Ion-selective Electrode Determination of Venlafaxine Hydrochloride in pure form and Capsules

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ABSTRACT
Venlafaxine ion-selective electrode was constructed from poly(vinyl chloride) containing venlafaxine-silicomolybdate (VE-SMA) as the sensing element in the presence of DOP as the plasticizing solvent mediator. The best PVC membrane electrode was made of a composition of 46% PVC, 46% DOP and 8% ion-pair. The electrode showed a fast, stable and Nernstian response over a wide venlafaxine concentration range 1.0×10^-2 to 1.0×10^-6 mol/L of the drug concentration with the slope of 58.8 mV/decade. The electrode exhibit good selectivity for the VE with respect to a large number of inorganic cations and organic substances of biological fluids. The method is precise as shown by the mean recoveries range of 99.69–101.94% with mean relative standard deviations 0.51–1.40%. Venlafaxine is determined successfully in pure solutions and in capsules using the standard additions and potentiometric titrations methods.

Keywords: Venlafaxine hydrochloride (VE); Ion-selective electrode; Potentiometry.

INTRODUCTION
Venlafaxine hydrochloride Figure 1, (1-[2-dimethylamino]-1-(4-methoxy phenyl) ethyl] cyclohexanol) hydrochloride is a third-generation, structurally novel phenethyl bicyclic antidepressant [1]. Venlafaxine inhibits synaptosomal re-uptake of both serotonin and noradrenalin, and it is also a relatively weak inhibitor of dopamine re-uptake [2]. There are several methods reported for the determination of venlafaxine in biological fluids [3-6] However, for its determination in drug formulations only two methods have been reported [7-9]. Most of these methods use sophisticated instruments, time consuming or needs expensive reagents.

Ion-selective electrodes have been increasingly used for quantitative measurement of drugs. Potentiometric methods based on this technique are simple, rapid, low cost, low detection limit, good accuracy, wide concentration range, applicability to coloured and turbid solutions and offer enough selectivity towards the drugs in the presence of various pharmaceutical excipients [10,11]. The present investigation deals with the fabrication and characterization of liquid membrane ion selective electrode for the determination of venlafaxine hydrochloride. The electrochemical sensitivity of the electrode is based on the incorporation of venlafaxine-silicomolybdate (VE-SMA) as a sensing element. The electrode was successfully applied for the determination of venlafaxine hydrochloride in pure form and in capsules.

Figure 1. Chemical structure of venlafaxine hydrochloride.
EXPIMENTAL
Reagent and Materials
All chemicals were of analytical grade, and double distilled water was used throughout the experiments. Venlafaxine hydrochloride was obtained from Sigma Co. Pharmaceutical formula (Efexor-XR), 75 mg venlafaxine hydrochloride in each capsule was obtained from local drug stores. Membrane components siliconolybdic acid (SMA) H$_2$SiO$_4$·12MoO$_3$. H$_2$O and dioctylphthalate (DOP) C$_{10}$H$_{16}$O$_4$ were obtained from Sigma-Aldrich. High molecular weight poly(vinyl chloride) (PVC), used as the electrode membrane material, and freshly distilled tetrahydrofuran (THF), used as a solvent for the membrane components, were obtained from Fluka. Stock venlafaxine hydrochloride solution (10$^{-2}$ mol/L) was prepared daily by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by appropriate dilution.

Preparation of Sensing Element
Sensing element used in electrode was an ion-pair complex composed of venlafaxine-siliconolybdic acid (VE-SMA). VE-SMA was prepared by mixing about 50 mL of 1.0$\times$10$^{-2}$ mol/L solution of venlafaxine hydrochloride with 50 mL of 1.0$\times$10$^{-2}$ mol/L solution siliconolybdic acid (SMA). The resulting precipitate was then filtered, washed with water and dried in room temperature for 2 days.

Preparation of PVC Membrane Electrode
Several membranes of different compositions as indicated in Table 1 were investigated. For preparation of PVC membrane, different amounts of ion-pair with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), and the solution was mixed well into a glass dish of 5 cm diameter. Then THF was evaporated slowly until an oily concentrated mixture was obtained. A glass tube (7 mm in diameter) was dipped into the mixture for about 10 s so a transparent membrane of about 0.3 mm in thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 12 h. Afterwards, the tube was filled with an internal filling solution (1.0$\times$10$^{-2}$ mol/L NaCl and 10$^{-2}$ mol/L VE). The electrode was finally conditioned for 2 h by soaking in 10$^{-3}$ mol/L VE drug.

Table 1. Composition of different VE-SMA membranes and slopes of the corresponding calibration graphs at 25.0 °C.

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Ion Pair</th>
<th>Composition % (w/w)</th>
<th>Slope mV/decade</th>
<th>Linear range</th>
<th>RSD= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.0</td>
<td>49.5 49.5</td>
<td>41.22</td>
<td>1.0$\times$10$^{-5}$ - 10$^{-2}$</td>
<td>0.36</td>
</tr>
<tr>
<td>B</td>
<td>3.0</td>
<td>48.5 48.5</td>
<td>48.00</td>
<td>6.0$\times$10$^{-5}$ - 10$^{-2}$</td>
<td>0.22</td>
</tr>
<tr>
<td>C</td>
<td>6.0</td>
<td>47.0 47.0</td>
<td>55.63</td>
<td>3.6$\times$10$^{-6}$ - 10$^{-2}$</td>
<td>0.18</td>
</tr>
<tr>
<td>D</td>
<td>8.0</td>
<td>46.0 46.0</td>
<td>58.80</td>
<td>1.0$\times$10$^{-6}$ - 10$^{-2}$</td>
<td>0.13</td>
</tr>
<tr>
<td>E</td>
<td>12.0</td>
<td>44.0 44.0</td>
<td>42.19</td>
<td>7.4$\times$10$^{-6}$ - 10$^{-2}$</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Relative standard deviation (three determinations)

Construction of the Calibration Graphs
Potentiometric measurements were carried out with an Orion (Cambridge, MA, USA) Model 701 A digital pH/mV-meter. Electromotive force (e.m.f) measurements were performed using the cell assembly:

$\text{Ag/AgCl/internal solution/PVC membrane/test solution/SCE}$

Suitable increments of standard drug solution were add to 50.0 ml doubly distilled water so as to cover the concentration range from 1.0$\times$ 10$^{-6}$ - 1.0$\times$ 10$^{-2}$ mol/L. In this solution the sensor and reference electrode were immersed and the e.m.f values were recorded after each addition. The electrode was washed with double distilled water and dried between measurements. The electrode potential was plotted versus negative logarithmic concentration of VE ($P_{VE}$). Slopes of the resulting calibration curves were calculated.

Analysis of Efexor- XR Capsule
The content of 10 capsules equivalent to 750 mg of VE was transferred to a beaker and diluted to 50 ml with bidistilled water. The mixture was filtered through a filter paper and washed with water. The filtrate and washings were collected in a 100-ml standard volumetric flask and diluted to volume with bidistilled water.

Standard Addition Method
The standard addition method [12] was applied, in which small increments of a standard VE solution $1 \times 10^{-2}$ M were added to 50 ml aliquot samples of various drug concentrations. The change in potential reading at a constant temperature of 25°C was recorded for each increment and used to calculate the concentration of the drug sample solution using the following equation:

$$C_x = C_s \left( \frac{V_x}{V_x + V_s} \right) \left( 10^{\frac{(\Delta E_s - \Delta E_x)}{S}} - \frac{V_x}{V_x + V_s} \right)^{-1} \quad \text{eq. (1)}$$

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

**Potentiometric Titration of VE**

An aliquot of VE solution was pipetted into a 100-ml titration vessel and the solution was diluted to 50 ml with bidistilled water. The resulting solution was titrated with $1.0 \times 10^{-3}$ mol/L SMA solution and the change of the cell potential upon addition of SMA was recorded. The volume of the titrant at the end point was obtained using the first derivative.

**RESULTS AND DISCUSSION**

**Optimization of the Electrode**

**Influence of membrane composition**

Several membranes of the different compositions were prepared. The slope and the working concentration range for the different membrane composition are given in Table 1. The best performance was exhibited by membrane D with VE-SMA,DOP and PVC in the ratio 8:46:46, respectively. This membrane showed a nearly Nernstian response with slope of 58.8 mV/decade and a linear concentration range $1.0 \times 10^{-5} - 1.0 \times 10^{-2}$ mol/L (Figure 2).

![Figure 2. Typical calibration graph of VE-SMA–PVC membrane electrode](image)

**Response Time**

The response time is the time which elapses between the instant when an ion-selective electrode and a reference electrode (ISE cell) are brought into contact with a sample solution. The response time was tested for $1.0 \times 10^{-6} - 1.0 \times 10^{-2}$ mol/L VE solutions. This electrode exhibit a fast dynamic response of about 20-35 s over the whole concentration range of VE drug. The electrode was used over a period of 5 weeks without any significant change in potential.

**Effect of pH**

The effect of pH of the VE solutions ($1.0 \times 10^{-3}$ and $1.0 \times 10^{-5}$ mol/L VE) on the electrode potential was investigated. Aliquots of VE drug (50 mL) were transferred to 100 mL beaker and the tested ion-selective electrode in conjunction with a saturated calomel electrode and a combined glass electrode were immersed in the same solution. The solutions were acidified by the addition of very small volumes of 0.1 M HCl acid then the pH value was increased gradually using NaOH (0.1 or 1.0 M) for each pH value, the potential readings corresponding to different pH values were recorded and thus the potential-pH curves were constructed as shown in Figure 3. As is obvious, within the pH range 3.0–8.0 the electrode
potential is practically independent of pH, and in this range, the electrode can be safely used for venlafaxine HCl determination.

![Figure 3. Effect of pH on electrode potential/mV of VE-SMA–PVC membrane electrode.]

**Selectivity**

Selectivity coefficients for different ions with respect to venlafaxine HCl were determined by the activity ratio method [13], in which the selectivity coefficient is measured as the ratio of ion activities or concentrations that generate the same membrane potential when measured in a separate solution type experiment. A venlafaxine HCl calibration graph carried out in water was used to calculate the concentration of venlafaxine HCl ($C_{VE}$) that corresponds to the potential observed for a certain concentration ($C_j$) of interfering ion. The selectivity coefficients were calculated as the ratio of these concentrations,

$$K_{VE,j}^{Pot} = \frac{C_{VE}}{C_j}, \text{ eq. (2)}$$

Where $j$ is the interfering ion.

The resulting selectivity coefficients are shown in Table 2. In the case of glucose and lactose, the high selectivity may be attributed to the difference in polarity and to the lipophilic nature of their molecules relative to VE cation. When the concentration of these species was substantially increased, the potential decreased (i.e. it provided negative interference).

<table>
<thead>
<tr>
<th>Interfering ions</th>
<th>$\log K_{VE,j}^{Pot}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K^+$</td>
<td>-3.54</td>
</tr>
<tr>
<td>$Zn^{2+}$</td>
<td>-4.89</td>
</tr>
<tr>
<td>$Fe^{3+}$</td>
<td>-5.53</td>
</tr>
<tr>
<td>Glucose</td>
<td>-</td>
</tr>
<tr>
<td>Lactose</td>
<td>-</td>
</tr>
<tr>
<td>Cysteine</td>
<td>-2.76</td>
</tr>
<tr>
<td>Glycine</td>
<td>-4.23</td>
</tr>
</tbody>
</table>

**Applications**

The proposed membrane sensor was proved to be useful in the potentiometric determination of VE drug in pure solutions and in capsules (Efexor-XR, 75mg), by both the standard addition and the potentiometric titration methods. Five replicate determinations at different concentration levels were carried out using the studied electrode to test the precision of the method. The result are shown in Tables 3 and 4. The standard deviations were found to be $\leq 1.5$, indicating reasonable repeatability and reproducibility of the selected method.

To compare the proposed method to a reported method, VE in Efexor-XR capsules was assayed by HPLC [14]. The results are in good agreement with those obtained from the reported method. The results were illustrated in Table 4 and the average recovery was between 99.81% and 100.76%. HPLC31 was also performed as comparative method. It was found that the results from the determination of venlafaxine...
hydrochloride using this method were almost the same as those from HPLC. Thus, this method was suitable to detect venlafaxine hydrochloride in capsules.

Table 3. Test of precision of the standard addition and potentiometric titration methods on pure venlafaxine hydrochloride.

<table>
<thead>
<tr>
<th>Amount taken (mol/L)</th>
<th>Recovery %</th>
<th>RSD*</th>
<th>Recovery %</th>
<th>RSD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 x 10^{-5}</td>
<td>99.45</td>
<td>1.23</td>
<td>99.30</td>
<td>0.32</td>
</tr>
<tr>
<td>1.5 x 10^{-4}</td>
<td>102.33</td>
<td>1.60</td>
<td>99.87</td>
<td>0.77</td>
</tr>
<tr>
<td>1.0 x 10^{-4}</td>
<td>101.03</td>
<td>1.42</td>
<td>99.89</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean</td>
<td>101.94</td>
<td>1.40</td>
<td>99.69</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>101.94±1.40</td>
<td></td>
<td>99.69±0.51</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Standard additions and potentiometric titration methods for determination of VE in Efexor-XR capsules.

<table>
<thead>
<tr>
<th>Amount taken (mol/L)</th>
<th>Standard addition</th>
<th>Potentiometric titration</th>
<th>Reported method [14]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recovery %</td>
<td>RSD*</td>
<td>Recovery %</td>
</tr>
<tr>
<td>1.0 x 10^{-5}</td>
<td>99.80</td>
<td>0.59</td>
<td>100.32</td>
</tr>
<tr>
<td>1.5 x 10^{-4}</td>
<td>100.42</td>
<td>0.89</td>
<td>101.54</td>
</tr>
<tr>
<td>1.0 x 10^{-4}</td>
<td>99.21</td>
<td>0.53</td>
<td>100.41</td>
</tr>
<tr>
<td>Mean</td>
<td>99.81</td>
<td>0.67</td>
<td>100.76</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>99.81±0.67</td>
<td></td>
<td>100.76±0.74</td>
</tr>
</tbody>
</table>

* RSD (Five determination)

CONCLUSION
The proposed electrode is sufficiently simple and selective for the determination of VE in pure form and in capsules. The electrode showed a very good selectivity to VE in the presence of various common inorganic cations, sugars and amino acids. Thus, this electrode can be used as alternative analytical tools to spectrophotometric and chromatographic methods, for the determination of this drug in bulk powder, pharmaceutical preparations

REFERENCES

CITATION OF THIS ARTICLE