Paper-Based Potentiometric Device for Rapid and Selective Determination of Salicylhydroxamate as a Urinary Struvite Stone Inhibitor

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1. INTRODUCTION

The hydroxamic acids have wide and diverse applications in biology and medicine. These compounds have revealed antibacterial and antifungal effects and can be considered as selective inhibitors for a variety of enzymes.1−7 Salicylhydroxamic acid (SHAM) or hydroxybenz-hydroxamic acid (HBHA), as a member of this family, can be considered as an intense and irreversible inhibitor for use against bacteria. It is used as a therapeutic agent for preventing the formation of calcium oxalate stones in kidneys.8 It is also used as a urease enzyme inhibitor, and so it prevents the formation of phosphate stones by reducing ammonia formation and retains the acidity of urea. In addition, it is used to reduce serum uric acid and reduces the incidence of urate and uric stones.9 SHAM is also used as an analytical spectrophotometric reagent for determination of iron, molybdenum, vanadium, and uranium ions.10,11

Different analytical methods have been reported in the literature for SHAM determination, two among which are spectrophotometry10,12−15 and liquid chromatography.16−18 The reported spectrophotometric methods have low sensitivity, involve reactions with metal ions under strictly controlled conditions, and have poor selectivity because of the interference arising from the major drug degradation and metabolite products. Chromatographic methods suffer from different drawbacks such as time consumption because they require several manipulation steps, require expensive equipment, and require highly skilled analysts.

Electrochemical methods are one of the most recommended analytical methods because they are simple to use, robust, sensitive, selective, and cost-effective.19,20 Only a few reports are available on voltammetric measurements of SHAM.21,22 These reported methods have poor selectivity, low precision, and narrow applicability. One of the most exciting and promising electrochemical methods is that based on potentiometric transduction. It overcomes the limitations of the other electrochemical methods. A wide variety of conventional potentiometric electrodes are commercially available in the
local market, and many are reported in the literature for sensitive and selective monitoring of different ionic species in different application fields. Only few reports are available on the potentiometric determination of SHAM.

Recently, great attention has been paid towards paper-based analytical devices as a powerful tool for environmental monitoring and point-of-care (POC) testing. This can be explained by their self-pumping ability and suitability for different analytical methods. The use of paper in the design of these analytical devices lies in its low cost, lightweight, flexible characteristics, compatibility with a wide range of patterning methods, and easily disposable flow generation without the need of external pumps. Due to all of these advantages of paper-based analytical devices, a significant growth of academic research has been seen in the past decade. These platforms have the ability to conduct sensitive and selective monitoring that is routinely performed using bench equipment.

Herein, we present for the first time a new design of an electrochemical paper-based analytical device for SHAM drug determination by integrating both the Ag/AgCl reference electrode and the SHAM-selective electrode. This paper-based device provides a stable reference potential for rapid, direct, and accurate assessment of SHAM levels. In addition, the device is inexpensive, lightweight, portable, easily disposable, and appropriate for mass production. There is no need for storage of the reference electrode in this device. It revealed a slope sensitivity of $-59.3 \pm 0.7 \text{ mV/decade}$ with a detection limit of $0.7 \mu\text{M}$. The advantages of the presented planar-paper-based device include its adequate repeatability, good accuracy, high analytical throughput, good response stability, and high selectivity. The presented device is thus recommended for SHAM assessment in different pharmaceutical products.

2. RESULTS AND DISCUSSION

2.1. Paper-Based Device Characteristics. The surface of the paper was painted with carbon ink. The resistance remained constant and reached about $95 \Omega$ after drying in the oven at 100°C for 10 min. The mechanical flexibility of the paper-based analytical device was checked after bending the paper several times with different angles of bending (i.e., 30, 60, and 90°). The potential and resistance drift were recorded and found to be $2.5 \pm 0.8 \text{ mV}$ and $2.5 \pm 2.3 \Omega$, respectively. From these obtained results, we conclude that the prepared paper-based sensor had a high conductivity and good mechanical flexibility. A schematic representation of the paper-based analytical device is shown in Figure 1.

2.2. Potentiometric Performance of the SHAM-Paper-Based Sensor. The analytical performance of the presented SHAM paper-based sensor was evaluated according to IUPAC guidelines. Figure 2 shows the calibration plots for the anionic response exhibited by metalloporphyrin membrane-based sensors is based on the oxidation state of the metal-center ion as previously reported. The potentiometric response shown by the Sn IV-TPP ionophore is the charged-carrier mechanism, in which a positively charged porphyrin complex binds to the anion to form a cationic complex within the membrane phase. Hence, lipophilic–anionic sites are necessary as additives to the membrane to stabilize the complex formed. The mechanism of the potentiometric response for the fabricated SHAM sensor is shown in Figure 3.
For comparison, the performance characteristics of the sensor on a glassy-carbon substrate (GC/SHAM-ISE) were studied. The sensor revealed a potentiometric slope of $-57.8 \pm 1.2$ mV/decade ($R^2 = 0.9997$) over the linear range $8.0 \times 10^{-7}$ to $1.0 \times 10^{-3}$ M, and a detection limit of 0.82 μM. Near-Nernstian sensitivity and comparable performance to the conventional ISEs (GC/SHAM-ISE) were obtained. This proves that the presented paper-based sensor can be successfully considered as a powerful tool for obtaining low-cost and disposable planar-paper-based sensing devices for potentiometric measurements.

The time response of the presented paper-based analytical device was evaluated after measuring the potential corresponding to each concentration decade (i.e., from $1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ M SHAM concentration) for 2 min. The time required to attain the equilibrium state was found to be $<5$ s. This reflects the excellent potential of using these sensors in de-centralized analysis.

The pH effect of the presented sensors was also investigated. It was found that at pH $> 8.5$, OH$^-$ ions show severe interference during the measurement of SHAM. This can be attributed to the favorable competition for the axial coordination sites of the central Sn(IV). The detection limit toward SHAM increases as the pH increases, ranging from $1.0 \times 10^{-6}$, $8.7 \times 10^{-7}$, and $5.0 \times 10^{-7}$ M at pH 5.5 to $1.0 \times 10^{-4}$, $9.5 \times 10^{-5}$, and $7.0 \times 10^{-5}$ M at pH 9.0 for sensors I, II, and III, respectively. At pH 7.4 (the physiological pH), the detection limit is about $2.5 \times 10^{-6}$, $2.0 \times 10^{-6}$, and $7.0 \times 10^{-7}$ (total drug concentration) for sensors I, II, and III, respectively. These values are quite sufficient for SHAM quantification in pharmaceutical formulations and physiological fluids.

### Table 1. Potentiometric Analytical Performance for the SHAM-Paper-Based Analytical Device

| parameter                  | sensor I          | sensor II         | sensor III         |
|----------------------------|-------------------|-------------------|--------------------|
| slope (mV/decade)          | $-50.9 \pm 1.1$   | $-52.1 \pm 1.4$   | $-59.3 \pm 0.7$    |
| correlation coefficient ($r^2$) | 0.9979            | 0.9981            | 0.99991            |
| detection limit (M)        | $2.5 \times 10^{-6}$ | $2.0 \times 10^{-6}$ | $7.0 \times 10^{-7}$ |
| lower limit of linear range (M) | $7.0 \times 10^{-6}$ | $4.0 \times 10^{-6}$ | $1.0 \times 10^{-6}$ |
| working pH value           | 7.2               | 7.2               | 7.2                |
| response time (s)          | <5                | <5                | <5                 |
| accuracy (mV%)             | 99.2              | 101.2             | 98.4               |
| intraday precision ($n = 9$) (RSD%) | 0.5               | 0.8               | 0.7                |
| interday precision ($n = 10$) (RSD%) | 0.9               | 1.1               | 0.7                |
| robustness (%)             | 0.7               | 0.6               | 0.5                |
| ruggedness (%)             | 0.4               | 0.7               | 0.3                |

**Figure 3.** Schematic representation of the response mechanism of the presented sensor.
Table 2. Selectivity Coefficient Values for SHAM-Paper-Based Sensors

| Interfering Ion, B | Interfering Ion, A | Sensor I   | Sensor II  | Sensor III  | TDMAC |
|-------------------|-------------------|------------|------------|-------------|-------|
| Cl^−              | −2.1 ± 0.3        | −3.6 ± 0.3 | −1.8 ± 0.1 | −1.9 ± 0.3  |       |
| ClO_3^−            | −0.5 ± 0.02       | −2.1 ± 0.7 | +1.9 ± 0.4 | +2.5 ± 0.4  |       |
| Sal^−              | −0.7 ± 0.01       | −1.8 ± 0.5 | +0.1 ± 0.02| +0.4 ± 0.02 |       |
| I^−                | −1.4 ± 0.4        | −2.3 ± 0.4 | +0.2 ± 0.05| +0.5 ± 0.01 |       |
| Br^−               | −1.9 ± 0.2        | −3.7 ± 0.2 | −1.7 ± 0.3 | −1.9 ± 0.2  |       |
| NO_3^−             | −1.8 ± 0.4        | −3.6 ± 0.1 | −1.0 ± 0.6 | −0.5 ± 0.06 |       |
| SCN^−              | −0.8 ± 0.05       | −2.5 ± 0.6 | +0.5 ± 0.02| +1.1 ± 0.5  |       |
| urate              | −3.2 ± 0.5        | −4.1 ± 0.4 | −2.9 ± 0.3 | −3.5 ± 0.4  |       |
| benzoate           | −0.7 ± 0.2        | −1.7 ± 0.5 | −0.2 ± 0.02| +0.2 ± 0.04 |       |
| acetyl salicylate   | −0.6 ± 0.03       | −1.5 ± 0.3 | −0.1 ± 0.04| +0.1 ± 0.03 |       |

^Average of 3 measurements.

2.3. Analytical Method Validation. 2.3.1. Linearity Range and Detection Limit. The performance characteristics of the displayed sensors revealed a linear dynamic range between 1.0 × 10⁻³−7.0 × 10⁻⁶ M, 1.0 × 10⁻³−4.0 × 10⁻⁶, and 1.0 × 10⁻³−1.0 × 10⁻⁶ M with near-Nernstian slopes of −50.9 ± 1.1, −52.1 ± 1.4, and −59.3 ± 0.7 mV/decade for sensors I, II, and III, respectively. The calibration plots with regression equations were found to be y (mV) = −50.9 log x−112.9, y (mV) = −52.1 log x−121.6, and y (mV) = −59.3 log x−166.6 with a correlation coefficient of 0.9979, 0.9981, and 0.9991 between the standard SHAM concentration (x) and the potential measured in triplicates (n = 3) for sensors I, II, and III, respectively. As shown in Table 1, the data obtained from the validation protocol supported both the applicability and suitability of the proposed paper-based electrodes for routine analysis of the SHAM drug.

The detection limit of the SHAM paper-based sensor (DL) was evaluated as the concentration corresponding to the intersection of the extrapolated linear segment of the calibration graph. The DLs of the presented sensors were found to be 2.5 × 10⁻⁶, 2.0 × 10⁻⁶, and 7.0 × 10⁻⁷ M for sensors I, II, and III, respectively.

2.3.2. Method Precision and Accuracy. The precision of the developed method was evaluated using intra- and interday tests. Three different standard SHAM solutions (i.e., 10, 20, and 50 μM) were analyzed for conducting these tests. The spread of results when the SHAM samples were measured on the same day and on different days confirmed the agreement between the results obtained with the SHAM reference sample under different conditions with different sensor assemblies and pH meters at different times. The relative standard deviation (% RSD) for intra- and interday precision for all of the three concentration levels were below 0.62 and 0.71%, respectively. This indicates the good precision of the presented method.

The method accuracy was evaluated by measuring a spiked known amount of the standard SHAM solution. Each sample was analyzed in triplicate (n = 3). The obtained accuracy was found to be 98.4−101.2%.

2.3.3. Method Robustness/Ruggedness. Method robustness/ruggedness was evaluated by examining the impact of the use of either 30 or 50 mM PBS, pH 7.2, during the study of the tested SHAM concentration to incorporate minor changes in the concentration of PBS. The calculated recovery percentage was 99.5 and 99.3% for the two buffer concentrations, respectively. The %RSD value was found to be <0.7%. The obtained results using another pH-meter model (Jenway 3505, U.K.) were compared to those obtained using the pH-meter model (PXSJ-216, China). The findings obtained are similar and the procedure also demonstrates validity (Table 1).

2.4. Sensor’s Selectivity. The selectivity of the SHAM paper-based sensor was evaluated toward the SHAM drug using the method presented by Bakker (i.e., the modified separate solution method (MSSM)). The selectivity coefficient values of the presented sensor over different interfering ions are presented in Table 2. It was found that the anion selectivity behavior of the presented paper-based sensor follows the anti-Hofmeister pattern. It exhibited an enhanced selectivity toward SHAM in the presence of a higher number of lipophilic anions (e.g., ClO_4^−, SCN^−, sal^−, and I^−). The oxidation state (+IV) of the Sn ion in SnIVTPP employs the selective ionophore to work as a charged-carrier ionophore. Therefore, addition of anionic sites such as KTpCIPB has an important role in improving the potentiometric selectivity as compared to those membranes without the anionic additives. On the contrary, addition of cationic sites such as TDMAC reverts the selectivity to the Hofmeister pattern. For membranes based on TDMAC only as a classical ion exchanger, the anion selectivity behavior showed no difference from that obtained by membranes based on SnIVTPP in the presence of TDMAC as a cationic additive. From the selectivity values shown in Table 2, we can conclude that the anion selectivity behavior of SnIVTPP is independent of the relative lipophilicity of the primary to the interfering anion. It is mainly dependent on the relative binding constants of the.
primary to the interfering anion with the SnIV ion in the SnIV-TPP ionophore.

2.5. Sensor’s Life Span. It is very important to analyze the life span of the presented paper-based sensors. This was evaluated by examining the day-to-day performance characteristics of these paper-based sensors by performing a daily calibration. Over three working days, for the same paper-based sensor, no change was observed in both the slope and the detection limit. A noticeable decay in these characteristics was observed starting from the fourth to the sixth day. A complete failure of the sensor was observed after one week of working (Figure 4). Therefore, all performance characteristics of the presented paper-based analytical device were found to be reproducible within their original values over a period of one week.

2.6. SHAM Assessment. The presented paper-based analytical device was successfully applied to assess the SHAM concentration in different commercially available pharmaceutical preparations. The drug assay was carried out by direct potentiometry using a standard calibration curve constructed using pure SHAM solutions prepared in 30 mM PBS, pH 7.2. Table 3 shows that the data analysis for two different SHAM samples (five replicate measurements) was acceptable, which confirms the applicability of the presented device for SHAM determination.

The paper-based analytical device was successfully applied for SHAM determination in human blood serum. The samples were collected and spiked with different amounts of SHAM. The results yield an average recovery of 98.6% with a relative standard deviation of ±0.9%. The results obtained for determination of SHAM in spiked human serum samples are listed in Table 4.

3. CONCLUSIONS

Paper-based analytical devices have gained attention as an attractive tool for reliable trace analysis. In addition, they offer an attractive outlook due to their economic aspects. Herein, a novel paper-based potentiometric device was designed, fabricated, and characterized for SHAM drug assessment. The device comprises both working and reference electrodes on a paper substrate. It is suitable for future mass production due to its realization of relatively low-cost off-the-shelf components. The presented device requires no pre-conditioning or any further liquid-handling requirement. The device can measure the SHAM drug with a detection limit of 0.7 μM over a concentration range from 1.0 × 10⁻⁶ to 1.0 × 10⁻⁵ M with a Nernstian slope of −59.3 ± 0.7 mV/decade. Intra- and interday precision were measured and found to be 1.7%. The relative standard deviation (RSD%) (n = 5) was calculated as 2.43% after utilizing five different electrodes (n = 5). The effect of adding ionic additives on the selectivity behavior of the prepared sensors was evaluated. The selectivity pattern showed a non-Hofmeister selectivity pattern in the presence of anionic additives, with enhanced potentiometric selectivity for SHAM over different lipophilic anions (e.g., ClO₄⁻, SCN⁻, and I⁻). The presented SHAM paper-based analytical device was applied successfully with high reproducibility for trace SHAM quantification in pharmaceutical preparations. In addition, this work can be directed to further low-cost and disposable paper-based analytical devices for potentiometric sensing produced at large scales with high speed and reproducible paper-printing technology. The advantages and limitations of the previously reported potentiometric sensors in comparison with the presented sensors are shown in Table 5.

4. EXPERIMENTAL SECTION

4.1. Apparatus. The potential measurements were carried out using a pH/mV meter (PXJS-216) (INESA Scientific Instrument Co., Ltd., Shanghai, China). A combined glass electrode (Orion 91-01) was used for all pH measurements.

4.2. Chemicals and Reagents. SnIV-tetraphenylporphyrin (SnIV-TPP), salicylhydroxamic acid (SHAM), potassium tetrakis (4-chlorophenyl) borate (KTpClPB) with >98% purity, 2-nitrophenyl octyl ether (o-NPOE), tridodecylmethylammonium...
nium chloride (TDMAC), high-molecular-weight poly(vinyl chloride) (PVC), and tetrahydrofuran (THF) were obtained from Sigma-Aldrich (St. Louis, Missouri, MO). Polyvinyl butyral (PVB) was obtained from Quimidroga S.A. (Barcelona, Spain). Ag/AgCl ink (E2414) was purchased from Ercon (Wareham, MA). MWCNTs were purchased from EPRI (Cairo, Egypt). Conductive-carbon ink was purchased from Bohui New Materials Tech. Co. Ltd., (Jiangsu, China). This ink is a composite between a conductive-carbon, metal powder, and resin, all of which are organic solvents. All solutions and standards were prepared using deionized water (18.2 MΩ·cm) obtained from Milli-Q PLUS (Millipore Corporation, Bedford, MA).

A definite weight of pure SHAM drug was dissolved in 100 mL of double-deionized water to prepare a stock solution of $1.0 \times 10^{-5}$ M. Phosphate-buffered solution, 30 mM, of pH 7.2 was used as a background during the potentiometric measurements. The working solutions ($1.0 \times 10^{-6} - 1.0 \times 10^{-8}$ M) were prepared with accurate dilutions using the phosphate-buffered solution.

4.3. Design of the Paper-Based Analytical Device. The paper-based analytical device was made from Whatman filter paper Grade 5. To prepare the working SHAM electrode, the qualitative filter paper was painted with carbon ink to form a homogeneous layer. The reference electrode was prepared after painting the paper with Ag/AgCl ink until a homogeneous layer was formed, and allowed to dry. The conductive papers were dried at 100 °C for 10 min until the carbon ink adhered to the surface of the paper. After drying, the conductive papers were sandwiched between two adhesive plastic masks, one of which had orifices (3.0 mm diameter) that would leave the conductive material exposed and acting as the electroactive windows. The SHAM-sensing membrane was prepared by dissolving 2.0 mg of SnV3TPP, 10 mol % of the ionic additive (either KTPCIPB or TDMAC), 33.0 mg of PVC, 64.0 mg of o-NPOE, and 1 mg of MWCNTs in 2 mL of THF. Fifteen microliters of this membrane cocktail was drop-cast onto the carbon orifice. The reference membrane was prepared by dissolving 78 mg of PVB and 50 mg of NaCl in 1 mL of methyl alcohol. Again, 15 μL of this reference-membrane cocktail was drop-cast onto the Ag/AgCl orifice. For electrode conditioning, the working electrode is firstly conditioned in $10^{-2}$ M SHAM solution for 5 h, followed by conditioning in $10^{-5}$ M SHAM solution for 30 min. The reference Ag/AgCl electrode was conditioned in 3 M KCl for 12 h.

4.4. SHAM Assay in Pharmaceutical Formulations. Ten capsules of SHAM (300 and 600 mg/capsule, El-Nasr Co. pharm. & chem. Indus., Cairo, Egypt) were taken and their contents were emptied. Hundred milligrams of the content was weighed and dissolved in 30 mM PBS, pH 7.2, transferred into a 100 mL calibrated volumetric flask, and shaken well. To 9 mL of PBS, 1 mL of the test solution was added and placed in a 20 mL beaker. The electrochemical cell was then inserted into this solution, and the potential reading after stabilization was recorded. The quantity of SHAM was evaluated using the prepared calibration curve.

SHAM was also determined in human serum; a 2.0 mL sample of clear blood serum was diluted to 50 mL with 30 mM PBS, pH 7.2. The sample was spiked with different known amounts of the SHAM drug (e.g., $10-50 \mu M$/SHAM). The mixture was mixed and used for SHAM measurements. Nine milliliters of 30 mM PBS, pH 7.2, was placed in a 20 mL beaker, and 1 mL of the sample solution was then introduced. The paper-based analytical device was then immersed into the sample solution, and the potential values were plotted versus the log [SHAM] concentration to construct the calibration plot.

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Author Contributions

The listed authors contributed to this work as follows: A.H.K. and A.E.A. designed the concepts of the work, interpretation of the results, performed the experimental part, and prepared the manuscript. A.H.K., H.S.M.A., and A.E.A.EA cooperated in the preparation of the manuscript, and A.H.K. performed the revision before submission. A.A.A and H.S.M.A provided the financial support for the work. All authors have read and agreed to the published version of the manuscript.

Notes

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