Synthesis by Precipitation Polymerization of a Molecularly Imprinted Polymer Membrane for the Potentiometric Determination of Sertraline in Tablets and Biological Fluids

Majid Arvand* and Masoumeh Hashemi

Department of Chemistry, Faculty of Science, University of Guilan, Namjoo Street, P.O. Box 1914, Rasht, Iran

A potentiometric chemosensor for selective determination of sertraline was developed based on the molecular imprinting technique. The molecularly imprinted polymer was synthesized by precipitation polymerization, using sertraline hydrochloride as a template molecule, methacrylic acid as a functional monomer and ethylene glycol dimethacrylate as a cross-linking agent. The sensor was developed by dispersing the sertraline imprinted polymer particles in dibutyl sebacate plasticizer and embedding in poly(vinyl chloride) matrix. Characteristics of the proposed sensor were evaluated by measuring the potential response to sertraline hydrochloride in the range from 1.0 µmol L\(^{-1}\) to 10 mmol L\(^{-1}\) with a near Nernstian response of 57.7 mV decade\(^{-1}\) and a limit of detection of 0.8 µmol L\(^{-1}\). The potentiometric selectivity coefficients of the proposed sensor were evaluated and it exhibited good selectivity to sertraline with respect to the other antidepressants. It was used as indicator electrode in potentiometric determination of sertraline in tablets and biological fluids.

Keywords: molecularly imprinted polymers, precipitation polymerization, sertraline, potentiometry, biological fluids

Introduction

Molecular imprinting is an emerging technology which enables us to synthesize the materials with highly specific receptor sites towards the target molecules. Molecularly imprinted polymers (MIPs) are a class of highly cross-linked polymer that can bind certain target compound with high specificity. The polymers are prepared in the presence of the target molecule itself as the template. After removal of the template, the polymer can be used as a selective binding medium for the print molecule or structurally related compounds. Various types of electrosynthesized polymers based on molecular imprinting have been reported in the literature, including polypyrrole and a copolymer of aniline with \(o\)-phenylenediamine. One of many attraction features of the molecular imprinting technique is its application to a wide range of target molecules such as drugs, herbicides, carbohydrates, amino acids and other biologically and environmentally important molecules. Detection applications are employing transduction mechanisms including conductometry, amperometry, voltammetry.
quartz microbalance, surface plasmon resonance and field effect devices.

Potentiometric technique is also well-known versatile, simple, rapid and inexpensive method for determination of target ion (molecule). Potentiometric technique is another approach to electrochemical transduction of ion selective sensors based on MIP. Generally this approach utilizes MIP as a selective molecular recognition membrane or layer in chemical sensing systems. The first ion selective electrode based on a templated polymer using a potentiometry method has been reported by Murray et al. showing selectivity to lead ions. Despite the relatively simple transduction of the potentiometric signal, only limited reports on the design of the potentiometric sensors have been based on the molecular imprinting technology. These reports describe the dispersion of the MIP particles in the plasticizer and their embedment in a polyvinylchloride (PVC) matrix, the formation of a glassy membrane, the template assembly on the polar surface of the indium tin oxide (ITO) glass plate and the deposition of an MIP polymeric film on the gate surface of an ion-sensitive field-effect transistor.

The prescription of new antidepressant drugs has increased dramatically in the last few years. Sertraline (1-S,cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalene amine (Ser) (Figure 1), is one of the new antidepressants of the selective serotonin re-uptake inhibitors. It is naphthalene amine-derivative that differs structurally from classic tricyclic antidepressants and has minimal side effects. Sertraline and other new antidepressants have been analyzed in biological fluids. Suitable aliquots of solution were filtered through a 0.45 µm milli-pore filter and the filtrate was analyzed by HPLC, tandem mass spectrometry, gas chromatography and flame ionization mass spectrometry. Some of them have either a very high limit of quantification (LOQ) or are too much complex, which limits its application for a larger number of samples.

This research explores the utilization of a sertraline hydrochloride templated polymer as a selective agent in an electrochemical sensor. To our knowledge, this is the first report describing recognition and potentiometric determination of sertraline hydrochloride based on MIP. The proposed electrode was successfully applied for the determination of sertraline in biological fluids.

Experimental

Reagents and materials

All reagents were of the highest grade commercially available and were used without further purification. High molecular weight poly(vinyl chloride) (PVC) powder, tetrahydrofuran (THF), acetonophene (AP), dibutyl sebacate (DBS), dibutyl phthalate (DBP), o-nitrophenyl octyl ether (o-NPOE) were obtained from Fluka. Inorganic salts, solvents, methacrylic acid (MAA), oleic acid (OA), sodium tetraphenylborate (NaTPB), potassium tetrakis(p-chlorophenyl)borate (KTpCIPB), ethylene glycol dimethacrylate (EGDMA) and 2,2’-azobisisobutyronitrile (AIBN) were all purchased from Merck with highest purity. Sertraline hydrochloride and other antidepressant drugs were kindly supplied by Sobhan Pharmacy Company (Industrial City, Rasht, Iran) and were used as received. Standard solutions and buffers were prepared freshly with deionized water. Drug free human serum was obtained from the Iranian blood transfusion service (Rasht, Iran) and stored at −20 °C until use after gentle thawing. Urine was also collected from healthy volunteers (males, around 30 years old).

Procedures

Preparation of tablets for assay

Ten tablets were weighed, crushed and mixed in a mortar and pestle for 10 min. A portion of powder equivalent to the weight of one tablet was accurately weighed into each of five 100 mL A-grade volumetric flasks and 70 mL of phosphate buffer (0.1 mol L⁻¹, pH 6.0) was added to each flask. The volumetric flasks were sonicated for 15 min to effect complete dissolution of the sertraline and the solutions were then made up to volume with phosphate buffer. Suitable aliquots of solution were filtered through a 0.45 µm milli-pore filter and the filtrate was analyzed by HPLC, tandem mass spectrometry, gas chromatography and flame ionization mass spectrometry. The desired concentrations were obtained by accurate dilution with phosphate buffer.

Preparation of urine samples and extraction procedure

For the preparation of urine standard solutions, 1 mL of sertraline hydrochloride aqueous solution was transferred in to a 5 mL volumetric flask and then the solution was diluted to the mark with urine and vortexed for 1 min. Then the solution was adjusted to pH 10 by the concentrated sodium hydroxide solution. For the determination of sertraline, 3 mL dichloromethane was added to 1 mL of urine samples and vortexed for 5 min. The mixture was centrifuged at 6000 rpm for 4 min to separate the aqueous and organic layers. After removal of the organic layer the extraction was repeated on the residual aqueous layer. The dichloromethane layers were pooled and dried at 40 °C under a gentle stream of nitrogen using an N-Evap® Model 112 analytical evaporator (Organomation Associates Inc., South Berlin, MA, USA). After drying, samples were
reconstituted with 5 mL of HCl, vortexed for 2 min. Then the analysis was followed up as indicated in the general analytical procedure. The calibration curve for urine samples was also prepared using buffer solution. These calibration solutions contained sertraline in the range of 1.0 μmol L\(^{-1}\) to 10 mmol L\(^{-1}\) and the buffer solution (10 mL standard sertraline solution were diluted with 2 mL phosphate buffer solution pH 6).

**Preparation of serum samples and extraction procedure**

Serum standard solutions were prepared by spiking drug free serum with known aliquots of an appropriate dilution
of an aqueous sertraline solution. For the determination of sertraline, 0.3 mL concentrated sodium hydroxide solution was added to 1 mL of serum standard samples. The mixture was vortexed for 1 min after which 2 mL dichloromethane was added and vortexed for two further minutes. Then it was prepared as directed for procedure under preparation of urine samples and extraction procedure, previously described, beginning with “The mixture was centrifuged”. Then the analysis was followed up as indicated in the general analytical procedure.

Preparation of molecularly imprinted (MIP) and non-imprinted polymers (NIP) with precipitation polymerization

The molecular imprinted polymer membranes for sertraline hydrochloride were prepared from a reagent mixture obtained by mixing 78.0 µL (0.915 mmol) of methacrylic acid, 721.5 µL (3.82 mmol) of ethylene glycol dimethacrylate, 88.7 mg (0.198 mmol) of sertraline hydrochloride and 14.5 mg (0.088 mmol) of AIBN in 40 mL chloroform. The mixture was uniformly dispersed by sonication (sonic bath model Ultrasonic UTD35-Falc, Via Piemonte, Italy). After sonication, it was purged with N₂ for 10 min and the glass tube was sealed under this atmosphere. It was, then, stirred in a water bath maintained at 60 °C for 20 h. The produced polymer was filtered using a Whatman filter number 1 and washed with acetone and methanol before the template removal. The template was removed by washing the MIP successively with 15 mL of a methanol/acetic acid solution (10:1, v/v, of 98% methanol and pure acetic acid) for three times, each time for 1 h, and then twice with 15 mL of pure water for 1 h. The template extraction of the polymer created the cavities, leading to the specific sorption of the template. In addition, the removal of other materials from the polymer took place (e.g. residual monomers or oligomers and initiator fragments). The non-imprinted polymers (NIP) were also synthesized following exactly the same procedure, but excluding the template sertraline hydrochloride from the formulation. Figure 2 shows the scanning electron microscopy (SEM) images of the MIPs and NIPs. It can be seen that in polymers there is no differences between the MIP and NIP with regards to the size and surface morphology of the polymeric particles.

Fabrication of the sensor

The PVC membrane sensors were fabricated by following the general procedure. A quantity of 60 mg of PVC powder with 30 mg of MIP or NIP particles, 10 mg of NaTPB (KT₃CIPB/OA) and 0.2 mL of DBS (o-NPPE/DBP/AP) were dissolved in 3.0 mL THF. The resulting mixture was adequately mixed for 20 min with a magnetic stirrer and then was poured into a Teflon mould of 20 mm of internal diameter. The THF was allowed to evaporate at room temperature. PVC based polymer membranes were obtained with thickness of ca. 0.45 mm. The membranes were glued to one end of a Pyrex glass tube using a viscous solution of PVC in THF as an adhesive. The tube was then filled with internal filling solution of 1.0 × 10⁻³ mol L⁻¹ of sertraline hydrochloride. The electrode was finally conditioned for 24 h by soaking in a 1 × 10⁻² mol L⁻¹ solution of sertraline hydrochloride. It is necessary to reach high stability readings and also decreasing of membrane resistance. On the other hand, without sufficient conditioning of the membrane, potential drifts arise as a consequence of slow equilibration of the corresponding surface layers with the bulk of the solution and/or membrane upon a change of the sample. The solutions for the calibration were prepared by consecutive dilution of 0.1 mol L⁻¹ sertraline hydrochloride with bidistilled water.

Figure 2. Scanning electron microscopy images of MIPs (left side) and NIPs (right side).
Emf measurements

The performance of the sensor was investigated by measuring the emf values of various sertraline hydrochloride solutions. Potentiometric evaluation of the electrodes was carried out using the following cell:

\[
\text{Ag–AgCl} \parallel \text{test solution} \parallel \text{MIP membrane} \parallel \text{internal solution}, 1.0 \times 10^{-3} \text{ mol L}^{-1} \text{ sertraline hydrochloride} \parallel \text{Hg–HgCl}_2, \text{KCl (saturated)}.
\]

All measurements were made with a digital pH/millivoltmeter (Jenway, Model 3305) at room temperature. The reference electrode was obtained from Azar Electrode Company (Urmia, Iran). A digital pH meter (Metrohm Model 827) was used for measuring pH. The calibration graphs were constructed by plotting the potential, \(E\), versus the logarithm of sertraline ion concentration.

Results and Discussion

Effect of membrane composition on the electrode response and calibration curve

Literature reports on conventional potentiometric sensors for inorganics show that the response behavior of the sensor depends on various features of membranes such as the properties of the plasticizer, nature and amount of ion recognizing material used.\(^{32-34}\) Thus, different aspects of the membrane preparation using sertraline imprinted polymer particles were optimized on similar lines.

The best formulation of polymer for synthesis of MIP in recognition of sertraline hydrochloride was described above. The template molecule and functional monomer are induced to form a covalently bound complex at the pre-polymerization stage. Polymerization with the crosslinker is carried out in the presence of the complex using an initiator, and subsequent removal of the template yields a substrate binding pocket complementary to the polymer (Scheme 1). When the MIP is introduced to an aqueous solution containing the target molecule, the template equilibrium partition between the polymer and the aqueous solution (template rebinding) occurs. According to this knowledge, the synthesized MIP was incorporated into the PVC membrane and was tested as a sensing material in the proposed potentiometric sensor. The variables performed in the optimization of the sensor include varying the amount of MIP, PVC, plasticizer and their relative amounts in the formulations and changing the membrane composition.

In a preliminary experiment, the templated polymer was used to prepare the PVC plasticized membrane based sensors with a composition of PVC:MIP:DBS:NaTPB = 20:10:66.7:3.3 wt.% and their potentiometric responses to sertraline were examined. To confirm the efficiency of the MIP, the potentiometric response of the non-imprinted

\[\text{Scheme 1. Schematic representation of the MIP synthesis.}\]
polymer modified sensor (NIP) was also examined. Typical potential response curves of the sensors based on NIP and MIP to sertraline in the concentration range of $1.0 \times 10^{-8}$ to $1.0 \times 10^{-2}$ mol L$^{-1}$ are shown in Figure 3. As seen, a specific response to sertraline could be observed with MIP but not with NIP, suggesting that the molecular imprinting is more effective in sertraline sensing than the untemplated polymer.

Nature of plasticizer

The plasticizer to be used in membrane should exhibit high lipophilicity, have high molecular weight, low tendency for exudation from the polymer matrix, low vapor pressure and high capacity to dissolve the substrate and other additives present in the membrane. Additionally, its viscosity and dielectric constant should be adequate. The nature of a plasticizer or membrane solvent greatly affects all the electrochemical characteristics including potentiometric selectivity because it influences both the dielectric constant of the membrane and the mobility of the molecule or ion in the membrane.$^{35-38}$ Therefore, several membrane compositions were investigated by varying the amount and nature of plasticizer (Table 1). Among four different plasticizers employed DBS (ε = 5.4), DBP (ε = 8.5), AP (ε = 17.4) and o-NPPE (ε = 24.0), the plasticized membrane with DBS (ε = 5.4) appeared to be more compatible with the MIP as a homogenous and clear membrane could be formed. It was found that the membrane with DBS provided a better slope with a wider linear response range (Table 1 and Figure 3). It was noticed that MIP based membranes were found to be brittle in the absence of plasticizer and sensor performance could not be checked.

Effect of MIP particles to PVC ratio

In case of imprinted polymer ion selective electrodes, it has been found that the ratio of PVC to MIP particles play a key role in the sensor performance since the amount of MIP particles determines the number of binding sites available for selective rebinding of target molecule.$^{18,39}$ To evaluate the response of MIPs to the specific binding of sertraline hydrochloride, the amount of the imprinted polymer was increased with a fixed amount of PVC. The results in Table 1 show that the membrane having the weight of PVC to MIP particles in the ratio 1:0.5 (10.3 wt.% of MIP) gave the best performance (membrane No. 2). In the case of the membrane with 1:0.25 ratio, the total number of binding sites available for rebinding of sertraline are relatively lower for the membrane to respond effectively (membrane No. 6). On the other hand, during the preparation of membranes with 1:1.5 ratio (25.7 wt.% of MIP), the MIP particles are dispersed non-uniformly resulting in poor performance (membrane No. 8). Since plasticizer/PVC ratio of about 3 resulted in very suitable performance characteristics, this ratio was kept almost constant in the optimization of the ingredients of the membrane.

Table 1. Optimization of membrane ingredients for the sensor based on MIP

<table>
<thead>
<tr>
<th>No.</th>
<th>PVC (wt.%)</th>
<th>MIP (wt.%)</th>
<th>DBS (mL)</th>
<th>DBP (mL)</th>
<th>o-NPPE (mL)</th>
<th>AP (mL)</th>
<th>Linear range / (mol L$^{-1}$)</th>
<th>Slope / (mV decade$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60.0 (20.7)</td>
<td>0.0$^b$</td>
<td>0.2 mL</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>$1.0 \times 10^{-2}$  to $1.0 \times 10^{-6}$</td>
<td>12.3</td>
</tr>
<tr>
<td>2</td>
<td>60.0 (20.7)</td>
<td>30.0 (10.3)</td>
<td>0.2 mL</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>$1.0 \times 10^{-2}$  to $1.0 \times 10^{-6}$</td>
<td>53.2</td>
</tr>
<tr>
<td>3</td>
<td>60.0 (20.7)</td>
<td>30.0 (10.3)</td>
<td>–</td>
<td>0.2 mL</td>
<td>(69)</td>
<td>–</td>
<td>$1.0 \times 10^{-2}$  to $5.0 \times 10^{-6}$</td>
<td>32.0</td>
</tr>
<tr>
<td>4</td>
<td>60.0 (20.7)</td>
<td>30.0 (10.3)</td>
<td>–</td>
<td>–</td>
<td>0.2 mL</td>
<td>(69)</td>
<td>$1.0 \times 10^{-2}$  to $5.0 \times 10^{-6}$</td>
<td>50.4</td>
</tr>
<tr>
<td>5</td>
<td>60.0 (20.7)</td>
<td>30.0 (10.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.2 mL (69)</td>
<td>$1.0 \times 10^{-2}$  to $3.0 \times 10^{-4}$</td>
<td>63.7</td>
</tr>
<tr>
<td>6</td>
<td>60.0 (21.8)</td>
<td>15.0 (5.5)</td>
<td>0.2 mL</td>
<td>(72.7)</td>
<td>–</td>
<td>–</td>
<td>$1.0 \times 10^{-2}$  to $1.0 \times 10^{-4}$</td>
<td>47.6</td>
</tr>
<tr>
<td>7</td>
<td>60.0 (18.8)</td>
<td>60.0 (18.8)</td>
<td>0.2 mL</td>
<td>(62.4)</td>
<td>–</td>
<td>–</td>
<td>$1.0 \times 10^{-2}$  to $3.0 \times 10^{-6}$</td>
<td>49.3</td>
</tr>
<tr>
<td>8</td>
<td>60.0 (17.1)</td>
<td>90.0 (25.7)</td>
<td>0.2 mL</td>
<td>(57.2)</td>
<td>–</td>
<td>–</td>
<td>$1.0 \times 10^{-2}$  to $3.0 \times 10^{-4}$</td>
<td>25.5</td>
</tr>
</tbody>
</table>

$^a$Mean values of slopes for three replicate measurements. $^b$Containing 30 mg (10.3 wt.%) NIP.
Effect of addition of lipophilic salts/ionic additives

The effect of addition of OA, KTpClPB or NaTPB on the performance of MIP based sensor for sertraline was examined (Table 2). Lipophilic salts and ionic additives can decrease the membrane resistance, reduce anion interference, improve selectivity and sensitivity of the electrode and enhance the response behavior. Their main role is attributed to the inducing permselectivity to some PVC membrane selective electrodes. The addition of NaTPB to MIP based membrane responds to sertraline in the range 1.0 × 10^{-6} to 1.0 × 10^{-2} mol L^{-1} in comparison with 1.0 × 10^{-5} to 1.0 × 10^{-2} mol L^{-1} (OA) and 5.0 × 10^{-6} to 1.0 × 10^{-2} mol L^{-1} (KTpClPB). We found out that the membrane with NaTPB addition gives better performance over other membranes with respect to working concentration range and slope.

Effect of pH

The pH effect of the tested solution on the electrochemical behavior of the sensor was studied under a constant concentration of sertraline hydrochloride and varying the content of the hydrogen ions in the pH range of 1.0-9.0 which was adjusted with HCl or NaOH solution. The results are illustrated in Figure 4. As can be seen, the potentials keep constant in the range of 2.0-7.0. The observed potential drift at lower pH values may be attributed to the membrane response to H^+ and at higher pH values (pH > 7) could be due to formation of sertraline in a non-ionic form (pK_a = 9.47). Accordingly, further studies were carried out at pH 6 by using 0.1 mol L^{-1} phosphate buffer solutions.

Response time, reversibility and life time of the electrode

Response time is the average time required for the electrodes to reach a potential response within ±1 mV of the final equilibrium value, after successive immersions in a series of sertraline solutions, each having a 10-fold concentration difference. After the investigation of this parameter, the resulting data are illustrated in Figure 5. In this Figure, the resulting potential-time responses for the MIP-based sertraline sensor are presented, obtained upon changing the sertraline concentration from 1.0 mmol L^{-1} to 10 mmol L^{-1} (by fast injection of µL amounts of a concentrated solution; rising part) and from 10 mmol L^{-1} to 1.0 mmol L^{-1} (by appropriate dilution of the solution; descending part). It is evident that the potentiometric response of the electrode is rapid (ca. 15 s) and reversible, although the time needed to reach the equilibrium value for the case of high-to-low sample concentration is longer than that of the low-to-high sample concentration. A similar trend is well documented in the literature.

### Table 2. Effect of the lipophilic anions on the slope of MIP-based sertraline sensor (DBS/PVC ratio ca. 3)

<table>
<thead>
<tr>
<th>No.</th>
<th>PVC / (%)</th>
<th>MIP / (%)</th>
<th>DBS / (%)</th>
<th>Lipophilic anion / (% m/m)</th>
<th>Slope / (mV decade^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60.0 (20)</td>
<td>30.0 (10)</td>
<td>0.2 mL (66.7)</td>
<td>NaTPB 10 (3.3)</td>
<td>57.7</td>
</tr>
<tr>
<td>2</td>
<td>60.0 (20)</td>
<td>30.0 (10)</td>
<td>0.2 mL (66.7)</td>
<td>KTpClPB 10 (3.3)</td>
<td>50.3</td>
</tr>
<tr>
<td>3</td>
<td>60.0 (20)</td>
<td>30.0 (10)</td>
<td>0.2 mL (66.7)</td>
<td>OA 10 (3.3)</td>
<td>41.2</td>
</tr>
</tbody>
</table>

![Figure 4. Effect of pH of test solution on the potential response of the proposed sensor based on the templated polymer using 10 and 1.0 mmol L^{-1} sertraline hydrochloride solutions.](image)

![Figure 5. Dynamic response of the MIP-based sertraline potentiometric sensor for a low-to-high (1.0 × 10^{-3} to 1.0 × 10^{-2} mol L^{-1}, left part) and high-to-low (1.0 × 10^{-2} to 1.0 × 10^{-3} mol L^{-1}, right part) step concentrations (pH 6.0).](image)
but at concentrations lower than 1.0 mmol L\(^{-1}\), the response time increased to 20-30 s.

The lifetime of the MIP-based electrode was studied by periodically recalibrating the potentiometric sertraline response in the standard sertraline solutions. After the conditioning step, the electrode was repeatedly calibrated five times every month. No significant change in the electrode performance was observed during 5 months. This indicated that its lifetime was longer than 5 months.

Determination of selectivity coefficients

The potentiometric selectivity coefficients were determined by two different procedures, namely the so-called separated solution method (SSM) and the matched potential method (MPM). MPM is recommended by IUPAC\(^{35}\) to overcome the difficulties associated with the methods based on the Nicolskii-Eisenman equation.\(^{41,42}\) The coefficients describe the preference of the suggested electrode for an interfering ion, X, with reference to the sertraline ion.

According to the MPM method, the specified activity (concentration) of the primary ions is added to a reference solution (1.0 \(\times\) \(10^{-4}\) mol L\(^{-1}\) sertraline, in this case) and the potential is measured. In another experiment, the interfering ions (X) are successively added to an identical reference solution, until the measured potential matches that obtained after the addition of the primary ions. The MPM selectivity coefficient, \(K_{\text{Ser,X}}^{\text{MPM}}\), is then given by the resulting primary ion activity (concentration) to the interfering ion activity ratio:

\[
K_{\text{Ser,X}}^{\text{MPM}} = \frac{a_{\text{Ser}}}{a_{X}}
\]

In separate solution method (SSM), the emf of a cell comprising a selective electrode and a reference electrode (ISE cell) is measured for each of two separate solutions, one containing the ion A of the activity \(a_{A}\) and charge \(Z_{A}\) (but not B), the other containing the ion B with charge \(Z_{B}\) at the same activity \(a_{B} = a_{A}\) (but not A). If the measured values are \(E_{A}\) and \(E_{B}\), respectively, then the value of \(K_{A,B}^{\text{SSM}}\) may be calculated from the equation:

\[
\log K_{A,B}^{\text{SSM}} = \frac{(E_{A} - E_{B})Z_{A}F}{2.303RT} + (1 - \frac{Z_{A}}{Z_{B}}) \log a_{A}
\]

The values of selectivity coefficients calculated by MPM and SSM at the constant pH value of 6.0 are shown in Figure 6. In this study, the arrangement was achieved by non-covalent interactions, such as hydrogen bonding and the hydrophobic effect. From the data, it is obvious that the interfering cations even of very similar structures could not affect the selectivity of the proposed sensor to sertraline. The MPM selectivity sequence of the employed MIP for different antidepressant drugs approximately obeys the order: venlafaxine > citalopram > bupropion > alprazolam ≈ fluoxetine > duloxetine = fluvoxamine > amitriptyline > mirtazapine > trazodone. As a result, the MIP molecular recognition is based both on the template molecular structure (shape) and on the interactions between the print molecule and the imprinted polymer.

Since the free energy of transfer of an ion is dependent on the solvent, which for a MIP based membrane means on the solvation properties of the membrane, it should be expected that the selectivity of the electrode will be influenced by the composition of the membrane material. Therefore, we have studied the selectivity of MIP based membrane with different plasticizers and ionic additives. In the first step, the effect of NaTPB as ionic additive, on the selectivity of MIP based membrane for sertraline was studied. A maximum change in selectivity (up to more than two orders of magnitude) due to the introduction of NaTPB was observed for membranes containing DBS as a plasticizer (e.g., \(\log K_{\text{Ser,Me}}^{\text{pot}}\) ca. \(-3.4\) compared with \(-1.2\) in the absence of NaTPB). The effect of the lipophilic ionic additive on the selectivity of electrodes with membranes plasticized with \(\sigma\)-NPPE decreased approximately by an order of magnitude. The selectivity of MIP based electrode with the membrane containing KT\text{pCIPB} as a cation exchanger showed disappointing results. The results obtained can be explained by the possibility of ion-pair formation in the membrane.

To have an actual idea of the level of interference caused by various ions when present at varying concentrations some mixed run studies were performed.\(^{43}\) Figure 7a shows...
the variations of potential with sertraline concentration in presence of $1.0 \times 10^{-4}$, $1.0 \times 10^{-3}$ and $1.0 \times 10^{-2}$ mol L$^{-1}$ Sn$^{2+}$ ion. Mixed run studies were also carried out for venlafaxine and result was shown in Figure 7b. It is shown that presence of Sn$^{2+}$ and venlafaxine do not overly contribute on membrane potentials.

**Effect of temperature**

Trend of changes of electrode performance with temperature, at test solution temperatures 5, 10, 20 and 30 ºC for the MIP based electrode was studied. The electrode exhibits good Nernstian behavior in the temperature range (5-30 ºC) (Figure 8). At higher temperatures, the slope of electrode did not show a good Nernstian behavior. Unfortunately this is a complicated relationship which cannot be simply quantified in terms of mV change per ºC since the effect is different at different concentrations. Moreover, the electrode slope, the liquid junction potential, and solubility of the salts in the reference system all vary with temperature. This behavior may be due to the disturbances occurring in phase boundary equilibrium at the membrane-test solution interface produced by the thermal agitation of the solution. The standard cell potentials ($E^\circ_{cell}$) were determined at different temperatures from the respective calibration plots as the intercepts of these plots at $p$[Ser] = 0, and were used to determine the isothermal temperature coefficient ($dE^\circ/dt$) of the cell with the aid of the following equation:

$$E^\circ_{cell} = E^\circ_{cell} (25^\circ C) + (dE^\circ/dt)_{cell} (t-25)$$

Plot of $E^\circ_{cell}$ versus (t-25) produced a straight line. The slope of this line was taken as the isothermal temperature coefficient of the cell. It amounts to 0.83 mV per ºC. The small values of $(dE^\circ/dt)_{cell}$ and $(dE^\circ/dt)_{electrode}$ reveal the high thermal stability of the electrode within the investigated temperature range.

$$E^\circ_{Hg/HgCl_2} = 0.241 - 0.00066 (t-25)$$

The values of the standard potentials of MIP-based electrode were calculated at the different temperatures from the following relation:

$$E^\circ_{reference} + E^\circ_{cell} = E^\circ_{electrode}$$

A plot of $E^\circ_{electrode}$ versus (t-25) gave a straight line. The slope of this line was taken as the isothermal temperature coefficient of the MIP-based sertraline electrode. It amounts to 0.17 mV per ºC. The small values of $(dE^\circ/dt)_{cell}$ and $(dE^\circ/dt)_{electrode}$ reveal the high thermal stability of the electrode within the investigated temperature range.

**Analytical application**

**Analysis of sertraline tablets**

Sertraline hydrochloride is available in tablet form for oral administration containing the equivalent to 100 mg as sertraline base (Soha Helal Pharmaceutical Company, Iran). An amount of 300 mg of sertraline hydrochloride is equivalent to 100 mg of sertraline base. The proposed described potentiometric procedure was successfully applied for the sertraline determination in tablets. The resulting data, using the calibration curve and standard addition procedures, were statistically compared with the labeled amounts on the tablets and those obtained by the official chromatographic method which shows a good agreement between the experimental and certified amounts of the drug in the tablet pharmaceutical form (Table 3). Consequently, it was concluded that the suggested method was accurate and precise.
Sertraline assay in spiked human serum

The proposed potentiometric procedure was also successfully applied to assay of sertraline in spiked human serum. The results of the recovery studies are listed in Table 4. The recoveries of the methods were in the range of 96-110% for the spiked serum. Consequently, it was concluded that the suggested method was sensitive and precise.

Sertraline assessment in spiked human urine

As another application of the present electrode to a real sample, the quantitative sertraline determination and recovery in human urine samples were carried out. Recovery studies were conducted with the sample containing various sertraline amounts. The calibration curve for urine samples was also prepared using the phosphate buffer solution. These calibration solutions contained sertraline in the range of 1.0 × 10⁻⁶ mol L⁻¹ to 1.0 × 10⁻³ mol L⁻¹ and the buffer solution (10 mL from the standard sertraline solution were diluted with 2 mL from the buffer solution). The results of the recovery studies are summarized in Table 4, varying from 94.5% to 109.5% for urine.

Conclusions

A novel potentiometric chemosensor for the direct, rapid and selective measurement of sertraline hydrochloride in pharmaceutical formulations and human blood was developed. High specificity, selectivity and sensitivity were obtained by the combination of chemical and physical recognition. The imprinted cavity works like a channel gate to open for the sertraline molecules. The sensor had a short response time, a wide operational span, and highly stability. The technique described here not only represents a rationally designed potentiometric sensor for sertraline, but also suggests a novel and general strategy for electrochemical discrimination for many kinds of drugs.

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