Potentiometric Sensor for Betahistine Determination in Pharmaceuticals, Urine and Blood Serum

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A construção, a avaliação e a aplicação analítica de um novo sensor potenciométrico para a determinação de beta-histina é descrito. A atuação do eletrodo de membrana está baseada em trocas iônicas da beta-histina-tetrafenilborato como material eletroativo. Este eletrodo tem uma escala dinâmica linear entre $1.0 \times 10^{-6}$ e $1.0 \times 10^{-1} \text{ mol L}^{-1}$ de beta-histina com uma inclinação Nernstiana de $(29.74 \pm 1.47) \text{ mV} / \text{década}$ e, com um limite de detecção $5.8 \times 10^{-7} \text{ mol L}^{-1}$. A resposta potenciométrica é independente do pH da solução na escala de pH entre 4.27 a 9.02. O eletrodo é de fácil construção, baixo custo, tempo de resposta rápido (dentro de 10 s) e pode ser usado por um período de oito semanas sem mudança significativa em suas características de desempenho. O sensor proposto indicou boa seletividade sobre uma variedade de outros compostos orgânicos e inorgânicos (carboxilatos e ânions inorgânicos). É relatada a aplicação do sensor potenciométrico na determinação de beta-histina em drogas farmacêuticas, na urina, e nas amostras do soro sanguíneo com resultados satisfatórios.

The construction, evaluation and analytical application of a new potentiometric sensor for the determination of betahistine are described. The membrane electrode acts based on betahistine-tetraphenylborate ion-exchangers as electroactive material. This electrode has a linear dynamic range between $1.0 \times 10^{-6}$ and $1.0 \times 10^{-1} \text{ mol L}^{-1}$ betahistine with a Nernstian slope of $(29.74 \pm 1.47) \text{ mV} / \text{decade}$ and a detection limit of $5.8 \times 10^{-7} \text{ mol L}^{-1}$. The potentiometric response is independent of the pH of the solution in the pH range of 4.27 to 9.02. The electrode shows easy construction, low-cost, fast response time (within 10 s) and can be used for a period of eight weeks without significant change in its performance characteristics. The proposed sensor displayed good selectivities over a variety of other organic and inorganic compounds (carboxylates and inorganic anions). Application of this potentiometric sensor for the betahistine determination in pharmaceuticals, urine, and blood serum samples is reported with satisfactory results.

Keywords: betahistine determination, ion selective electrode, potentiometry, pharmaceutical and biological fluids

Introduction

Betahistine, $N$-methyl-2-(2-pyridyl)-ethylamine (Figure 1), is a histamine analogue indicated in Menière’s disease.\(^1\) Betahistine (BHT) is a histaminelike drug that acts as both a partial histamine H1 receptor agonist and as a histamine H3 receptor antagonist.\(^2\) It is generally assumed that the efficacy of BHT results from vascular effects,\(^3\) inducing an increase in cochlear blood flow as shown in the rat and the guinea pig.\(^4\) In addition, other effects on the central nervous system have been suspected by BHT because betahistine was also found to be effective in vestibular syndromes unrelated to vascular insufficiency. Few publications have been reported for the determination of BHT including calorimetry through its reaction with chloranil,\(^5\) high performance liquid chromatography (HPLC) technique.\(^6,7\) However, many of these methods are often time-consuming,\(^6\) technically demanding and require the use of costly instrumentations,\(^6\) and suffer from many interfering substances.\(^5,7\) Thus, there is an important

![Figure 1. Structure of betahistine dihydrochloride.](image-url)
demand for sensitive, low-cost, simple, and rapid method for the determination of BTH in pharmaceuticals and biological samples.

Potentiometric membrane sensors are now widely used for the direct potentiometric determination of different compounds in various samples.\textsuperscript{8–10} The polymeric membranes can easily be manufactured in different sizes and shapes and are less affected by the response of biological substrates such as protein, enzyme, antibody, etc. Thus, solvent polymeric membranes have proved to be suited for clinical analysis.\textsuperscript{11,12} Their advantages are low detection limit, adequate selectivity, high accuracy, simple design, low cost, wide concentration range and applicability to coloured and turbid solutions.\textsuperscript{13} Many membranes were made from liquid and plasticized poly(vinylchloride) (PVC) and are based on a water-insoluble ion-pair complex acting as ion-exchanger.\textsuperscript{14–17}

To the best of our knowledge, there is no report on the use of ion-selective potentiometric sensor and/or voltammetric method for the determination of BTH. In this paper, a plastic membrane-selective electrode of the conventional type has been constructed. The membrane sensor is based on incorporation of betahistine-tetraphenylborate (BTH-TPB) ion-exchanger in PVC matrix on a platinum wire (Pt-wire) electrode that is plasticized with dioctyl phtalate (DOP). The electrode is fully characterized under batch conditions and then used for the determination of BTH in pharmaceutical, urine, and blood serum samples. The proposed sensor has the advantages of versatility, fast response, simplicity, stability, and repeatability along with low limit of detection.

**Experimental**

**Reagents**

All chemicals used were of analytical reagents grade and were used without further purification. All solutions were prepared by dissolving the salts in deionized water.

Polyvinyl chloride (PVC) of high relative molecular weight, dibutyl phthalate (DBP), dioctyl phthalate (DOP), sodium tetrphenylborate (NaTPB), diocyl sebacate (DOS), tetrahydrofuran (THF), and all other chemicals were of highest purity available from Aldrich (Milwaukee, USA), and were used without further purifications, except THF, which was distilled before using. The other drugs used as interferences were purchased from Fluka and Sigma. All the solutions were prepared in doubly distilled deionized water and stored in dark to prevent photochemical oxidation of the substances.\textsuperscript{18}

Sodium hydroxide and nitric acid solutions of concentrations within the range of 0.1-1.0 mol L\textsuperscript{-1} were used for adjusting the pH of the solutions.

A stock solution of 1.0 × 10\textsuperscript{-1} mol L\textsuperscript{-1} BTH dihydrochloride was prepared by dissolving an accurate mass of BTH dihydrochloride (Sigma, St. Louis, USA) in water, kept in a dark glass bottle and then stored at 4 °C. More dilute solutions of BTH dihydrochloride were prepared by accurate dilution of the stock solution with water.

Urine and blood samples were obtained from fasting healthy people during morning hours.

**Apparatus**

Potentials were measured by direct potentiometry at 25 ± 0.1 °C with the help of ceramic junction calomel electrode as the external reference electrode and the cell set-up was as follow:

\[
\text{Hg/Hg}_2\text{Cl}_2, \text{KCl(sat)} || \text{Betahistine solution} || \text{Membrane} || \text{Pt-wire}
\]

All potentiometric measurements were made with a pHmeter, Corning, model 140 (Switzerland). All emf measurements were carried out in a 50 mL double walled glass cell with a constant magnetic stirring. Response times were determined after the potential of the solution had become constant, and similar measurements were carried out in another solution of 10 fold lower concentration. A brief scheme of the cell is shown in (Figure 2).

![Figure 2. Schematic diagram of the cell.](image)

For adjustment of the pH of the solution, a pHmeter, Corning model 140 (Switzerland), with a double junction glass electrode was used to check the pH of the solutions.

IR spectra were recorded using FT-IR (Jasco, 680 plus, Tokyo, Japan) with a resolution of 1.0 cm\textsuperscript{-1}.

Chromatographic separation was accomplished in the Shimadzu (Tokyo, Japan) with a C\textsubscript{18} column (150 × 4.6 mm and 3.0 μm as particle size).
Electrode preparation and calibration

BTH-TPB was embedded in a PVC matrix containing DOP as a plasticizer. The membrane was made by the following procedure: 29.2 mg PVC plus 67.0 mg DOP and 4.1 mg BTH-TPB were dissolved in 3 mL of THF with shaking the mixture for 20 min. The coating process of the platinum-wire electrode was performed by dipping 1.5 cm of a Pt-wire, 20 times into the solution mixture. After each coating, the membrane was dried with a stream of air still a thin film was formed. Then, the electrode was immersed into BTH solution with concentration range from 1.0 \times 10^{-1} to 1.0 \times 10^{-7} \text{ mol L}^{-1}. Then, the potential of the membrane electrode was recorded vs. saturated calomel electrode after stabilization of the cell potential to ± 0.1 mV and at 25 ± 1 °C. The cell potentials, $E_{\text{cell}}$, were recorded and plotted vs. $-\log[\text{BTH}]$. The resulting graphs were used for subsequent determination of unknown BTH concentration.

Determination of BTH in human blood serum, urine and pharmaceutical samples

For analysis of tablets, a group of five tablets was individually weighted, finely powdered and mixed. A portion of the powder (500 mg) was accurately weighed and transferred into a 50 mL volumetric flask containing 25 mL of H₂O. After being continuously shaken for 30 min, the flask was made up to volume with H₂O, and the solid was left to decant for 30 min; then, 1.0 mL aliquot was diluted to 25 mL with H₂O in a 25 mL volumetric flask.

Drug-free human serum and urine, used in this study, was obtained from healthy volunteers. Urine and blood plasma were also obtained from non-healthy volunteers. Urine samples were stored in a refrigerator immediately after collection. The urine and plasma samples were analyzed before 3 h of their sampling, except stated. The urine and/or blood samples were taken from humans and were used for measurements after its centrifuged (3,000 rpm, 10 min at 25 °C) and diluted two-time with water without any further pretreatment. In addition, the diluted samples were spiked with stock solution of BTH to get the final concentrations of BTH (between 1.0 \times 10^{-5} and 1.0 \times 10^{-1} \text{ mol L}^{-1}) in the diluted sample. The samples were spiked just before analysis.

High performance liquid chromatography (HPLC) was used for real sample analysis. The analyte (BTH) was separated with a C₁₈ column (250 mm x 4.6 mm i.d., 5 μm particle diameter). The mobile phase was programmed to deliver 30% acetonitrile and 70% sodium acetate (0.02 mol L⁻¹, pH 4.5) with a flow rate of 1.0 mL min⁻¹, for 1 min and linear gradient elution from 1 to 21 min to end with 70% acetonitrile and 30% sodium acetate solution. The UV detector was set at 254 nm.

Results and Discussion

Electrode characteristics

BTH has two –NH functional groups that can make ion association with tetraphenyl borate (TPB) to produce a white solid. The IR spectrum of BTH showed one C=NH⁺ band at 2426 cm⁻¹, an –NH⁺ band based on pyridine ring at 3435 cm⁻¹ and an –NH₂⁺ band at 2769 cm⁻¹, whereas for the ion-pair, those bands became C=N and N–H that showed at 1601 cm⁻¹ and 3416 cm⁻¹. This means that BTH has a strong interaction with TPB. Moreover, Job’s method was used to prove the stoichiometry of the association of the species (BTH-TPB). The concentrations of BTH and TPB were taken to be constant (2.0 \times 10^{-3} \text{ mol L}^{-1}). Seven aqueous solutions were prepared containing BTH and TPB at various molar ratios so that the final volume always reached 10 mL. Then, the extraction was performed using 10 mL of chloroform, and the absorbance was measured at 249 nm. The plot reached a maximum value at a mole fraction of $X_{\text{BTH}} = 0.70$, which indicates the formation of 1:2 complex between BTH and TPB. The observations confirm special interactions between BTH and TPB.

We have checked the PVC membrane response with and without the carrier to different BTH concentrations. The results showed that the membrane with no carrier displayed insignificant selectivity toward BTH and their response was not reliable. However, in the presence of the ion-pair (BTH-TPB), the optimized membrane demonstrated the Nernstian response and remarkable selectivity for BTH over several compounds. The selectivity of the membrane to BTH is due to the fact that insufficient interaction occurs among the other substances with BTH-TPB.

Proper equilibration of membranes is essential to have a sensor showing good response characteristics. The ratio of various membrane ingredients such as amount of the ionophore, nature of the solvent mediator (plasticizer), amount of plasticizer to PVC ratio, and especially the nature of the additives, time of contact and the concentration of equilibrating solution were optimized, so that the membranes develop reproducible, stable and noiseless potentials. Membrane to membrane and batch to batch reproducibility was assured carefully following the optimum conditions of fabrication.

Several membrane compositions were investigated by varying the ratio of PVC, plasticizer, and the ionophore. The potentiometric response of the membrane was greatly improved in the presence of the ionophore. In
general, the sensitivity and selectivity of an ion-selective electrode is strongly influenced by the nature and amount of the plasticizer. The effect of the plasticizer on the characteristics of BTH-selective electrode was investigated by using three kinds of plasticizers including DOP, DBP and DOS. The electrodes plasticized with DOP exhibited the better response sensitivity than that with DOS or DBP. The potential responses of the ion-selective electrodes to BTH are shown in Table 1. It is also known that the nature and amount of lipophilic additive strongly influence the response of the BTH selective electrode. The results showed that the presence of lipophilic anion in cation-selective membrane electrodes diminished the ohmic resistance, enhanced the response behavior selectivity, and also increased the sensitivity of the electrode. As shown in Table 1, nine membrane compositions were prepared by varying the percentage of the ion-exchangers (BTH-TPB) while the percentage of the PVC and the plasticizer also were changed. The final results showed that 28.94 wt.% PVC, 67.00 wt.% DOP, and 4.06 wt.% BTH-TPB (No. 7, Table 1) result in the best sensitivity with a Nernstian slope of 29.74 ± 1.47 mV decade⁻¹ over a relatively wide concentration range of BTH (1.0 × 10⁻⁶ to 1.0 × 10⁻¹ mol L⁻¹).

**Influence of pH**

The dependence of the potentials of the proposed electrode to different pH was investigated by measuring the sensor potential in a 1.0 × 10⁻³ mol L⁻¹ BHT solution over a pH range of 2.0-11.0. The solution pH was adjusted with dilute HNO₃ and NaOH solutions. As it is obvious from Figure 3 the response of the electrode is independent of pH in the range of about 4.3-9.0, which can be taken as the working pH range of the electrode. A significant change in the potential response was observed when the pH was above 9.8. With more acidic conditions, BTH may be protonated, then deactivated. On the other hand, in basic solution, hydroxide ions may react with BHT to produce neutral species, which could not extract into the membrane.

**Response and lifetime**

Response time is an important factor for any ion-selective electrode. Thus, in the case of all electrodes, the average response time required for the electrodes to reach a potential response within ± 1 mV of final equilibrium values after successive immersing of sensor into a series of solutions each having a 10 fold difference in their concentration, was obtained. The resulting potential-time for the coated wire electrode obtained upon changing the BTH concentration from 1.0 × 10⁻¹ to 8.0 × 10⁻⁶ mol L⁻¹ is shown in Figure 4. The response time of the electrode to reach the final equilibrium value was different in different BTH concentrations. The response time of the sensor was found to be less than 10 s at various BTH concentrations.

<table>
<thead>
<tr>
<th>No.</th>
<th>Composition (%)</th>
<th>Slope (mV decade⁻¹)</th>
<th>Dynamic range (mol L⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.24</td>
<td>6.99</td>
<td>DOP 61.76</td>
</tr>
<tr>
<td>2</td>
<td>31.19</td>
<td>7.31</td>
<td>DBP 61.59</td>
</tr>
<tr>
<td>3</td>
<td>31.33</td>
<td>6.36</td>
<td>DOS, 62.31</td>
</tr>
<tr>
<td>4</td>
<td>31.61</td>
<td>5.88</td>
<td>DOP, 56.80</td>
</tr>
<tr>
<td>5</td>
<td>29.25</td>
<td>5.60</td>
<td>DOP, 60.77</td>
</tr>
<tr>
<td>6</td>
<td>31.37</td>
<td>6.5</td>
<td>DOP, 62.13</td>
</tr>
<tr>
<td>7</td>
<td>28.94</td>
<td>4.06</td>
<td>DOP, 67.00</td>
</tr>
<tr>
<td>8</td>
<td>37.56</td>
<td>6.29</td>
<td>DOP, 56.15</td>
</tr>
<tr>
<td>9</td>
<td>62.46</td>
<td>5.78</td>
<td>DOP, 31.75</td>
</tr>
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</table>
and found to remain stable for several days without much drift in the potentials.

**Nernstian slope**

The plot of the potential difference between the ion selective electrode and calomel reference electrode vs. the logarithm of the BTH concentration is shown in Figure 5. This figure shows that electrode No. 7 gives a linear Nernstian response in the BTH concentration range of $1.0 \times 10^{-6}$ to $1.0 \times 10^{-1}$ mol L$^{-1}$ with a slope of $29.74 \pm 1.47$ mV decade$^{-1}$.

The limit of detection (LOD), defined as the concentration of BTH obtained when the two linear regions of the calibration graph are extrapolated to the baseline potentials, $5.8 \times 10^{-7}$ mol L$^{-1}$ was obtained. The limit of quantitation (LOQ) was equal to $8.1 \times 10^{-7}$ mol L$^{-1}$ BTH.

ANOVA test method used to show the reproducibility and repeatability of the sensor for the slope of BTH calibration curve for BTH concentrations of $1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ mol L$^{-1}$ on three different days. The results are given in Table 2. The results showed that $F_{\text{cal}(a,2,b)}$ between-treatment ($= 0.378$) was less than $F_{\text{tab}(a,2,b)}$ ($= 6.944$, $P = 0.05$), meaning that there was no significant difference between the sensor response signals during measurements, comparing the between-block and residual mean squares gives $F_{\text{cal}(a,2,b)} = 0.142$. The critical value of F being 6.944 ($P = 0.05$), no significant difference exists among different days, and confirmed the stability and reproducibility of the sensor. The repeatability of the sensor was investigated by preparing ten similar electrodes with the optimum membrane composition and then the slopes of each electrode were determined over $1.0 \times 10^{-1}$ and $1.0 \times 10^{-4}$ mol L$^{-1}$ BTH concentration. An average slope of $29.74 \pm 1.42$ mV decade$^{-1}$ was achieved.

**Figure 4.** Response time of the electrode: (A) $1.0 \times 10^{-1}$ mol L$^{-1}$; (B) $1.0 \times 10^{-2}$ mol L$^{-1}$; (C) $1.0 \times 10^{-3}$ mol L$^{-1}$; (D) $1.0 \times 10^{-4}$ mol L$^{-1}$; (E) $1.0 \times 10^{-5}$ mol L$^{-1}$; (F) $9.0 \times 10^{-6}$ mol L$^{-1}$ and (G) $8.0 \times 10^{-6}$ mol L$^{-1}$ BHT.

**Figure 5.** Potentiometric response of the electrode with the optimum conditions.

**Table 2.** ANOVA test method for the measuring of the repeatability and reproducibility of the slope for sensor

<table>
<thead>
<tr>
<th></th>
<th>day 1</th>
<th>day 2</th>
<th>day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrode 1</td>
<td>31.72</td>
<td>26.83</td>
<td>26.81</td>
</tr>
<tr>
<td>Electrode 2</td>
<td>26.00</td>
<td>29.20</td>
<td>27.80</td>
</tr>
<tr>
<td>Electrode 3</td>
<td>27.42</td>
<td>26.50</td>
<td>29.64</td>
</tr>
<tr>
<td>RSD %</td>
<td>10.50</td>
<td>5.65</td>
<td>5.11</td>
</tr>
<tr>
<td>Repeatability of preparation sensors on any day (%)</td>
<td>89.5</td>
<td>94.4</td>
<td>94.9</td>
</tr>
<tr>
<td>Reproducibility of preparation sensors on any day (%)</td>
<td>92.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-treatment mean square</td>
<td>0.378</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-block mean square</td>
<td>0.741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F_{\text{cal}(a,2,b)}$ treatment</td>
<td>0.072</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F_{\text{cal}(a,2,b)}$ block</td>
<td>0.142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F_{\text{tab}(a,2,b)}$</td>
<td>6.944</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The electrode was used over a period of 8 weeks without any significant effect on the membrane potential when used for analysis of BTH in urine samples. The lifetime of the electrode was determined by reading the potential values of the calibration solutions and plotting the calibration curves for the 10 weeks period (Figure 6), when used for analysis of BTH in urine samples 5 times per day. The slope of the electrode (29.74 mV per decade change) was observed to show a gradual decrease after 56 days. We can therefore, concluded that the lifetime of the proposed electrode is at least 8 weeks. After this period, the slight change in the slope was observed. The lifetime of ion selective electrodes mainly depends on the type of ionophores and plasticizers used, and also on the number of times it is used. After 10 weeks, the electrode response deteriorated which may be attributed to the aging of the PVC matrices, ionophore as well as plasticizer.
Sensor selectivity

The effect of interfering substances on the response behavior of a selective membrane electrode is usually described in terms of selectivity coefficients, $K_{i,j}$. In this work, the selectivity coefficients for BTH with respect to a variety of interfering substances were determined by separation solution method (SSM)\textsuperscript{22} with a fixed concentration of interference compounds at $1.0 \times 10^{-4}$ mol L$^{-1}$ BTH. Then, the selectivity coefficients were evaluated. The resulting selectivity coefficients for BTH are summarized in Table 3. From the results given in Table 3, it is obvious the proposed electrode is highly selective with respect to a variety of other substances.

Analytical applications

It can be seen that the amount of BTH can be accurately determined using the proposed sensor. To assess the applicability of the proposed sensor to real samples, an attempt was made to determine BTH in urine, plasma and pharmaceutical samples. The results were also compared by HPLC method.\textsuperscript{23} Each sample was analyzed in triplicate by standard addition method, using the sensor. The changes in the potential were recorded for each increment and used to calculate the concentration of BTH in the sample solutions using the following equation:

$$C_x = C_s \frac{V_s(V_s + V_x)}{(V_s + V_x)^2} \left[ 10^{\frac{\Delta E}{S}} - \frac{V_x(V_s + V_x)}{(V_s + V_x)^2} \right]^{-1}$$

where $V_x$ and $C_x$ are the volume and concentration of the unknown sample, respectively. $C_s$ and $V_s$ are the concentration and volume of the standard solution, respectively, $\Delta E$ is the change in potential due to the addition of the standard solution, and $S$ is the slope of the

**Table 3.** Potentiometric selectivity coefficient of various potential interfering substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>logK</th>
<th>Substance</th>
<th>logK</th>
<th>Substance</th>
<th>logK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co$^{2+}$</td>
<td>$-2.70$</td>
<td>Zn$^{2+}$</td>
<td>$-2.80$</td>
<td>Fructose</td>
<td>$-5.84$</td>
</tr>
<tr>
<td>NO$_3^-$</td>
<td>$-9.91$</td>
<td>Mn$^{2+}$</td>
<td>$-1.28$</td>
<td>Diphenhydramine</td>
<td>$-1.17$</td>
</tr>
<tr>
<td>Cr$^{3+}$</td>
<td>$-2.28$</td>
<td>CO$_3^{2-}$</td>
<td>$-6.59$</td>
<td>Captopril</td>
<td>$-4.52$</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>$-4.60$</td>
<td>Cl$^-$</td>
<td>$-6.91$</td>
<td>Isoproterenol</td>
<td>$-4.21$</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>$-4.32$</td>
<td>IO$_3^-$</td>
<td>$-9.57$</td>
<td>Desipramine</td>
<td>$-1.10$</td>
</tr>
<tr>
<td>Ni$^{2+}$</td>
<td>$-2.97$</td>
<td>K$^+$</td>
<td>$-2.08$</td>
<td>Uric acid</td>
<td>$-5.56$</td>
</tr>
<tr>
<td>Cd$^{2+}$</td>
<td>$-2.89$</td>
<td>NH$_4^+$</td>
<td>$-2.68$</td>
<td>Ciprofloxacin</td>
<td>$-1.93$</td>
</tr>
<tr>
<td>Fe$^{3+}$</td>
<td>$-3.07$</td>
<td>Glucose</td>
<td>$-5.70$</td>
<td>Sulfurhodamine G</td>
<td>$-6.48$</td>
</tr>
<tr>
<td>Na$^+$</td>
<td>$-2.42$</td>
<td>Sucrose</td>
<td>$-5.81$</td>
<td></td>
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</tr>
</tbody>
</table>
The sensor was also successfully applied as an indicator electrode in the potentiometric titration of BTH solution with NaTPB. Typical results for the titration of a 25 mL of $1.0 \times 10^{-3}$ mol L$^{-1}$ BTH solution with $1.0 \times 10^{-2}$ mol L$^{-1}$ NaTPB is shown in Figure 8 with a very high recovery and precision.

![Figure 8](image-url)
good inflection point, showing perfect stoichiometry that is observed in the titration plot. Before the titration end point, the measured potential shows a usual logarithmic change with amount of the titrant added, while the potential response after the end point was almost constant, due to the low concentration of free BTH ions in the solution.

Conclusion

BTH-TPB ion-exchangers as electroactive material are successfully exploited to use as a neutral carrier in PVC membrane as a coated wire. The new potentiometric sensor revealed Nernstian response over a wide concentration range for BTH. Meanwhile, it also has some other advantages, such as wide dynamic range, fine selectivity and long lifetime. These characteristics make us believe that this electrode will be used widely. The electrode is very easy to prepare and use. Its LOD for BTH is low \( 5.8 \times 10^{-7} \text{ mol L}^{-1} \). The comparison between the proposed ionophores in ion-selective electrode indicated that the presented electrode is remarkably superior in terms of the detection limit, especially the selectivity over other substances. These characteristics and the typical applications presented in this paper make the sensor suitable for measuring BTH content in pharmaceutical and biological fluids samples without any significant interaction from concomitant substances. The proposed membrane sensor work well under laboratory conditions.

Acknowledgements

The authors express their appreciation to the Isfahan University of Technology Research Councils and Center of Excellence in Sensors and Green Chemistry for financial support of this work.

References