K_{DPH.I} = \frac{[DPH]_E}{[I]_E^{z_{DPH}/z_I}} = \frac{[DPH]_{Int}}{[I]_{add}^{z_{DPH}/z_I}}$$

where z_{DPH} and z_I are the cationic and anionic charges on DPH and added interferent, respectively. $[DPH]_E$ and $[I]_E$ are concentrations of DPH and interferent to generate indistinguishable values of E_{Cell}. $[DPH]_{Int}$ is the concentration in the internal DPH solution and $[I]_{add}$ is the concentration of intereferent present or added with DPH solution.

2.3.9. Establishing of stoichiometry between DPH and STPB or SPT

A 10 mL solution of 0.01 M DPH was accurately measured and transferred in to a beaker present on magnetic stirrer. The conductivity cell was immersed and titration was performed separately with 0.01 M STPB and SPT and the data of recorded conductance and volume of titrant was tabulated. For each sensor, the graph of conductance against the molar ratio of STPB or SPT was constructed and used to evaluate the stoichiometry between DPH and STPB in Sensor 1 and DPH and SPT in Sensor 2.

3. RESULTS AND DISCUSSION

Two different ISEs have been fabricated for DPH using two cation exchangers, namely STPB and STP, β-CD as ionophore and NPOE as plasticizer in the PVC matrix. The basic nitrogenous group of free basic form of DPH, i.e. DP, gets protonated and exists as DPH^+. Cl^- in the aqueous solution. After immersing the sensor into the DPH solution, during the interaction of aqueous DPH solution containing DPH^+ cation and Cl^- anion with either STPB or SPT containing anionic TPB^- or PT^- in the membrane, the *in-situ* exchange of anions take place [38] and consequently ion association complex of $DPH^+.TPB^-$ or $DPH^+.PT^-$ is formed. The probable reaction scheme is proposed in scheme 1. The product of *in-situ* reaction is responsible for potential of aqueous solution of drug. Besides, the E_{Cell} is also attributes to different concentration of DPH at opposite sides of the membrane which is present at the working electrode. Thus, the membranes constructed here should therefore selectively respond to DPH, as the artificial ion-selective sensors. The potentiometry will enable their use to confirm the selective functioning by generating the potential difference which could be ably measured using membrane sensors [37].

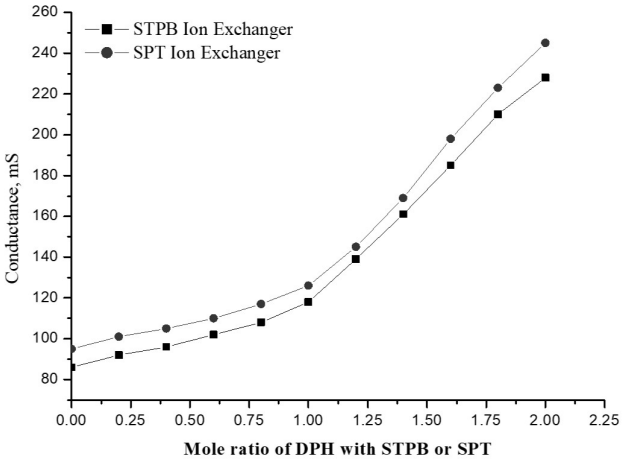
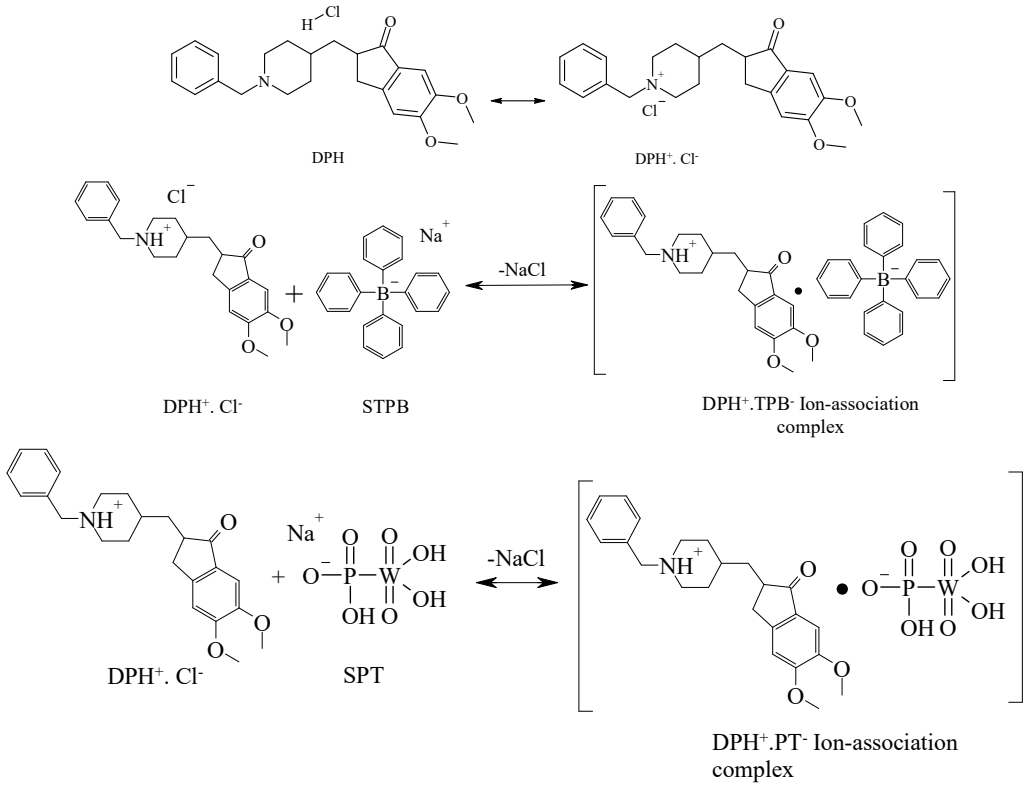


Fig. 2. Plots of conductance *versus* mole ratio of DPH with either STPB or SPT for showing the stoichiometry between reactants

Using STPB and SPT as ion exchangers in designing the membranes for Sensor 1 and 2, respectively, the results such as Nernstian slope of the calibration line and the stoichiometric ratios between DPH and exchanger were highly satisfactory. The stoichiometry between DPH and STPB in Sensor 1, and DPH and SPT in Sensor 2, were investigated by simple conductometric analysis. The mole ratio of DPH with STPB or SPT was evaluated as 1.0 (Fig. 2) and this confirmed the 1:1 composition between DPH and each of ion-exchanger to form ion-association complex in two sensors.



Scheme 1. Probable reaction scheme in forming DPH^+-TPB^- and DPH^+-PT^- ion-association complexes

3.1. Optimization of variables

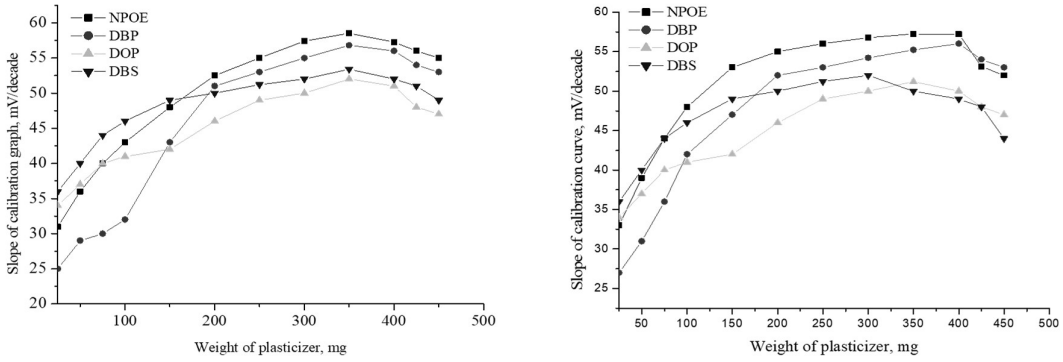
3.1.1. Membrane components

At the beginning, a series of experiments with different amounts of materials such as ion exchangers, ionophore, plasticizer and PVC were executed to obtain the membranes. The obtained membranes with different amounts of each of the above components were used for construction of ISEs and checked the effective functioning for sensing to DPH by potentiometry. The results of membrane sensors obtained using 15 mg of ion-exchanger (STPB

for Sensor 1; SPT for Sensor 2), 220 mg of PVC and 350 mg of NPOE were highly reliable. Moreover, the slopes of the calibration lines of the sensors prepared using varying amounts of materials than indicated above were not acceptable to Nernstian behavior. A 10 mL of solvent, THF, was found convenient for complete dissolution of materials. At volumes larger than 10 mL, no much variation was seen. The membranes become dried enough in 24 h after pouring to Petri Dish and hence the same standing evaporation time was fixed. Thus, the procedure followed to prepare the membranes is the optimised one.

3.1.2. Choice of plasticizer

Different plasticizers viz. dibutyl sebacate (DBS), dibutyl phthalate (DBP), dioctyl phthalate (DOP) and o-nitrophenyl octylether (NPOE) in different amounts were used to obtain suitable membrane. Nernstian behaviour seen with the membranes prepared using 350 mg of NPOE for both Sensor 1 and 2. The sensors were seen to perform quickly with consistent potentials and ease of conditioning. However, the evaporation and response time were prolonged when NPOE amount greater than 425 mg was used. Therefore, a 350 mg of NPOE is recommended to use as plasticizer to design DPH-STPB and DPH-PTA sensors. Other plasticizers did not yielded acceptable results in relation to calibration, Nernstian behaviour, quick or rapid response and consistent E_{Cell} values. The resulted variations in behaviour of sensors prepared using NPOE and other plasticizers are graphed in Fig. 3.



(a) (b)

Fig. 3. Effect of quantities of different plasticizers on response behaviour of: (a) Sensor 1 (DPH-STPB) and (b) Sensor 2 (DPH-SPT)

3.1.3. Internal reference solution

Calibration curves were prepared for potentials and logarithmic concentrations of DPH data using the constructed sensors with varied concentrations of internal DPH and KCl solutions with the intent to obtain the linearity between potentials and logarithmic concentration of DPH solutions with Nernstian slope. The required result obtained when used a mixture of 2 mM each

of DPH and KCl solutions as internal standard. Acceptable correlation between potentials and *log[DPH]* was observed with Nernstian slopes of 58.51 and 57.24 mV/decade for Sensor 1 and 2, respectively. The slopes were too much varied around 60 mV at DPH and KCl concentrations other than 2 mM. Therefore, the mixture of 2 mM each of DPH and KCl solutions was used as internal reference solution for both the sensors. The consequent calibration curves for Sensor 1 and 2 are showed in Fig. 4.

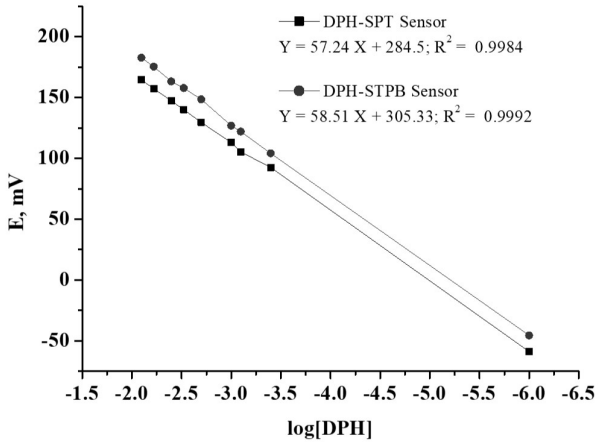


Fig. 4. Calibration plots of E_{Cell} against *log[DPH]* for DPH concentration range from 1×10^{-6} to 8×10^{-3} M under optimum conditions with Sensor 1 (DPH-STPB sensor) and Sensor 2 (DPH-SPT sensor)

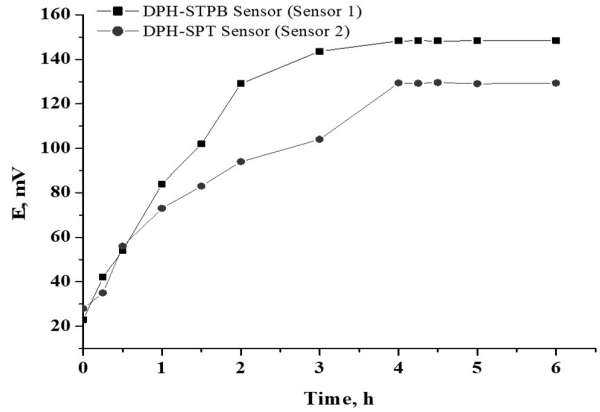


Fig. 5. Effect of soaking/conditioning time on potential of 2 mM DPH solution measured with Sensor 1 and 2

3.1.4. Soaking time

Sensors were soaked in standard solution of DPH for different intervals of times to sufficiently activate their surfaces. The duration was finalised by locating the time point from

which potential become steady and constant. The experimental results indicated the need soaking the sensors for 4 h. Thus, this time was fixed as time duration required to make membrane's active surface ready for effective use at 25° C. The time factor fixed and its variation to measure potential using DPH sensors (Sensor 1 and 2) is indicated in Fig. 5. This study also revealed and endorsed that the dried sensors may be placed in any closed opaque vessel and able for using further after conditioning by soaking in standard DPH for 4 h.

3.1.5. Effect of pH

The pH effect on the E_{Cell} of DPH solutions using Sensor 1 and Sensor 2 in reference to Ag-AgCl electrode was evaluated. The E_{Cell} values of solutions of DPH at pH range from 0.5 to 10 were measured using the proposed electrochemical cell assemblies for Sensor 1 and 2 separately. The pHs of solutions were brought to the required values by adding 1 M NaOAc or diluted NH_3 solutions and the potentials were recorded. While using both the sensors, the potentials steady state attained in the pH range from 5 to 8. However, below and beyond this range the potentials were lesser and inconsistent. This effect of pH on E_{Cell} of DPH solutions measured using Sensor 1 and 2 is showed in Fig. 6. According to the trend in the plot and thus, the pH ranged between 5 and 8 was fixed as optimum for measurement of potentials of DPH solutions using both sensors.

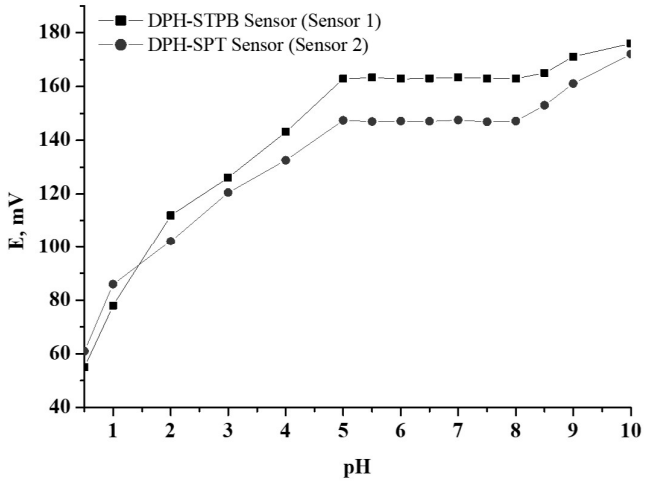


Fig. 6. The effect of pH on potential of 4 mM DPH solution measured with Sensor 1 and 2

3.1.6. Response time

The experimental response time [39] of the conditioned sensors were evaluated. Sensor 1 and 2 were found to respond to DPH solutions in 30 s after immersing into analyte solution. Therefore, the conditioned sensors were immersed into sample solutions of DPH and after 30 s the potentials were recorded.

3.1.7. Life time of sensors

The sensors were assessed for their stable and uncompromised performance ability. It was true that resulted Nernstian slopes were free from deviations while they were used for at least 45 and 55 days for Sensor 1 and 2, respectively. But after this period, response with the Nernstian behaviour was disturbed (Fig. 7). Therefore, the validity was declared as 45 and 55 days for DPH-STPB and DPH-SPT sensors, respectively.

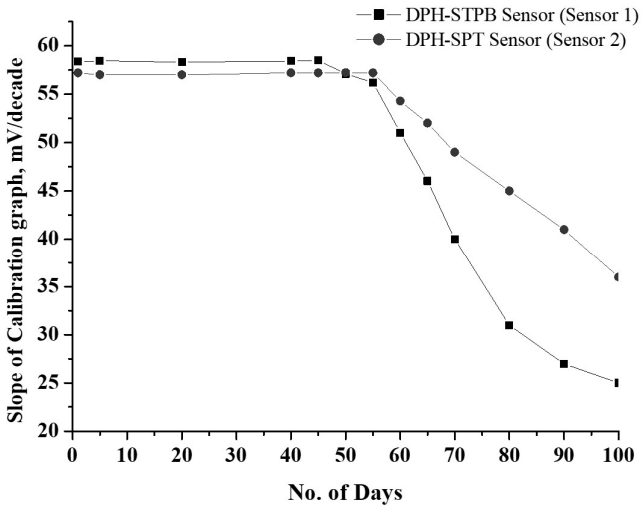


Fig. 7. Life time of DPH-STPB and DPH-SPT Sensors

3.2. Evaluation of selectivity coefficients

The chemical interaction between the active sites of the membrane surface and the analyte is responsible for generation of membrane potential (E_m). The poor selectivity of membranes towards a single species is owed by the factor of chemical process on the signal. Practically, E_m is in proportion to the concentration of ions capable of interacting at the membrane's active sites. The generalized Nernst equation to include the contribution of an interferent, *I,* is convened as below:

$$E_{cell} = K + \frac{0.05916}{Z_{DPH}} \log([DPH] + K_{DPH,I}[I]^{\frac{Z_{DPH}}{Z_I}}) \quad (1)$$

where the constant K includes reference electrode's potential, liquid junction potential and E_m; The charges on DPH and I are denoted by Z_{DPH} and Z_I, respectively. The parameter $K_{DPH,I}$ is known as selectivity coefficient and is defined as

$$K_{DPH,I} = \frac{[DPH]_E}{[I]_E^{Z_{DPH}/Z_I}} \quad (2)$$

where $[DPH]_E$ and $[I]_E$ are the DPH's and I's concentrations to yield same cell potentials, i.e. E. When the $K_{DPH,I}$ is equal to unity, the membrane responds for both DPH and I. A selective membrane must always possess $K_{DPH,I}$ value of < 1.0.

Thus, as an important feature, $K_{A,I}$ can be evaluated using the data of potentials of solutions contained with known but constant amount of I, $[I]_{add}$, and varying amounts of DPH. Two distinct linear regions in the plot of E_{cell} against logarithmic values of the analyte's concentration are very informative in evaluating the value of $K_{A,I}$. When the [DPH] is significantly larger than $K_{DPH,I}$ $[I]_{add}$, E_{cell} is a linear function of log [A]. If $K_{A,I}$ $[I]_{add}$ is significantly larger than [A], however, the E_{cell} remains constant. The analyte's and interferent's concentrations at the intersection of the two linear regions are used to calculate $K_{A,I}$.

Thus, $K_{A,I}$ values for DPH with different I were calculated and are given below in table 1. Both the sensors were checked with various inorganic and organic compounds, anions and cations. A 1 M solution of each interferent was spiked into pre-analyzed DPH solution and analysis done [40,41]. The summarised results indicated non-interference from the added species as showed by the calculated $K_{A,I}$ values in Table 1. Therefore, the developed sensors are most suitable electrodes for DPH analysis even in such interferents' presence.

3.3. Validation of sensors

The designed DPH-STPB and DPH-SPT sensors were validated by adhering to IUPAC recommendations [40,41] and ICH Guidelines [42]. The consequent results for individual parameters are described in the following sections.

3.3.1. Linearity of calibration curve, regression data and performance characteristics

The measured potentials and DPH concentrations were in very good correlation of linearity as showed in the calibration curves presented in Figure 4. The linearity obeyed the Nernstian behavior from both the sensors as reflected by the slopes of 58.51±0.80 and 57.24±0.67 mV/decade, for DPH-STPB and DPH-SPT sensors, respectively with the corresponding curve fitting equations from the regression data of Y =58.51 X+305.33 and Y= 57.24 X+284.5. The regression coefficient for showing very good linearity between measured potentials and log[DPH] were calculated. All these data along with the limit of detection (LOD), calculated according to IUPAC recommended procedures [40,41], from intersection of the two extrapolated linear portions of the calibration line and other performance measurement values for DPH-STPB and DPH-SPT sensors are given below in Table 2.

Table 1. The selectivity coefficients of sensors for different interferents

Interferent	**Selectivity coefficient, $K_{A,I}^{*}$**	
	DPH-STPB Sensor	**DPH-SPT Sensor**
NaOH	0.194	0.216
KNO_2	0.454	0.432
$NaNO_2$	0.196	0.196
$C_2O_4H_2$	0.099	0.431
Na_2CO_3	0.234	0.241
NaCl	0.174	0.204
$CaCl_2$	0.512	0.539
$ZnSO_4$	0.113	0.216
NaoAc	0.224	0.322
Glycine	0.091	0.105
Ammonium oxalate	0.060	0.111
Formic acid	0.092	0.213
Citric acid	0.123	0.334
Tartaric acid	0.231	0.322
Benzoic acid	0.103	0.199
Salicylic acid	0.124	0.146
Phthalic acid	0.087	0.123
Oxalic acid	0.132	0.189
Na_2SO_4	0.113	0.156
Boric acid	0.573	0.566
Talc	0.074	0.087

*Average of 5 determinations

3.3.2. Evaluation of sensors' precision and accuracy

For studying precision by intra-day variations, seven replicates each of 0.4, 4.0 and 8.0 mM DPH solutions were obtained by diluting 0.01 M standard solution and were put under analysis. The [DPH] and %RSD for each concentration were calculated and filled in Table 3. However, for studying inter-day deviations, the analysis of five replicates each of 0.4, 4.0 and 8.0 mM DPH were analysed in three days. The values of [DPH] found and RSD in these variations are also encapsulated in Table 3.

The calculations were also undertaken to obtain RE (relative error) values and used because as a metric to accuracy. The values of RE from inter- and intra- day analysis are also placed in

Table 3. As in Table 3, values of %RSD between 2.11 and 5.11% and %RE values from 2.00 to 5.0 have indicated the accurate and precise functioning of sensors.

Table 2. Sensors' performance features and regression data

Parameters	**DPH-STPB Sensor**	**DPH-SPT Sensor**
Linear range, M	1×10^{-6} to 8×10^{-3}	
Limit of detection (LOD), M	6.3×10^{-7}	7.14×10^{-7}
Slope (m), mV/decade	58.51	57.24
Intercept (b), mV	305.33	284.50
Correlation coefficient (R)	0.9996	0.9992
Regression coefficient (R^2)	0.9992	0.9984
Operative pH	5-8	
Life time, days	45	55

Table 3. Results of precision and accuracy

Sensor	DPH taken, mM	Intra-day variations			Inter-day variations		
		DPH found*, mM	%RSD	%RE	DPH found$, mM	%RSD	%RE
DPH - STPB	0.40	0.38	4.56	5.00	0.41	3.97	2.50
	4.00	3.86	5.11	3.50	3.81	4.11	4.75
	8.00	8.26	4.32	3.35	7.72	3.44	3.50
DPH -SPT	0.40	0.37	5.39	3.25	0.42	4.77	5.00
	4.00	4.12	3.25	3.00	3.90	4.26	2.50
	8.00	7.79	2.11	2.62	8.16	3.14	2.00

*Mean value of seven measurements; $Mean value of five measurements.

3.3.3. Robustness and ruggedness

The sensor's robustness was assessed by purposely changing the optimum operating temperature by 2 ^{O} C in the analysis of 0.4, 4.0 and 8.0 mM DPH solutions. The %RSD values for the potentials at 23, 25 and 27^{O} C were calculated and found in the range of 4.52 - 5.38 (Table 4). The DPH-STPB and DPH-SPT sensors were used for analysing DPH by three chemists. The instrumental variations were also evaluated with three different potentiometers. The values of %RSD were calculated and are included in Table 4.

The variation from both cases for both the sensors with RSD of <5% confirmed the robust and rugged behaviour.

3.3.4. Applicability of DPH-STPB and DPH-SPT sensors for DPH tablet analysis

The procedure for tablets analyses of five replicates each of 2, 4 and 6 mM tablet extracts containing DPH was followed using DPH-STPB and DPH-SPT sensors separately. The found and %recovery values for DPH with the relative standard deviation values were calculated. The mean recovery and deviation were compared with those of the official USP method [4], which describes an HPLC procedure to determine DPH in tablets, by Student-t and F- test. The analytical recovery of DPH from tablet extract obtained by proposed and official methods, RSD, experimental values of t (t_{Cal}) and F (F_{Cal}), are all presented below in Table 5. The values of t_{Cal} and F_{Cal} were less than 2.77 (t_{tab}) and 6.39 (F_{tab}), respectively, at 95% confidence level for four degrees of freedom and hence this has statistically given the inference of accurate and precise results of sensors.

Table 4. Results of robustness and ruggedness of DPH-STPB and DPH-SPT sensors (expressed in %RSD)

Sensor	Concentration of DPH, mM	%RSD values for varied parameters		
		Robustness (by varying T)	Ruggedness	
			Inter-analysts	Inter-potentiometric
DPH-STPB	0.40	4.52	3.45	3.26
	4.00	4.65	3.98	4.12
	8.00	4.59	4.11	3.77
DPH-SPT	0.40	4.67	4.87	3.76
	4.00	5.38	4.23	4.12
	8.00	5.12	4.88	4.00

Table 5. Results of analysis of DPH tablets using proposed sensors and statistical comparison with results of the official USP method

Tablets analyzed	mg of DPH/Tablet	Found*		
		%Label claim±SD		
		USP method	Proposed methods using sensor	
			DPH-STPB	DPH-SPT
Aricept	10.00	98.46±1.18	98.32±1.25 ***t*** = 0.18 ***F*** = 1.12	97.99±2.15 ***t*** = 0.44 ***F*** = 3.32

*Mean value of five determinations.

3.3.5. Recovery study

Proposed DPH-STPB and DPH-SPT sensors were used for recovery experiments. Three different levels DPH solutions of pure drug spiked into a pre-analyzed tablet extract were obtained and potentials were recorded using DPH-STPB and DPH-SPT sensors separately. Into five replicates of 8 mL tablet extract of 0.01 M DPH, 4, 8 and 12 mL 0.01 M DPH standard solution were spiked, pH adjusted to optimum value and after adding water up to 25 mL and mixing, the potentials measured. The total amounts of DPH in each case were calculated and finally the recovery values were computed. The values of DPH recovered (Table 6) were from 97.81 to 101.67 and these have highlighted the accuracy of the assay procedures using DPH-STPB and DPH-SPT sensors.

Table 6. Results of accuracy assessment in recovery study by standard-addition procedure.

Sensor	DPH from tablet extract, mM	Pure DPH added, M	Total DPH found, M	% DPH recovered*	%RSD
DPH-STPB	3.20	1.60	4.77	98.13	3.21
	3.20	3.20	6.39	99.69	2.78
	3.20	4.80	8.08	101.67	3.11
DPH-SPT	3.20	1.60	4.82	101.25	2.24
	3.20	3.20	6.33	97.81	4.11
	3.20	4.80	7.95	98.96	3.98

*Mean value of three measurements

4. CONCLUSIONS

Two simple and cost-effective sensors are devised and proposed for the very first time for potentiometric assay of donepezil hydrochloride (DPH). The methods uses two newly constructed sensors with sodium tetraphenyl boron (STPB) and sodium phosphotungstate (SPT) as ion-exchangers, β-cyclodextrin (β-CD) as ionophore and nitrophenyl octyl ether (NPOE) as plasticizer using PVC matrix for selective and rapid determination of DPH. The sensors do not produce any environment hazard and thus these methods are highly greener approaches. A simple potentiometer and simple and analyst friendly chemicals are required and these have made the approaches economic. The reported articles have described many analytical procedures for DPH but they are with the disadvantages such as need of sophisticated instruments, highly skilful operator or personnel and costly and toxic solvents. With the greener approaches, these two sensors are applicable for DPH quantification in wide linear range with Nernstian response and low detection limits. The statistical tests confirmed the accessibility of these procedures for assay of DPH in pure and in tableted forms with excellent recoveries and

closed agreement with the results of official USP method. The excipients in Aricept tablets did not showed any interference and hence the methods are of highest selectivity. Therefore, DPH-STPB and DPH-SPT sensors are applicable to use as analytical tools to determine DPH in quality control laboratories on routine basis.

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