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Dynamic potential and surface morphology study of sertraline membrane sensors

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ABSTRACT

New rapid, sensitive and simple electrometric method was developed to determine sertraline hydrochloride (Ser-Cl) in its pure raw material and pharmaceutical formulations. Membrane sensors based on heteropolyacids as ion associating material were prepared. Silicomolybdic acid (SMA), silicotungstic acid (STA) and phosphomolybdic acid (PMA) were used. The slope and limit of detection are 50.00, 60.00 and 53.24 mV/decade and 2.51, 5.62 and 4.85 μmol L⁻¹ for Ser-ST, Ser-PM and Ser-SM membrane sensors, respectively. Linear range is 0.01–10.00 for the three sensors. These new sensors were used for the potentiometric titration of Ser-Cl using sodium tetraphenylborate as titrant. The surface morphologies of the prepared membranes with and without the modifier (ion-associate) were studied using scanning and atomic force microscopes.

Introduction

Several HPLC, electrometric and spectrophotometric methods were reported in a review for the determination of Ser⁺ and its metabolites in pharmaceutical formulations [1]. Potentiometric chemosensor for the selective determination of sertraline based on heteropolyacids as ion associating material were prepared. Siliconomolybdic acid (SMA), silicotungstic acid (STA) and phosphomolybdic acid (PMA) were used. The slope and limit of detection are 50.00, 60.00 and 53.24 mV/decade and 2.51, 5.62 and 4.85 μmol L⁻¹ for Ser-ST, Ser-PM and Ser-SM membrane sensors, respectively. Linear range is 0.01–10.00 for the three sensors. These new sensors were used for the potentiometric titration of Ser-Cl using sodium tetraphenylborate as titrant. The surface morphologies of the prepared membranes with and without the modifier (ion-associate) were studied using scanning and atomic force microscopes.

As ion-selective sensors (ISSs) have found wide use for the direct determination of ionic species in complex samples [8–19], it is a point of view in this study. In the early days, their selectivity was often the limiting factor in determining low levels of analyte ions. Potentiometric detectors based on ISSs offer advantages such as selectivity, sensitivity, good precision, simplicity, wide linear concentration range and long lifetime.

This study involves construction and analytical applications of membrane sensors for the determination of sertraline hydrochloride. Due to the low solubility of the formed Ser-SM, Ser-PM and Ser-ST ion-associates, their suitability as active ingredients in membrane sensors was examined. The sensitivity and selectivity of a potentiometric sensor is related to the composition of membrane, nature of the plasticizer, plasticizer/PVC ratio and type of additive [20–22].

(1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride is known as sertraline hydrochloride, a widely used antidepressant belonging to the selective serotonin reuptake inhibitor class. It is a white
crystalline powder slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Its efficacy has been demonstrated in the treatment of major depression, obsessive compulsive and panic disorders, eating, premenstrual dysphoric and post-traumatic stress disorders [1] (see Scheme 1).

Characterization of a surface of different solids is often of vital importance in a number of fields, including heterogeneous catalysis, semiconductor thin-film technology, corrosion and adhesion mechanisms, activity of metal surfaces, embrittlement properties and studies of the behavior and functions of biological membranes [23–28]. The surface of a solid is considered as a part of the solid that differs in composition from the average composition of its bulk [29]. This study deals with construction of membrane sensors and their surface characterization using scanning and atomic force microscope.

Methodology

Reagents and materials

All reagents used were chemically pure grade. Doubly distilled water was used throughout all experiments. Sertraline HCl (Mol. wt. = 342.7 g mol⁻¹), and its pharmaceutical preparations (Serlift® tablets, 100 mg/tablet, Global Napi Pharmaceuticals, Egypt) and Moodapex® tablet (50 mg/tablet, Multi-Apex phama-Badr City-Cairo, Egypt), were used throughout this study.

Silicotungstic acid (H₄[W₁₂SiO₄₀]), silicomolybdic acid H₄[SiMo₁₂O₄₀], phosphomolybdic acid (H₃PMo₁₂O₄₀), dibutyl phthalate (DBP), dioctyl phthalate (DOP), tricresyl phosphate (TCP), ethylhexyl adipate (EHA), ortho-nitrophenyl phenyl ether (o-NPPE), ethylhexyl sebacate (EHS), ortho-nitophenyloctyl ether (o-NPOE), poly (vinyl chloride) (PVC) of high relative molecular weight and tetrahydrofuran (THF), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFMPB) were obtained from Aldrich chemical company.

Preparation of solutions

Stock solution of Ser-Cl was prepared by dissolving 342.7 mg in hot doubly distilled water and then completed to 100 mL. Lower concentrations were prepared by appropriate dilutions and kept in dark bottles at room temperature. Aqueous solutions of 0.1 mol L⁻¹ NaTPB, STA, SMA, and PMA were prepared using analytical grade purity chemicals. Lower concentrations were prepared by dilution.

Preparation of the ion-associates

The ion-associates, sertraline silicotungstate (Ser-ST), sertraline silicomolybdate (Ser-SM) and sertraline phosphomolybdate (Ser-PM) were prepared by addition of 100 mL of 10.0 mmol L⁻¹ Ser-Cl solution to 2.5, 2.5 and 3.3 mmol L⁻¹ of STA, SMA and PMA, respectively. The resulting precipitates were left in contact with their mother liquor overnight to assure complete coagulation. The precipitates were then filtered and washed thoroughly with distilled water, dried at room temperature and ground to fine powders. The chemical compositions of the precipitates were confirmed by C, H and N elemental analyses using automatic CHN analyzer (Perkin–Elmer model 2400) in the Micro Analytical Center, Faculty of Science, Cairo University, and the results are given in Table 1.

From the elemental analyses, it was found that the molar ratios were 4:1, 4:1 and 3:1 (D:R) for Ser-ST, Ser-SM and Ser-PM, respectively, as seen in the following equations.

\[
4\text{Ser}^+ + ST^4- \leftrightarrow \text{Ser}_4\text{ST} \\
4\text{Ser}^+ + SM^4- \leftrightarrow \text{Ser}_4\text{SM} \\
3\text{Ser}^+ + PM^3- \leftrightarrow \text{Ser}_3\text{PM}
\]

These stoichiometric ratios were confirmed using conductometric titrations. It was performed to give further insight into the nature and stoichiometry of ion-associates. The conductance of 50 mL 1.0 mmol L⁻¹ R (STA, SMA or PMA) was titrated against 0.1 mmol L⁻¹ Ser-Cl solution. Volume corrections due to volume change were done and the molar concentrations of R and drug solutions were calculated after each addition. [R]/[Ser-Cl] was plotted against the corrected specific conductance. Characteristic breaks at molar ratio 4:1, 4:1 and 3:1 (D:R) were observed for Ser-ST, Ser-SM and Ser-PM, respectively.

Table 1 Elemental analyses of the ion-associates.

| Ion-associate | Color          | C (%) | H (%) | N (%) |
|--------------|----------------|-------|-------|-------|
| Ser-PM       | Yellowish green| Found | 23.63 | 2.07  | 1.53  |
|              |                | Calc. | 22.33 | 1.96  | 1.53  |
| Ser-SM       | Yellowish green| Found | 27.20 | 2.36  | 1.76  |
|              |                | Calc. | 26.77 | 2.36  | 1.84  |
| Ser-ST       | White          | Found | 20.02 | 1.76  | 1.17  |
|              |                | Calc. | 19.88 | 1.75  | 1.36  |
Preparation of membrane sensors

Membranes of different compositions were prepared. The percentages of each ion-associate were changed to cover the ranges of 0.5–5.0% Ser-ST 1.0–7.0% Ser-SM and 1.0–7.0% Ser-PM. The membranes of optimum composition were prepared by dissolving the required amount of PVC in 5 mL THF. The calculated amount of ion-associate was dissolved intimately in THF and mixed with the PVC solution in Petri-dish (5.0 cm diameter) then the calculated volume of plasticizer was added. The total weight of constituents in each batch is fixed at 200 mg. To obtain homogenous and uniform thickness, the membranes were left to dry freely in air for 24 h. Disks (7.5 mm diameter) were punched from the cast films and mounted in a homemade electrode body. The sensors were filled with a solution that is 10.0 mmol L\(^{-1}\) with respect to KCl and 1.0 mmol L\(^{-1}\) with respect to Ser-Cl solution. Then, preconditioning the sensors was carried out by soaking in 1.0 mmol L\(^{-1}\) Ser-Cl solution for different time intervals. The electrochemical system is represented as follows: Ag/AgCl//inner solution/membrane/test solution//Ag/AgCl/Sat. KCl.

Methods and apparatus

Potentiometric measurement

The Potentiometric and pH measurements were carried out with a Jenway 3010 digital pH/mV meter. A techne circulator thermostat Model C-100 (Cambridge-England) was used to control the temperature of the test solution. Ag/AgCl/Sat. KCl, was used as an external reference electrode.

Surface characterization

SEM and AFM were carried out by JEOL JSM-6360LA and Philips XL30 and Shimadzu Wet-SPM (Scanning Probe microscope), Japan, respectively, Micro Analytical Center, Faculty of Science, Cairo University.

Optimization of the operating conditions of the prepared sensors

Potentiometric study involved construction of calibration graphs, effect of soaking on life span, effect of temperature, effect of pH, effect of interfering ions and effect of anionic additives on the performance characteristics of the sensors.

To construct the calibration graph[30], the sensor and the reference electrode were immersed in 50 mL doubly distilled water, to which suitable increments of 10 mmol L\(^{-1}\) solutions were added in order to cover the concentration range 1.0 \(\times \) 10\(^{-3}\)–10.0 mmol L\(^{-1}\) Ser-Cl. After each addition, the emf values were recorded at 25 \(\pm\) 1.0 °C then plotted versus the negative logarithmic value of the drug concentration \((-\log[\text{Ser-Cl, mol L}^{-1}])\).

To study the effect of soaking time, the electrodes were soaked in 1.0 mmol L\(^{-1}\) solution of Ser-Cl at 25 \(\pm\) 1.0 °C. A calibration graph was constructed for the sensor after different time intervals. The measurements were stopped when the slope of the graph deviates from the linear range by an absolute value of 0.2 mV.

| No. | Ion-associate% | Plasticizer (%) | Slope (mV/decade) | Linear range (mmol L\(^{-1}\)) | LOD (μmol L\(^{-1}\)) |
|-----|----------------|-----------------|-------------------|-------------------|-------------------|
| Ser-ST |
| 1 | 0.5 | 49.75 TCP | 39.20 | 0.01–3.38 | 2.13 |
| 2 | 1.0 | 49.50 TCP | 49.80 | 0.01–10.00 | 3.31 |
| 3 | 3.0 | 48.50 TCP | 48.99 | 0.01–10.00 | 4.07 |
| 4 | 5.0 | 47.50 TCP | 47.93 | 0.01–10.00 | 4.16 |
| 5 | 1.0 | 49.50 DOP | 49.32 | 0.01–10.00 | 3.13 |
| 6 | 1.0 | 49.50 DBP | 41.86 | 0.02–10.00 | 5.88 |
| 7 | 1.0 | 49.50 o-NPPE | 50.00 | 0.01–10.00 | 2.51 |
| 8 | 1.0 | 49.50 EHS | 44.53 | 0.04–4.47 | 11.75 |
| 9 | 1.0 | 49.50 EHA | 24.71 | 0.01–2.29 | 2.51 |
| 10 | 1.0 | 9.50 oleic acid + 40.00 ONPPE | 62.78 | 0.04–2.95 | 18.92 |
| Ser-PM |
| 11 | 1.0* | 49.50 TCP | 60.00 | 0.01–10.00 | 5.62 |
| 12 | 3.0 | 48.50 TCP | 58.61 | 0.01–10.00 | 3.01 |
| 13 | 5.0 | 47.50 TCP | 57.19 | 0.01–10.00 | 7.41 |
| 14 | 7.0 | 46.50 TCP | 57.52 | 0.01–10.00 | 7.76 |
| 15 | 1.0 | 49.50 DBP | 57.23 | 0.01–10.00 | 10.23 |
| 16 | 1.0 | 49.50 o-NPPE | 59.73 | 0.01–10.00 | 4.46 |
| 17 | 1.0 | 49.50 DOP | 52.41 | 0.01–10.00 | 5.13 |
| 18 | 1.0 | 49.50 EHA | 48.46 | 0.01–5.37 | 5.62 |
| Ser-SM |
| 19 | 1.0 | 49.50 TCP | 32.10 | 0.01–10.00 | 2.60 |
| 20 | 2.0 | 49.00 TCP | 45.32 | 0.01–10.00 | 3.46 |
| 21 | 3.0 | 48.50 TCP | 45.65 | 0.01–10.00 | 3.46 |
| 22 | 5.0 | 47.50 TCP | 48.75 | 0.01–10.00 | 6.46 |
| 23 | 7.0 | 46.50 TCP | 44.75 | 0.01–10.00 | 3.63 |
| 24 | 3.0* | 48.50 EHA | 53.24 | 0.01–10.00 | 4.85 |
| 25 | 3.0 | 48.50 o-NPPE | 51.76 | 0.01–10.00 | 7.76 |
| 26 | 3.0 | 48.50 DOP | 44.37 | 0.01–10.00 | 6.46 |
| 27 | 3.0 | 48.50 DBP | 52.22 | 0.01–10.00 | 16.22 |

* The selected composition.
of the calibration graph deviated largely from Nernstian value and the sensor becomes out of use.

The effect of the test solution pH on the potential values of the sensor system in different concentrations of Ser-Cl solutions was studied. 50 mL Ser-Cl was transferred to 100 mL titration cell and the tested ion-selective sensor in conjunction with the Ag/AgCl/Sat. KCl, and a combined glass electrode were immersed in the same solution. The mV and pH readings were simultaneously recorded. The pH of the solution was varied over the range of 2.0–12.0 by addition of very small volumes of 1.0 mol L\(^{-1}\) HCl and/or (0.1–1.0 mol L\(^{-1}\)) NaOH solution. The mV-readings were plotted against the pH-values for different concentrations.

To study the sensors thermal stability, calibration graphs were constructed at different test solution-temperatures covering the range 30–60\(^\circ\)C. The slope, usable concentration range and LOD of the sensors were determined at each temperature.

The influence of some inorganic cations and some excipients or additives which may be present in the pharmaceuticals on the ISS performance was investigated. The matched potential methods (MPM)\[31,32\] were applied. Among the different mixed solution methods, the matched potential method is unique in that it depends neither on the Nicolsky–Eisenman equation nor on any of its modifications. This method was recommended in 1995 by IUPAC as a method that gives analytically relevant practical selectivity coefficient values.

**Table 3** Selectivity coefficient values (\(-\log K_{\text{ser,pH}}^{\text{ss}}\)) for Ser-HCl membrane sensors at 25.0 ± 1.0\(^\circ\)C.

| Interferent     | Ser-PM sensor | Ser-SM sensor | Ser-ST sensor |
|-----------------|---------------|---------------|---------------|
| Na\(^+\)        | 2.77          | 2.49          | 3.20          |
| NH\(_4^+\)      | 2.71          | 2.40          | 2.60          |
| K\(^+\)         | 2.89          | 2.70          | 2.60          |
| Zn\(^{2+}\)     | -             | 2.18          | 2.62          |
| Ni\(^{2+}\)     | 2.90          | 2.15          | 2.30          |
| Mg\(^{2+}\)     | 2.75          | 2.30          | 2.61          |
| Cu\(^{2+}\)     | -             | 2.00          | 2.77          |
| Ca\(^{2+}\)     | -             | 2.48          | -             |
| Fe\(^{3+}\)     | 2.14          | 1.70          | 2.27          |
| Lactose         | 3.20          | 2.47          | 2.30          |
| Maltose         | 3.08          | 2.47          | 2.30          |
| Sucrose         | 3.08          | 2.45          | 2.30          |
| dL-Asparagine   | 3.14          | 2.90          | 2.77          |
| dL-Serine       | 3.14          | 2.85          | 2.77          |
| dL-Threonine    | 3.14          | 2.78          | 3.20          |
| d-Alanine       | 3.00          | 2.79          | 3.00          |
| l-Cysteine HCl  | 2.78          | 2.70          | 2.15          |
| dL-Histidine    | 2.30          | 2.00          | 1.60          |

**Fig. 1** Effect of pH on the potential response of Ser-PM (A), Ser-SM (B) and Ser-ST membrane sensors.

**Potentiometric determination**

The drug was determined using potentiometric titration and standard addition method. In potentiometric titration, an aliquot of the investigated compound (2–10 mL), 10 mmol L\(^{-1}\) Ser-Cl, was transferred into 100 mL titration cell and diluted to 50 mL by doubly distilled water; the resulting solutions were titrated against 10 mmol L\(^{-1}\) NaTPB using the corresponding sensors. The end points were determined from the conventional S-shaped curves by the zero and the first derivative plots. Similar method was done to 1.0 mmol L\(^{-1}\) Ser-Cl solution against 1.0 mmol L\(^{-1}\) NaTPB solution.

The standard addition technique was applied [20,33] in which a known incremental change is made through the addition of standard solution to the sample. This was achieved by
adding known volumes of standard Ser-Cl to 50 mL solution containing different amounts of Ser-Cl in its pure state or pharmaceutical preparations. The change in mV reading was recorded for each increment and used to calculate the concentration of the drug in sample solution. The concentration of the unknown solution was determined using the following equation:

\[
C_x = C_i \left( \frac{V_S}{V_X + V_S} \right) \left[ 10^{(\Delta E/S)} - \frac{V_X}{V_S + V_X} \right]^{-1}
\]

where \(C_x\) is the concentration to be determined, \(V_i\) is the volume of the original sample solution, \(V_s\) and \(C_s\) are the volume and concentration of the standard solution added to the sample under test, respectively, \(\Delta E\) is the change in potential caused by the addition, and \(S\) is the slope of the calibration graph.

**Analysis of tablets**

For analysis of tablets, 10 tablets were weighed and ground to fine powder and an appropriate weight from this powder was taken as samples and dissolved in 25 mL hot doubly distilled water then, the solution was filtrated in a 50 mL measuring flask and completed to the mark by doubly distilled water. The concentration of this solution was determined using potentiometric titration, and standard addition method as described for pure solutions.

**Surface characterization**

To study the change in surface morphologies of the prepared membrane films, a freshly prepared membranes containing PVC only, PVC + plasticizer, PVC + plasticizer + ion-associates and PVC + plasticizer + ion-associates + additives, were prepared and tested by SEM and AFM.

**Results and discussion**

**Potentiometric behavior of sensors**

The potentiometric behavior of the prepared sensors based on the composition of membrane mixtures is preliminary described. Several trials were carried out to reach a better linear response, Nernstian slope and low LOD, changing the per-
percentage of the ion-associate was the first trial. On the other hand, plasticizers play a vital role in the sensor performance as it is responsible for ion-associate salvation and distribution in the membrane matrix, thus, controlling the selectivity, sensitivity and LOD [15,21,34,35]. Also, the polar plasticizer lowers the membrane resistance as they contain a functional group with potential coordinate sites that can compete with the carrier [22]. In this work, several plasticizers were tested as potential plasticizers. For Ser-ST sensor, 0.5–5.0% were tested (sensors 1–4), Table 2. Sensor 1 (0.50% Ser-ST, 49.75% TCP, 49.75% PVC) has the lowest LOD of 2.13 mmol L⁻¹; however it has slope far than the Nernstian value, Sensor 2 contains 1% Ser-ST has high LOD, 3.31 mmol L⁻¹, but the slope was increased from 39.20 to 49.80 mV/decade. As Ser-ST percentage increases, the slope decreases. 1.0% Ser-ST and 49.50% PVC were mixed with 49.50% DOP, DBP, o-NPPE, EHA, and EHA, Table 2. The best plasticizer was found to be o-NPPE, sensor 7, which has low LOD of 2.51 mmol L⁻¹, wide linear range, 0.01–10.00 mmol L⁻¹, and slope, 50.00 mV/decade, Table 2, this may be due to the high polarity of o-NPPE [22]. Addition of fatty acids improves the sensitivity of sensors and accelerates the exchange at the sample membrane interface [36,37], oleic acid was added to improve the slope value to 62.78 mV/decade. It may be interposed between the matrix and ion-associate (Ser-ST) facilitating the effective binding and preventing the localization of the ion-associate in the membrane [22,35,38]. Although, the slope value was increased but the LOD increased from 2.51 to 18.92 mmol L⁻¹, Table 2. The best sensor in this case was found to be sensor 7 (1.0% Ser-ST and 49.50% PVC and 49.50% o-NPPE), Table 2. 1.0–7.0% Ser-PM were tested. Repeatable results were observed with sensor 11, (1.0% Ser-PM, 49.50% TCP and 49.50% PVC) with 5.62 mmol L⁻¹, 0.01–10.00 mmol L⁻¹, 60.00 mV/decade, LOD, linear range and slope, respectively. 1.0% Ser-PM and 49.50 PVC were mixed with 49.50% DBP, o-NPPE, DOP, and EHA, Table 2. The best compatible plasticizer was tested to be TCP, sensor 11, Table 2. For Ser-SM 1.0–7.0% were tested, Table 1. Sensor 19 (1.0% Ser-SM, 49.50% TCP, 49.50% PVC) has the lowest LOD, 2.60 μmol L⁻¹, but it has low Nernstian slope value 32.10 mV/decade. Sensor 22 (5.0% Ser-SM, 47.50% TCP, 47.50% PVC) has the highest slope value, 48.75 mV/decade. 5.0% Ser-SM and 47.50 PVC were mixed with 47.50% o-NPOE, EHA, DOP, and DBP, Table 2. Sensor 24 (5.0% Ser-SM, 47.50% EHA, 47.50% PVC) was the best one in this case.

Sensor life span

The period through which the sensor retains a Nernstian response is known as the sensor age or, life span. The performance characteristics of the investigated sensors were studied as a function of soaking time. For this purpose, the sensors were soaked in 1.0 mmol L⁻¹ Ser-Cl for different time intervals. The effect of soaking time on the slope of the calibration graphs, usable concentration range and LOD were studied for each sensor independently. As the responses of ISSs have been proved to be due to phase boundary process [13], so leaching of the active ingredient and plasticizer from the polymeric film is the primary reason for decreasing the sensitivity of the sensor [20,22,39]. The results of Ser-PM and Ser-SM sensors, show that they give Nernstian behavior up to 1 month and 24 days, respectively. For Ser-ST, it must be freshly prepared or kept in refrigerator.

Studying the sensor behavior in solutions of different pHs

The effect of pH of the test solutions on the sensor response was studied as described in the experimental part. The response was pH independent over the pH range 2.13–7.30, 2.25–7.24 and 2.12–7.85 for Ser-PM, Ser-SM and Ser-ST sensors, respectively. At higher pH values, the potential decrease due to the decrease of Ser⁺ concentration because of the formation of the free base by action of NaOH [13,21,22,40–43], Fig. 1.

Sensors selectivity

The effect of interference was studied using Ser-PM, Ser-SM, and Ser-ST membrane sensors. The response of the sensors toward different substances and ionic species such as inorganic cations, amino acids and sugars which may be present in the pharmaceutical preparations was checked. In the present study, matched potential method (MPM) was applied. The selectivity coefficient K_{ser,M} was determined in the presence of many species as described in the experimental part. Table 3 reflects a very high selectivity of these sensors for the studied drug.

The mechanism of selectivity is mainly based on the stereospecificity and electrostatic environment and it is dependent on compatibility between the locations of the lipophilicity sites in the two competing species in the bathing solution side and those present in the receptor of the ion associate [13,19,44]. The tested cations do not interfere because of differences in ionic size, mobility and permeability. The sensors are selective...
to Ser⁺ over a number of sugars and amino acids. The effect of interference was also observed by plotting the calibration curve using the studied sensors for different cations[16]. Fig. 2(A)–(C) shows that, there were limited interference with mono, di, and tri basic cations for the cited sensors. They also indicated that the tested cations would not significantly disturb the functioning of Ser-membrane sensors.

**Thermal stability of sensors**

Studying the response of the sensors at different temperatures is an important factor in the characterization of new sensors [45,46]. By knowing the temperature effect on the sensor we can determine the temperature range in which the sensor can be used. To study the thermal stability of the sensor, calibration graphs (sensor potential, \( E_{\text{sen}} \) vs. \( \log[\text{Ser-Cl}, \text{mol L}^{-1}] \)) were constructed at different test solution temperatures covering the range 30–60 °C. The slope, LOD and usable concentration range of the sensor at different test solution temperatures were studied. The results show that, the slope of the calibration graphs increased by increasing the test solution temperature but it is still in the Nernstian range. Fig. 3 shows a representative graph for the effect of temperature on Ser-PM membrane sensor at 30–60 °C.

To calculate the temperature coefficient \( (dE'/dt)_{\text{cell}} \) of the cell and the standard cell potentials, \( E°_{\text{cell}} \) were determined at different temperatures from the respective calibration plots as the intercept of these plots at-log [Ser-Cl, mol L⁻¹] = 0, [46,47]. The values of \( (dE'/dt)_{\text{cell}} \) and \( (dE'/dt)_{\text{sen}} \) are 3.70 × 10⁻⁴ and 4.50 × 10⁻⁴, 3.19 × 10⁻³ and 3.69 × 10⁻³, and 4.52 × 10⁻³ and 3.79 × 10⁻³ V/°C for Ser-PM, Ser-SM, and Ser-ST sensors, respectively, Fig. 4. These small values reveal high thermal stability of the studied sensors within the investigated temperature range.

**Analytical applications**

From the performance characteristics of the studied sensors, it was shown that most of these sensors have closely similar behavior (linear concentration range, working pH range and

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**Table 4** Determination of Ser-HCl in the pure form applying potentiometric titration.

| Sensor | Weight (mg) | Recovery ± S.E (%) | RSD (%) | Potential jump (mV) |
|--------|-------------|---------------------|---------|---------------------|
| Ser-PM | 1.03        | 106.66 ± 0.96       | 1.56    | 134.0               |
|        | 1.71        | 106.60 ± 0.70       | 1.14    | 130.0               |
|        | 3.43        | 104.50 ± 0.29       | 0.48    | 131.0               |
|        | 10.28       | 104.33 ± 0.69       | 1.15    | 169.0               |
|        | 17.14       | 99.20 ± 0.83        | 1.45    | 220.0               |
|        | 34.27       | 96.57 ± 0.30        | 0.53    | 216.0               |
| Ser-SM | 1.03        | 105.89 ± 0.48       | 0.79    | 130.0               |
|        | 1.71        | 103.00 ± 0.58       | 0.97    | 130.5               |
|        | 3.43        | 103.66 ± 0.33       | 0.56    | 117.5               |
|        | 10.28       | 103.22 ± 0.62       | 1.04    | 194.5               |
|        | 17.14       | 103.87 ± 0.70       | 1.16    | 197.5               |
|        | 34.27       | 101.93 ± 0.23       | 0.39    | 215.5               |
| Ser-ST | 1.03        | 103.22 ± 0.49       | 0.81    | 54.5                |
|        | 1.71        | 104.87 ± 0.52       | 0.86    | 55.5                |
|        | 3.43        | 100.57 ± 0.34       | 0.58    | 84.0                |
|        | 10.28       | 100.00 ± 0.77       | 1.33    | 93.0                |
|        | 17.14       | 100.20 ± 0.31       | 0.53    | 85.0                |
|        | 34.27       | 99.97 ± 0.26        | 0.45    | 88.0                |

* Average of three replicate measurement.
Ser-PM, Ser-ST and Ser-SM sensors were used in the determination of Ser-Cl in both pure raw material and its commercially available pharmaceutical formulations (Serlift®/C210 and Moodapex®/C210 tablets).

Two Potentiometric methods were used, the first involves potentiometric titration using NaTPB as titrant and the second is the standard addition method.

Potentiometric titration

Potentiometric titration for pure raw material

The potentiometric titration described in the experimental part was proved to be successful for the determination of Ser-Cl in its pure raw and pharmaceutical formulations using the new prepared sensors. The feasibility of such titration depends on the degree of completeness of the reaction. Since the equilibrium constant (K) of precipitation titration is inversely proportional to the solubility product, so the smaller the solubility product of the formed ion-associate, the sharper is the end point. The titration process was carried out manually in aqueous solution containing 0.34–34.27 mg Ser-Cl with average recoveries, relative standard deviation values and potential jumps at the vicinity of end point ranging from 96.57–106.66, 101.93–105.89 and 99.97–104.87%, 0.48–1.56, 0.39–1.16 and 0.45–1.33%, 130–220, 130.0–215.5 and 54.5–93.0 mV by Ser-PM, Ser-SM and Ser-ST membrane sensors, respectively, Table 4. From these results, it is concluded that high concentrations of the drug give sharp and large potential jump at the end point.

Potentiometric titration for the pharmaceutical preparations

The above results show that, the potential jump at the vicinity of end point reflects that the constructed sensors can be used successfully as indicator electrodes in potentiometric titrations of the drug in different sample solutions with very high percentage recovery. These new sensors were used for the determination of Ser-Cl in its pharmaceutical preparations (Serlift®, 100 mg/tablet and Moodapex®, 50 mg/tablet). 5.83 mmol L⁻¹ Serlift® and Moodapex® solutions were prepared by dissolving weight equivalent to 100 mg Ser-Cl as described in the experimental part. Different volumes of these solutions equivalent to 1.99–19.99 mg were taken and titrated against 5.83 mmol L⁻¹ NaTPB using the prepared membrane and CMCP sensors.

The results showed that upon using Ser-TPB, Ser-PM, Ser-ST and Ser-SM membrane sensors, the potential jumps at the vicinity of end point ranged from 98.95–103.32, 93.67–104.22, 95.63–103.13 and 94.00–102.43% and 0.11–0.41, 0.73–1.77, 0.75–1.15 and 0.50–0.94% for the potentiometric titration of Moodapex® and Serlift® tablets as shown in Table 5.

Potentiometric determination of Ser-Cl applying the standard additions method

The standard addition method described in the experimental part, was proved to be successful for the determination of Ser-Cl in the pure and pharmaceutical preparations. This determination is based on spiked samples with known amounts of the drug, using the prepared sensors as indicator electrodes.

| Weight (mg) | Recovery ± S.E% | RSD% | Recovery ± S.E% | RSD% | Recovery ± S.E% | RSD% |
|-------------|----------------|------|----------------|------|----------------|------|
| 1.99        | 101.83 ± 0.44  | 0.75 | 102.43 ± 0.29  | 0.50 | 101.83 ± 0.44  | 0.75 |
| 5.99        | 100.67 ± 0.51  | 0.87 | 98.44 ± 0.29   | 0.50 | 100.67 ± 0.51  | 0.87 |
| 9.99        | 103.13 ± 0.47  | 0.77 | –              | –    | 103.13 ± 0.47  | 0.77 |
| 19.99       | 103.93 ± 0.52  | 0.87 | –              | –    | 103.93 ± 0.52  | 0.87 |

Table 5 Determination of Ser-HCl in pharmaceutical preparations applying potentiometric titration.

* Average of three replicate measurement.
The obtained recovery values for the determination of 0.017, 0.171 and 1.713 mg pure Ser-Cl were 100.17, 100.05 and 96.05% using Ser-PM. It was determined in the pharmaceutical formulations, Moodapex® and Serlift® with recovery and RSD ranged 97.81–99.13 and 0.60–1.47%, respectively.

Surface characterization of Ser-membrane sensors
Surface characterization plays a significant role in ion selective electrode [48–56]. The current work tends to relate the data obtained from the potentiometric measurements to the surface morphology of membrane sensors. The scanning electron microscope (SEM) is one of the most versatile instruments available for the examination and analysis of the microstructure morphology of the conducting surfaces. The microspores, amorphous phase and the chain segments of the plasticized polymer electrolytes are responsible for the enhancement of ionic conductivity.

For Ser-PM sensor
The calibration graphs of 100.00% PVC, 50.00% PVC + 50.00% TCP, 49.50% PVC + 49.50% TCP + 1.00% Ser-PM and 49.25% PVC + 49.25% TCP + 1.00% Ser-PM + 0.50% NaTFMPB shows that adding Ser-PM increases the slope value from 22.74 to 60.00 mV/decade, Fig. 5. Fig. 6 shows SEM images for these membranes. The PVC-membrane without the Ser-ion-exchanger exhibited a physically tight structure while the membranes with the Ser-ion-exchanger showed a surface with a loose and permeable structure that included grains to diffuse the Ser-ion [56]. The rearrangement and the size of the grains change as a result of adding an active ingredient where the slope and LOD amount to 60.00 mV/decade and 5.62 μmol L⁻¹, respectively, Fig. 5. It was modified by adding NaTFMPB to the prepared mixture, this rearrangement and size change of the formed grains lead to increasing the slope and LOD values to 63.42 mV/decade and 8.12 μmol L⁻¹, respectively. Typical 2 and 3D AFM images of these are in close agreement with the data obtained from SEM.

For Ser-ST sensors
Calibration graphs for sensors composed of 100.00% PVC, 50.00% PVC + 50.00% ONPPE, 49.50% PVC + 49.50% ONPPE + 1.00% Ser-ST and 49.50% PVC + 40.00% ONPPE + 1.00% Ser-ST + 9.50% oleic acid were constructed, Fig. a sup. SEM images of them show that formation of grains differs in size and arrangement than those formed upon adding o-NPPE to the prepared mixture, Fig. b sup.(B) (slope = 32.99 mV/decade). Adding Ser-ST increased the number of grains, Fig. b sup.(C) (slope = 50 mV/decade, LOD = 2.51 μmol L⁻¹). A large change in the surface morphology was observed upon adding oleic acid to membrane C which may be attributed to the presence of two different plasticizers, Fig. b sup.(D) (slope and LOD amounted to
62.78 mV/decade and 18.92 μmol L\(^{-1}\), respectively). Typical 2 and 3D AFM images of these membranes are in close agreement with the data obtained from SEM.

For Ser-SM sensors

Membranes composed of 100.00% PVC, 50.00% PVC + 50.00% EHA, 48.50% PVC + 48.50% EHA + 3.00% Ser-SM and 48.25% PVC + 48.25% EHA + 3.00% Ser-SM + 0.50% NaTPB, were prepared and used for the determination of Ser-Cl by constructing the calibration graphs of them. Fig. c sup. Fig. d sup.(A-D) shows the SEM images of these membranes. It was observed that upon adding EHA to the prepared mixture, the formed grains differ in size and arrangement than those formed with TCP and o-NPPE, Fig. d sup.(B) (slope = 43.37 mV/decade). Upon adding Ser-SM, the surface morphology and the grains arrangement changed, Fig. d sup.(C) (slope = 53.24 mV/decade, LOD = 4.85 μmol L\(^{-1}\)). After adding NaTPB to membrane C, the grains enlarged and their arrangement changed Fig. d sup.(D) (slope and LOD amount to 57.39 mV/decade and 6.16 μmol L\(^{-1}\), respectively). Typical 2 and 3D AFM images of these membranes are in close agreement with the data obtained from SEM.

Conclusions

The suggested sensors were characterized to obtain the best composition and conditions for constructing the calibration curves. They exhibit near Nernstian response with slope and limit of detection 50.00, 60.00 and 53.24 mV/decade and 2.51, 5.62 and 4.85 μmol L\(^{-1}\) for Ser-ST, Ser-PM and Ser-SM membrane sensors, respectively. Linear range is 0.01–10.00 for the three sensors. The response time is less than 10 s. The selectivity studies revealed that the prepared sensors are highly selective toward Ser\(^{+}\) over a wide range of other cations and molecules. These sensors were successfully applied for the determination of Ser\(^{+}\) in pure raw material and pharmaceutical formulations. Scanning electron microscope was done for the prepared membranes in absence and presence of the modifier (ion-associates). The data indicated that the surface morphologies in close agreement with the potential dynamic data. Typical 2 and 3D AFM images of these membranes confirmed the data obtained from SEM and potential dynamic study.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jare.2014.11.005.

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