Ion Selective Electrodes for Potentiometric Determination of Baclofen in Pharmaceutical Preparations

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Abstract - Two different sets of baclofen sensors were developed for its potentiometric determination in pharmaceutical preparations, based on the fact that baclofen behaves as cation in acidic medium and anion in basic medium ($pK_1$=9.62 and $pK_2$=3.87; respectively). Six baclofen-selective electrodes were investigated using precipitation based technique with either sodium tetraphenyl borate as an anionic exchanger or 1,10-ortho-phenanthroline-ferrous as a cationic exchanger; respectively upon using polyvinyl chloride (PVC) matrix and dioctylsebacate (DOS) as a plasticizer. The resultant sensors have different forms, either as membrane electrodes (sensors I&IV), coated wire electrodes (sensors II&V) or as microsized graphite electrodes (sensors III&VI). Linear responses of $10^{-6}$–$10^{-2}$ M with slopes of 43.05, 43.11, and 43.05 mV/decade within pH range 4-6 were obtained for sensors I, II and III. On the other hand, Linear responses of $10^{-7}$–$10^{-3}$ M with slopes of 55.90, 57.13 and 57.37 mV/decade within pH 6-8 range were obtained for sensors IV, V and VI; respectively. All these sensors were prepared and fully characterized in terms of composition, life span, usable pH range, response time and temperature. The sensors show good selectivity to the drug in presence of a variety of inorganic and organic interferent substances. The proposed procedures were compared to the USP pharmacopoeial method and showed no significant difference. The proposed sensors displayed useful analytical characteristics for the potentiometric determination of baclofen in pure form and in pharmaceutical preparations.

Keywords - Baclofen, Selective Electrodes, Sodium Tetraphenyl Borate, 1,10-ortho-Phenanthroline-Ferrous and Polyvinyl Chloride (PVC)
1. INTRODUCTION

Baclofen (Fig. 1), (4-amino-3 (P-chlorophenyl) butyric acid) is a skeletal muscle relaxant drug widely used in the treatment of spasticity and musculoskeletal disorders [1]. The drug depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the GABA–receptors which in turn inhibit the release of excitatory amino acid glutamate and aspartate [2].

![Structural formula of baclofen](image)

Fig. 1. Structural formula of baclofen

It is effective in the treatment of neuralgias, central pain following spinal lesions or painful strokes, migraine and chronic daily headache. The USP XXII (2005) adopts a colorimetric method for the determination of baclofen in baclofen tablets [3]. Several methods have been reported for the quantitative determination of baclofen including spectrophotometry [4-7], spectrofluorimetry[8-9], thin layer chromatography [10], gas chromatography [11-12], high pressure liquid chromatography [13-25], capillary electrophoresis [26-30], potentiometry [31,32] and polarographic [33] methods. Modern ion selective electrodes (ISEs) based on material transport across a specific membrane are now widely used in the determination of trace amounts of analytes as well as drugs in pure form and pharmaceutical dosage forms [34]. The material transport includes either neutral and charged complex species, or simple ions [35,36]. The high selectivity of these electrodes imparts a great advantage over other techniques [37].

Analytes in colored, turbid or viscous samples can be determined accurately over a wide concentration range. ISEs are generally tolerant of small pH changes. They show rapid responses to changes in the concentration. Furthermore, the electrodes exhibit good selectivity for baclofen with respect to a large number of inorganic and/or organic anions or cations, sugars and amino acids. Further advantages are that they are relatively cheap and simple to develop, setup and run and devoid of the use of organic solvents or excessive chemicals i.e. green chemistry. Moreover, the chemical designs of the electrodes have been developed to give superior selectivity and response [38]. In the present work, six different sensors were constructed and studied,
depending on the anionic and cationic properties of baclofen which allow the usage of precipitation-based technique with either 1,10-orthophenanthroline-ferrous complex or with sodium tetrphenyl borate ion association complex.

2. EXPERIMENTAL

2.1. Instrument

- Jenway digital ion analyser model 3330 (UK) with Ag/AgCl double junction reference electrode no 924017-LO-Q11C containing 10% (W/V) KNO₃ solution in the outer compartment.
- Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian).
- PH glass electrode Jenway (UK), No. 924005-BO3-Q11C.
- Thermostatic shaker Schutzart DIN 40050-IP 20, 1 Nenn temp: 100 °C, Type: WB 14.
Elemental analysis was carried out in Micro Analytical Center, Faculty of Science, and Cairo University.

2.2. Reagent and Materials

2.2.1. Reference samples

Baclofen reference sample, kindly provided by the Misr Co. for pharmaceutical industry, Cairo, Egypt. Its purity was found to be 99.85±0.28 according to the the USP XXII method [3].

2.2.2. Pharmaceutical preparations

Baclofen® (10 and 25 mg) tablets: batch numbers: 114122 and 125092 manufactured by Misr Co. for pharmaceutical industry, for Al Delta pharmaceutical trading Co. Each tablet was labeled to contain 10 and 25 mg; respectively of baclofen.

2.2.3. Reagents

All reagents and solvents used were of analytical reagent grade. Water used was bi-distilled.
- Stock standard solution of baclofen (1.0×10⁻², M.wt. 213.67) was prepared in 0.1 N HCl.
- Baclofen standard solutions (1.0×10⁻² M-1.0×10⁻⁷ M) were freshly prepared by serial dilution of a 1.0×10⁻² M stock standard solution using 0.1 N HCl.
- 1,10-ortho-phenanthroline, Sigma, GmbH, Germany
- Ferrous ammonium sulphate, Prolabo
- Sodium tetrphenyl borate, Aldrich
- Graphite rod
- Dibutyl phthalate (DBP), Sigma
- Dioctyl phthalate (DOP), Aldrich
- Dioctyl sebacate (DOS), Aldrich
- Tricresyl phosphate (TCP), Aldrich
Poly (vinyl chloride) (PVC) of high molecular weight, Fluka Chemie GmbH, Germany
-Sodium hydroxide, 0.1 M aqueous solution, Prolabo
-Hydrochloric acid, 0.1 M aqueous solution, Prolabo
-Ammonia solution, 30% aqueous solution, Prolabo
-Potassium chloride, 1×10⁻² M aqueous solution, Prolabo
-1,10-orthophenanthroline–iron(II) complex, prepared by dissolving 100 mg of orthophenanthroline in 25 ml of 10⁻² M iron(II) ammonium sulphate.

2.3. Procedures

2.3.1. Precipitation-based technique for preparation of the proposed sensors Fabrication of PVC based membrane electrodes (sensors I&IV)

In two different beakers, five ml aliquot of 10⁻² M aqueous standard baclofen solution was treated separately with 5 ml of aqueous 1.0×10⁻² M NaTPB and 5 ml 1.0×10⁻² M orthophenanthroline–ferrous solution (mixed with 1 ml of 30% ammonia solution); respectively. The mixture was shaken well for 5 minutes. The precipitates formed were filtered using Whitman no.42 filter paper, washed with cold water, dried at room temperature (≈25°C) and ground to fine powder. In two separate glass petri dishes (5 cm diameter), 10 mg of baclofen ion exchangers were separately mixed with 0.35 ml of DOS and 0.19 g PVC. The mixtures were dissolved in 5 ml THF. The petri dishes were covered by a filter papers and left to stand for 24 h to allow solvent evaporation at room temperature. Master membranes of 0.1 mm thickness were obtained. From the formed master membranes, disks (≈10 mm diameter) were cut using a cork borer and pasted using THF to interchangeable PVC tips that were clipped into the end of the electrodes glass bodies. Equal volumes of 10⁻² M baclofen and 10⁻² M KCl were mixed and this solution was used as an internal reference solution. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrodes were preconditioned by immersing in 10⁻² M baclofen solution for 24 h. The electrochemical cell for potential measurements was: Ag/AgCl (internal reference electrode)/ 1.0×10⁻² M baclofen solution, 1.0×10⁻² M KCl (internal reference solution)/PVC membrane/test solution (pH 6-8)&(pH 4-6)//Ag/AgCl double junction reference electrode. The membrane sensors were calibrated by immersion in 1.0×10⁻²-1×10⁻⁷ M baclofen solution and allowed to equilibrate with constant stirring in conjunction with a reference electrode. The sensors were stored in bi-distilled deionized water between measurements. The electrodes potential were recorded as a function of baclofen concentration. The calibration plots obtained were used for subsequent measurements of unknown baclofen concentrations.
2.3.2. Fabrication of PVC based coated wire electrode (sensors II&V)

The previously prepared (baclofen–ionexchangers, DOS, PVC and THF) mixtures were left at room temperature to allow solvent evaporation to obtain colloidal solutions. The covers of two insulated platinum wires (12 cm length, 1 mm diameter) were removed for a length of about one cm at both ends. Two electrodes were prepared by applying layers of the pervious mixtures onto a platinum wires tip at 10 minutes interval until a globular membrane of about 3 mm diameter around the wire ends were formed. The electrodes were left standing at room temperature for 24 h to dry. The resultant dry coated wires membrane sensors had to be conditioned by soaking in $1.0 \times 10^{-2}$ M drug solution for 3 h and stored in the same solution when not in use. The electrochemical cell for potential measurements was: Platinum wire//PVC membrane//test solution (pH 6-8&pH 4-6)// Ag/AgCl double junction reference electrodes.

The potential readings of stirred $1.0 \times 10^{-2}$ - $1.0 \times 10^{-7}$ M baclofen solutions were measured at $25 \pm 1$ °C and recorded after stabilization to ±0.2 mV. A calibration graphs were constructed and used for subsequent measurements of unknown baclofen test solutions.

Preconditioning was done by immersing these sensors in $10^{-2}$ M baclofen solution for 2 h. Prior to use, the electrodes were washed with distilled water.

2.3.3. Fabrication of PVC based microsized graphite sensors (sensors III&VI)

Two separate graphite rods (5 mm in diameter and 15 mm long) were inserted in different polyethylene tubes, such that its tips were exposed (5 mm diameter & 0.3 mm length) from the other end of the protruded rods served as a measuring surface. This end of the rods were washed with acetone, dried in air for 3 h, and dipped rapidly into the previously prepared master thick PVC colloidal solution prepared before. The solvent was allowed to evaporate in air after each dipping, and the dipping process was repeated 4-6 times to produce a uniform membrane on the surface of the graphite rod. Drops of mercury were added in the polyethylene tubes to ensure electrical contact with the connection cables. The coated graphite rods were conditioned by soaking in a $10^{-2}$ M baclofen solution for 2 h, the sensors stored in the same solution when not in use. The electrochemical cell for potential measurements was: Metallic mercury//graphite rod//PVC membrane//test solution (pH 6-8 & pH 4-6) Ag/AgCl double junction reference electrodes.

2.4. Determination of baclofen in its pure powdered sample

The prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode were immersed in 50 ml aliquots of solutions of baclofen covering the concentration range of ($1 \times 10^{-7}$ - $1 \times 10^{-2}$ M) into a series of 100 ml beakers, followed by careful adjustment of pH by either 0.1 M NaOH or 0.1 M HCl to the required pH. They were allowed to equilibrate while stirring using a magnetic stirrer and the emfs were recorded within
±1 mV. The membrane sensors were washed with bi-distilled water between measurements. Calibration graphs were plotted relating the recorded potentials vs. –log drug concentrations. These calibration graphs or the computed regression equations were used for subsequent measurements of unknown concentrations of baclofen.

2.5. Potentiometric determination of baclofen in its pharmaceutical formulations

Twenty tablets of baclofen were finely powdered, mixed and weighed; the average weight of a tablet was calculated. A quantity of powder equivalent to 106.8 mg of baclofen was transferred to 50 ml volumetric flask and dissolved in 0.1 N HCl using 20 ml 0.1 N HCl. The flask was stirred for 15 min, and the volume was then completed to the mark with 0.1 N HCl. The solution was filtered and a suitable volume was transferred into a 100 ml volumetric flask and diluted to volume with 0.1 N HCl to prepare 1×10⁻³ M aqueous solution of baclofen. Suitable dilutions were performed using 0.1 N HCl to obtain serial of 10⁻⁵ to 10⁻⁴ M baclofen.

Procedure was then completed as under pure powdered sample.

3. RESULTS AND DISCUSSION

The present study originates from the fact that baclofen behaves both as cation in acid medium or as anion in basic medium, it has two dissociation constants (pKₐ₂=9.62 due to -NH₂ group) and (pKₐ₁=3.87 due to -COOH group) [39]. This fact suggests the use of ion exchangers of both the anionic and cationic types namely tetraphenyl borate in acid medium and ortho-phenanthroline – ferrous solution in alkaline medium respectively. It was found that the two ionic exchangers have low solubility product and suitable grain size. Baclofen was found to form 1:1 and 2:1 ion association complex with sodium tetraphenyl borate and ortho-phenanthroline-ferrous, respectively as proven by elemental analysis (as monovalent cation & anion) and the obtained Nernstian slopes.

The electrochemical performance characteristics of the investigated baclofen – selective sensors were evaluated according to the IUPAC recommendation data [40,41] and summarized in Table 1. It has been reported that PVC matrix is a regular support and reproducible trap for ion association complexes in ISEs. Nevertheless, its use creates a need for plasticization and places a constraint on the choice of mediator [42].

In the present study, dioctyl sebacate (DOS) has been used in the fabrication of sensor I and other proposed sensors, respectively. It plasticized the membrane and adjusted both permittivity of the final organic membranes and mobility of the ion exchanger sites. The membranes constituents were dissolved in THF that was slowly evaporated at room temperature leading to membrane formation.
Table 1. Response characteristics for baclofen by the proposed sensors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensor I</th>
<th>Sensor II</th>
<th>Sensor III</th>
<th>Sensor IV</th>
<th>Sensor V</th>
<th>Sensor VI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Validation of the regression equations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Slope (mV per decade)</strong></td>
<td>43.05</td>
<td>43.11</td>
<td>43.05</td>
<td>55.90</td>
<td>57.13</td>
<td>57.37</td>
</tr>
<tr>
<td><strong>Intercept (mV)</strong></td>
<td>198.70</td>
<td>209.88</td>
<td>204.92</td>
<td>193.10</td>
<td>190.09</td>
<td>201.29</td>
</tr>
<tr>
<td><strong>Correlation coefficient (r)</strong></td>
<td>0.9997</td>
<td>0.9999</td>
<td>0.9997</td>
<td>0.9999</td>
<td>0.9999</td>
<td>0.9999</td>
</tr>
</tbody>
</table>

| **Validation of the responses**                       |          |           |            |           |          |           |
| **Response time (Sec.)**                              | 60       | 60        | 60         | 60        | 60       | 60        |
| **Working pH range**                                  | 4-6      | 4-6       | 4-6        | 6-8       | 6-8      | 6-8       |
| **Conc. range (M)**                                   | 1×10^{-2}-1×10^{-1} | 1×10^{-2}-1×10^{-1} | 1×10^{-2}-1×10^{-1} | 1×10^{-3}-1×10^{-2} | 1×10^{-3}-1×10^{-2} | 1×10^{-3}-1×10^{-2} |
| **LOD (M)**                                          | 5.50×10^{-7} | 2.5×10^{-7} | 3.50×10^{-7} | 5.00×10^{-8} | 2.50×10^{-8} | 3.50×10^{-8} |
| **Life time (weeks)**                                 | 5        | 5         | 5          | 5         | 5        | 5         |
| **Average recovery(%)**                               | 99.30    | 97.75     | 98.55      | 99.05     | 97.50    | 98.20     |
| **R.S.D**                                            | 0.9      | 0.9       | 0.8        | 0.8       | 0.9      | 0.9       |

| **Precision**                                         |          |           |            |           |          |           |
| **Repeatability %**                                   | 100.11±0.60 | 98.56±0.34 | 99.80±0.41 | 98.95±0.22 | 98.94±0.50 | 99.31±0.19 |
| **Intermediate precision %**                          | 98.35±0.67 | 100.20±0.49 | 100.00±0.29 | 98.29±0.73 | 99.27±0.49 | 100.10±0.55 |

*a* Limit of Detection (LOD) defined as drug concentration obtained at the intersection of the extrapolated high concentration (linear segment) with the low concentration (zero slope segment) of the calibration plot

*b* Results of five determinations

\[ C_n = 3\times(1\times10^{-3}, 1\times10^{-4}, 1\times10^{-5} \text{M}) \]

\[ \text{dn}=3\times(1\times10^{-3},1\times10^{-4},1\times10^{-5}\text{M}) \]

The influence of pH on the potential response of these electrodes was studied using concentrations 10^{-4} and 10^{-5} M for the proposed six sensors over the pH range 4-10. The potential–pH profile shows that for electrodes I, II&III the responses were constant over the pH range 4-6. Above pH 6, the potential showed a sharp decrease due to the formation of non-protonated primary amino group of baclofen. Below pH 4, the electrode response increased with the increase of analyte acidity; the membrane may extract H⁺ [43], leading to noisy responses, while, for electrodes IV, V&VI the responses are constant over the pH range 6–8. In this pH range baclofen is completely ionized, dissociated and sensed. Above pH 8 variable electrode responses was observed, this may be explained by a variable increase of dissociation of the formed ion association complex. While below pH 6, the electrode response decreased with the increase of analyte acidity; at such high acidity the dissociation of the carboxyl group of the drug in solution are limited, also the membrane may extract H⁺ [43], Fig. 2A&2B.
Fig. 2. (A). Effect of pH on the response of the baclofen-TPB sensors upon using $10^{-4}$ M and $10^{-5}$ M drug (SI, SII, SIII) (B). Effect of pH on the response of the baclofen-1, 10-phenanthroline ferrous sensors upon using $10^{-4}$ M and $10^{-5}$ M drug (SIV, SV, SVI)

The suggested electrodes exhibit slight increase in their potentials as the temperature rises in the range of 25–45 °C; however, the calibration graphs obtained at different temperatures were parallel. The limit of detection, slope and response time did not significantly vary with variation of temperature, indicating reasonable thermal stability up to 35 °C.

The effect of interfering substances upon the performance of these sensors was studied by separate solution method using the following equation [44]:
\[
-\log (K_{\text{pot,primaryion,interferent}}) = \frac{(E_B - E_A)}{(2.303RT/Z_\text{AF})} + [1 - Z_A/Z_B] \log[A]
\]

Where \( E_A \) is the potential measured in 10\(^{-4} \) M baclofen solution, \( E_B \) is the potential measured in 10\(^{-4} \) M interferent solution, \( Z_A \) and \( Z_B \) are the charges of the drug and interferent, respectively, and 2.303RT/Z_\text{AF} represents the slope of the calibration plot (mV/concentration decade).

Table 2 shows the selectivity of the proposed sensors in the presence of the related substances that always present with the drug dosage formulations.

Typical calibration plots of the six sensors were shown in (Fig. 3) which declare linear responses of baclofen over the concentration ranges of 1.0×10\(^{-2}\)-1.0×10\(^{-6}\) and 1.0×10\(^{-3}\)-1.0×10\(^{-7}\) M for tetraphenyl borate and ortho-phenanthroline-ferrous sensors, respectively. The reliability of the proposed sensors for quantification of baclofen was assessed by determining 10\(^{-2}\)-10\(^{-7}\) M of the pure powder of the drug on the investigated sensors using both the calibration graph and the computed regression equation. The good agreement between the results obtained for the determination of the tablets by both the proposed potentiometric procedures and the pharmacopeial method [3], suggests the successful application of the proposed method for the pharmaceutical formulation.

Table 2. Potentiometric selectivity coefficients (−\( \log K_{\text{pot,Baclofen,interferent}} \)) of the six proposed sensors by separate selectivity method (SSM)[44].

<table>
<thead>
<tr>
<th>Interferent(^a)</th>
<th>Sensor I</th>
<th>Sensor II</th>
<th>Sensor III</th>
<th>Sensor IV</th>
<th>Sensor V</th>
<th>Sensor VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>1.2×10(^3)</td>
<td>1.1×10(^3)</td>
<td>2.8×10(^3)</td>
<td>3.5×10(^3)</td>
<td>1.1×10(^3)</td>
<td>1.7×10(^3)</td>
</tr>
<tr>
<td>Glucose</td>
<td>3.4×10(^3)</td>
<td>2.7×10(^3)</td>
<td>4.9×10(^3)</td>
<td>3.1×10(^3)</td>
<td>3.5×10(^3)</td>
<td>3.7×10(^3)</td>
</tr>
<tr>
<td>Mannitol</td>
<td>2.6×10(^3)</td>
<td>3.4×10(^3)</td>
<td>1.1×10(^3)</td>
<td>2.6×10(^3)</td>
<td>3.6×10(^3)</td>
<td>2.9×10(^3)</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>2.8×10(^3)</td>
<td>3.1×10(^3)</td>
<td>2.7×10(^3)</td>
<td>4.0×10(^3)</td>
<td>2.1×10(^3)</td>
<td>1.6×10(^3)</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>1.9×10(^3)</td>
<td>1.5×10(^3)</td>
<td>3.0×10(^3)</td>
<td>3.7×10(^3)</td>
<td>4.8×10(^3)</td>
<td>4.5×10(^3)</td>
</tr>
<tr>
<td>Ammonium chloride</td>
<td>2.5×10(^3)</td>
<td>2.1×10(^3)</td>
<td>2.2×10(^3)</td>
<td>1.7×10(^3)</td>
<td>3.8×10(^3)</td>
<td>3.0×10(^3)</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>2.6×10(^3)</td>
<td>2.0×10(^3)</td>
<td>2.9×10(^3)</td>
<td>2.0×10(^3)</td>
<td>2.1×10(^3)</td>
<td>3.4×10(^3)</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>2.3×10(^3)</td>
<td>2.4×10(^3)</td>
<td>2.0×10(^3)</td>
<td>2.2×10(^3)</td>
<td>2.9×10(^3)</td>
<td>2.8×10(^3)</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>1.6×10(^2)</td>
<td>3.5×10(^2)</td>
<td>4.4×10(^2)</td>
<td>1.3×10(^2)</td>
<td>2.1×10(^2)</td>
<td>1.6×10(^2)</td>
</tr>
</tbody>
</table>

\(^a\) All interferents above were in the form of 10\(^{-3}\) M, aqueous solution
Fig. 3. Profile of the potential in mV to the –Log concentration of baclofen

Table 3 shows the results obtained for the determination of baclofen in pharmaceutical formulations that proves the applicability of the method, as demonstrated by the accurate and precise percentage recovery. Placebo experiments contain all additives in the same ratio as that used in pharmaceutical formulations were investigated. Thus, analysis was carried out without prior treatment or extraction. The proposed baclofen-selective sensors have shown excellent selectivity.

**Table 3.** Determination of baclofen in its pharmaceutical preparation by the proposed sensors

<table>
<thead>
<tr>
<th></th>
<th>Drug Recovery * %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen 10 mg (B.N. 114122)</td>
<td>100.20±0.18</td>
</tr>
<tr>
<td>Baclofen 25 mg (B.N. 125092)</td>
<td>99.27±0.38</td>
</tr>
</tbody>
</table>

*Average of five measurements

*Colorimetric method: measuring the yellow color produced by reacting baclofen with 10% salicylaldehyde in methanol at 400 nm
4. CONCLUSIONS

The described novel sensors are sufficiently simple, cheap and selective for the quantitative determination of baclofen in pure form and pharmaceutical formulations. The use of the proposed sensors offers advantages of fast response and elimination of drug pretreatment or separation steps. They can therefore, be used for routine analysis of baclofen in quality control laboratories.

REFERENCES


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