Construction of New Coated Carbon Electrodes for Determination of Sildenafil Citrate Drug

Aveen K. Mohammed¹, Ali I. Khaleel², Nawzad N. Ahmed³

¹,²Department of Chemistry, College of Science, Tikrit University, Tikrit, Iraq.
³Department of Chemistry, College of Science, Sulaymaniyah University, Sulaymaniyah, Iraq.

¹chemtrysara@yahoo.com, ²ali.ebrahim@tu.edu.iq, ³Nawzad.ahmed@univsul.edu.iq

Abstract

In this research, new coated carbon electrodes were constructed and used for the determination of Sildenafil citrate (SILC) drug. The electrodes were constructed by preparing ion-pair for (SILC) with phosphotungstic acid (PTA) or phosphomolybdic (PMA) acid using dibutyl phthalate (DBP) as a plasticizer. These electrodes showed good sensitivity towards SILC with linear range of (1.0×10⁻⁷-1.0×10⁻²) M, correlation coefficient, (0.9990), the life time (120) days, optimum temperature range (23-65) °C and optimum pH range (2-5) for both electrodes, limit of detection (5.055×10⁻⁸ and 5.116×10⁻⁸) M, slope (57.29 and 59.10) mV/decade for SILC-PTA and SILC-PMA electrodes respectively. These electrodes were successfully applied for determination of SILC in pure and pharmaceutical preparation form(tablets) with recovery of not less than 98%.

Keywords: Coated carbon electrode, Sildenafil citrate drug, Potentiometry method.

DOI: http://doi.org/10.32894/kujss.2020.15.2.1
بناء أقطاب جديدة من الكربون المغلف لتقدير عقار السيلدينافيل سترات

أفني خيرالله محمد1، علي إبراهيم خليل2، نوزاد نوري أحمد3

قسم الكيمياء، كلية العلوم، جامعة تكريت، تكريت، العراق.

قسم الكيمياء، كلية العلوم، جامعة السليمانية، السليمانية، العراق.

1chemistrysara@yahoo.com, 2ali.ebrahim@tu.edu.iq, 3Nawzad.ahmed@univsul.edu.iq

الملخص

في هذا البحث تم بناء أقطاب جديدة من الكربون المطلي واستخدامه لتقدير عقار السيلدينافيل سترات. وتم تصنيع هذه الأقطاب لتحضير مزيج أيوني للعقار مع حامض الفوسفورتستك أو حامض الفوسفورموليبديك واستخدام ثنائي بيوتيل الفثالين كملدن. هذه الأقطاب أعطت حساسية جيدة لعقار السيلدينافيل سترات بمدى خطي (10^-7 - 10^-2) مولاري مع معامل ارتباط 0.9990، وعمر زمني 120 يوم، مدى درجة الحرارة المثلى (23 - 65) درجة مئوية ومدى الدالة مولاري وميل (59.10 و57.29) و(9.10×10^-5 و0.555) و(5.116×10^-5) الحمضية (2-5) كلا القطبين وحد الكشف لكل من قطب حامض الموليبديك وحامض الفوسفورتستك على التوالي. تم استخدام هذه الأقطاب بنجاح لتقدير العقار بشكلها النقي وفي الحبوب باسترجاعية لاتقل عن 98%.

الكلمات الدالة: قطب الكربون المطلي، عقار السيلدينافيل سترات، طريقة الجهدية.

DOI: http://doi.org/10.32894/kujss.2020.15.2.1
1. Introduction:

Viagra (Sildenafil citrate SILC) is a white to off-white crystalline powder of molecular weight of 666.7 g/mole and its formula is C\textsubscript{28}H\textsubscript{38}N\textsubscript{6}O\textsubscript{11}S. Has chemical structure showed in Fig. 1. SILC is the first drug which approved for the treatment of erectile dysfunction, due to organic causes SILC is an effective and best drug for erectile dysfunction (ED) [1-3]. The studies show that Viagra successfully treats erectile dysfunction in men with comorbidities such as hypertension [4], diabetes [5], and depression [6]. The side effects of SILC have been reported such as headache, congestion, flushing and dyspepsia [7-9].

Different methods have been reported for the determination of SILC drug in products and biological samples such as high-performance liquid chromatography (HPLC) [10,11], spectrophotometry [12-13], fluorometry [15], voltammetry [16] atomic absorption [17] and LC-ESI-MS [18,19]. The present work describes preparation, characterization and application of coated carbon electrodes for determination of Viagra in pure and pharmaceutical preparations. Performance characteristics of (SILC-PMA) and (SILC-PTA) coated carbon electrodes reveal low detection limit, high sensitivity, good selectivity, fast response time, very long life time and application with accurate determination of Viagra in pharmaceutical preparations.

![Sildenafil citrate](image)

**Fig. 1:** Chemical Structure of SILC drug.
2. Reagents and Materials:

All chemicals were of analytical reagent grade. Distilled water was used for the preparation of stock solutions. The following materials: SILC (SDI, Samara-Iraq) Poly vinyl chloride (PVC) high molecular weight (Fluka), Di butyl phthalate (Sigma, Germany), Acetic acid (Merck, Germany), Carbon rod (Ultra carbon com), Tetra hydro furan. (THF) (Aldrich, USA). phosphomolybdic acid (BDH, England) and Phosphotungstic acid (Merck, Germany) were used in this work. A stock solution of 0.01 M of SILC drug was prepared by dissolving 0.6667 g in 5 ml of 1M acetic acid then completed to 100 ml distilled water. Dilute solutions (1.0×10⁻⁸ to 1.0×10⁻³) M of drug were prepared by appropriate dilution with distilled water. Jeansiagra tablets (50 mg SILC) Laborite pharmaceuticals ltd- India and Vegamax (100 mg SILC) MacLeod’s pharmaceutical LTD-India were purchased from local pharmacies.

2.1 Apparatus:

Potentiometric measurements were performed using HANNA instruments301 pH meter, HANNA HI2216 pH meter, Jenway3545 pH meter, calomel electrodes No 13-639-52, Fisher Scientific Co. (Germany). For elemental analysis CHN ElementarIsoprime100-Germany was used.

2.2 Sample Preparation:

Four tablets of Jeansiagra 50 mg/tablet (the total tablets weight 0.9746 g) and four tablets of Vegamax 100 mg/tablet (the total tablets weight 2.1404 g) were finely powdered and mixed homogeneously, (0.2437) g of Jeansiagra and (0.5351)g of Vegamax powder was dissolved in (5) ml acetic acid (1.0 M) then adding amount of distilled water in a 100 mL beaker. The resulting solution was then filtered through Whatman filter paper (No. 42) and the volume was completed to the mark with water in a 100-mL volumetric flask. Solutions of concentration range of (1.0×10⁻⁷-1.5×10⁻³ and 1.0×10⁻²-7.5×10⁻⁴) M for Vegamax and Jeansiagra respectively were prepared by appropriate dilution with distilled water.

2.3 Stock Solutions of Interfering Ions:

Solutions of 1.0×10⁻³ M for each of NaOH, NaCl, BaCl₂.2H₂O, CaCl₂.2H₂O, NH₄Cl, Fe(NO₃)₃.9H₂O, Fructose, Cholesterol, Uric acid, Methyl paraben (M.H.B), Propyl paraben (P.H.B), Talc, Mg.stearate, Talc and Titanium oxide were prepared by dissolving appropriate...
amount of these materials in distilled water in 50ml volumetric flasks.

2.4 Preparation of Ion-Pairs:

The ion-pairs were prepared by mixing 50 mL of equimolar of \((1.0 \times 10^{-2})\) M SILC to 50 mL of either PTA or PMA, a light orange and yellow precipitate of SILC-PTA and SILC-PMA were formed respectively. The precipitate was filtered through Whitman filter paper (No. 42), and washed several times with distilled water. The precipitate was left for 2 days to dry at room temperature.

2.5 Preparation of Coated Carbon Sensor:

The two sensors were prepared by using a pure carbon rod 4.0 cm length and 4.0 mm diameter using a tight polyethylene tube. The sensors surface were coated with the active membrane by dipping one end in the coating mixture \([10 \text{ mg ion-pair (SILC-PTA) or (SILC-PMA), } 190 \text{ mg poly vinyl chloride (PVC), } 0.35 \text{ mL plasticizer di butyl phthalate (DBP) and } 1 \text{ mL THF}]\) for seven times and allowing to dry in the air for 5 min each time. The other end of carbon rod was left for connection [17,18].

3. Results and Discussion:

SILC-PTA and SILC-PMA as an electro active compounds were used to prepare new sensors. Elemental analysis and FT-IR spectroscopy was carried out to confirm the composition of the ion-pair (SILC-PTA) and (SILC-PMA). Elemental analysis the obtained results revealed 2:1 composition for both \([\text{SILC:PMA}]\) and \([\text{SILC-PTA}]\) ion pair as indicated in Table 1 and peaks that appeared in the FT-IR spectra for SILC-PMA ion pair the broad peak at 3577 cm\(^{-1}\) is attributed to the O-H stretching and the peak observed in all samples at \((1780, 1730)\) cm\(^{-1}\) is related to the C=O bond. The peaks at around 2962 and 2933 cm\(^{-1}\) are related to the symmetric and asymmetric alkane stretching of C-H bond. The disappearance of N-H bond attributed to react with PMA as shown in Fig. 2.
Table 1: Elemental analysis of the (SILC-PMA) and (SILC-PTA) ion pair

| Element analysis | SILC-PTA | SILC-PMA |
|------------------|----------|----------|
|                  | % C      | % H      | % N    | % C      | % H      | % N    |
| Found            | 16.25    | 1.49     | 4.15   | 20.11    | 2.40     | 5.23   |
| Calculated       | 15.95    | 1.87     | 3.99   | 20.89    | 2.64     | 5.22   |
| Formula          | \([C_{28}H_{38}N_6O_{11}S]_2[H_3PW_{12}O_{40}]\) | \([C_{28}H_{38}N_6O_{11}S]_2[H_3PMo_{12}O_{40}]\).3H_2O |

Fig. 2: IR chart for SILC-PMA ion pair.

3.1 Calibration Plot of the Fabricated Electrodes and Limit of Detection:

The fabricated electrodes (SILC-PTA) and (SILC-PMA) were immersed along with Calomel reference electrode in solutions of SILC in the concentration range \((1.0 \times 10^{-8} - 1.0 \times 10^{-2})\) M. The E (mV) against –log [SILC] was plotted as shown in Fig. 3. Both electrodes show a linear response over the concentration ranges from \((1.0 \times 10^{-7} - 1.0 \times 10^{-2})\) M with near Nernstian slopes of and \((57.29 \text{ and } 59.10)\) mV /decade for (SILC-PTA) and (SILC-PMA),
and values of LOD (5.116×10^{-8} and 5.055×10^{-8}) for (SILC-PMA) and (SILC-PTA) electrodes respectively indicating that the sensors under investigation are highly sensitive and can be applied for determination of trace amounts of SILC drug.

![Graph showing standard curve of SILC using new SILC-PTA and SILC-PMA electrodes.](image)

**Fig. 3:** Standard curve of SILC using new SILC-PTA and SILC-PMA electrodes.

### 3.2 Effect of pH:

The effect of pH on the performance of the two electrodes was investigated using concentration of (1.0×10^{-3})M of SILC drug at different pH values (1-9). The pH value was adjusted by addition of small volumes of HCl and/or NaOH solution (0.1-1 M of each). The potential at each pH value was recorded. It is obvious Fig. 4 that the best pH range is from (2-5) for both electrodes where the potential is independent on pH. However the potential decreases gradually at pH values higher than 5 for (SILC-PMA) and (SILC-PTA). It is worth noting that at more than pH 7 a white precipitate of drug is formed and that may be the cause of potential decrease. At pH values lower than 2 the potential readings decrease which can be related to interference of hydronium ion [22,23].
3.3 Effect of Temperature:

The change of potential was measured by changing the temperature of the drug solution from (23-65) °C for concentration of (1.0×10⁻²) M SILC. The relationship between the temperature and the measured potential was plotted. The results in Fig. 5 showed that the appropriate working temperature is (23-65) °C for both electrodes.

![Fig. 5: Effect of temperature on the response of SILC-PMA and SILC-PTA electrodes.](image-url)
3.4 Selectivity of the Studied Sensors:

The selectivity coefficients (log K) of the studied sensors were determined applying separate solution method (SSM) [24, 25]. In SSM, the potential of cell comprising the new constructed electrode and a reference electrode is measured in two separate solutions, where (SILC) and (interfering ion or compound) are at the same activity. Selectivity coefficients were calculated using Nicolsky equation [25]:

$$\log K = \frac{(E_j - E_i)}{S}$$

Where $E_i$ is the potential measured in $(1.0 \times 10^{-3})$ M SILC, $E_j$ the potential measured in $1.0 \times 10^{-3}$ M of the interfering ion or compound, $S$ is the slope of the calibration plot. The $K$ value represents the difference in potential in the presence of interfering ion (j) and when (j) is not present. When the value is less than 1 this indicates that the electrode show slow response to the interfering ions. The results of selectivity are shown on Table 2. The $K$ values shows a very high selectivity of the electrodes towards the SILC.

**Table 2:** K value of both SILC-PMA and SILC-PTA electrodes.

| Interfering ion or compound | K SILC-PTA | K SILC-PMA |
|----------------------------|------------|------------|
| Na$^{+1}$                  | 5.21$\times 10^{-3}$ | 7.42$\times 10^{-4}$ |
| NH4$^{+1}$                 | 1.909$\times 10^{-2}$ | 2.093$\times 10^{-2}$ |
| Ba$^{2+}$                  | 5.217$\times 10^{-2}$ | 1.955$\times 10^{-2}$ |
| Ca$^{2+}$                  | 1.725$\times 10^{-2}$ | 1.811$\times 10^{-2}$ |
| Fe$^{3+}$                  | 1.371$\times 10^{-2}$ | 1.855$\times 10^{-2}$ |
| Fructose                   | 3.420$\times 10^{-3}$ | 1.631$\times 10^{-2}$ |
| Cholesterol                | 3.519$\times 10^{-2}$ | 1.725$\times 10^{-2}$ |
| Uric acid                  | 5.5743$\times 10^{-2}$ | 1.691$\times 10^{-2}$ |
| Mg.stearate                | 3.506$\times 10^{-2}$ | 1.658$\times 10^{-2}$ |
| M.H.B                      | 7.37$\times 10^{-3}$ | 1.885$\times 10^{-2}$ |
| P.H.B                      | 7.642$\times 10^{-2}$ | 1.469$\times 10^{-2}$ |
| Talc                       | 4.788$\times 10^{-2}$ | 1.658$\times 10^{-2}$ |
| Ti$^{4+}$                  | 7.350$\times 10^{-2}$ | 1.638$\times 10^{-2}$ |
3.5 Life time and response time:

For the determination of the storage stability for (SILC-PTA) and (SILC-PMA) electrodes, the potentiometric measurements were carried out at optimum conditions of (pH and Temperature) for several times every week. The performance of the electrodes have been tested by potentiometric calibration of SILC standard solutions on different days. The results showed that (SILC-PTA) and (SILC-PMA) electrodes can be used for 120 days without significant change in the value of potential. The IUPAC definition of response time is the time required to reach the steady state with potential change of ± 1 mv from the moment of contact of the (SILC-PTA) and (SILC-PMA) electrodes and the calomel electrode of the drug solution. The lowest response time of the new coated carbon for the (SILC-PMA) electrode was 12 second for concentration $1.0 \times 10^{-7}$ M and 56 second for concentration $1.0 \times 10^{-2}$ M and the lowest response time for new coated carbon of the (SILC-PTA) electrode was 15 second for concentration $1.0 \times 10^{-7}$ M and 60 second for concentration $1.0 \times 10^{-2}$ M as shown in Fig. 6.

![Fig. 6: Response time of SILC-PMA electrode.](image)

3.6 Precision and Accuracy:

To evaluate the accuracy and precision of the proposed method, pure and pharmaceutical drug solutions at two different levels (within the working limits) was analyzed, each solution was repeated for (5) times. Precision and accuracy were based on the calculated percent
relative standard deviation (RSD%) and percent relative error (RE %). The value of RE% is not more than (-0.78) and value or RSD% is not more than (0.426). The results Table 3 show that these methods have reasonable precision and accuracy.

4. Analytical Applications:

Viagra was determined using a direct calibration method for both pure and pharmaceutical forms. The results were calculated as the recoveries % using the prepared electrodes (SILC-PTA) and (SILC-PMA). The percentage recoveries for determination of SILC pure drug solutions are (99.61 and 99.58) for (SILC-PMA and SILC-PTA) electrodes respectively. The percentage recoveries for determination of SILC tablets (Vegamax 100 mg tablet) are (99.49 and 99.22) and for (Jeansiagra 50 mg tablet) are (99.52 and 99.31) for (SILC-PMA and SILC-PTA) electrodes respectively shown in Table 3.

Table 3: Statistical treatment of data for determinations of SILC in pure and pharmaceutical preparations using new (SILC-PTA) and (SILC-PMA) electrodes.

| Sample | SILC-PMA | SILC-PTA |
|--------|----------|----------|
|        | Taken [SILC] M | Found [SILC] M | % Recovery | Taken [SILC] M | Found [SILC] M | % Recovery |
| Pure drug | 1.0×10⁻² | 9.988×10⁻¹ | 99.88 | 1.0×10⁻² | 9.995×10⁻³ | 99.95 |
|          | 1.0×10⁻³ | 9.914×10⁻⁴ | 99.14 | 1.0×10⁻³ | 9.860×10⁻³ | 98.60 |
|          | 1.0×10⁻⁴ | 9.896×10⁻⁵ | 98.96 | 1.0×10⁻⁴ | 9.887×10⁻⁵ | 98.87 |
|          | 1.0×10⁻⁵ | 9.991×10⁻⁶ | 99.91 | 1.0×10⁻⁵ | 9.929×10⁻⁶ | 99.29 |
|          | 1.0×10⁻⁶ | 9.922×10⁻⁷ | 99.22 | 1.0×10⁻⁶ | 1.0166×10⁻⁶ | 101.66 |
|          | 1.0×10⁻⁷ | 1.0056×10⁻⁷ | 100.56 | 1.0×10⁻⁷ | 9.911×10⁻⁸ | 99.11 |
| %Mean±SD | 99.61±0.225 | 5 | 99.58±0.365 | 5 |
| Variance | 0.050 | 1.493×10⁻¹ | 99.53 | 1.5×10⁻³ | 9.54×10⁻³ | 98.20 |
| %RE | -0.39 | 9.976×10⁻⁴ | 99.76 | 1.0×10⁻³ | 9.954×10⁻⁴ | 99.54 |
| %RSD | 0.225 | 9.876×10⁻⁵ | 98.76 | 1.0×10⁻⁴ | 9.944×10⁻⁵ | 99.44 |
| Vegamax (100 mg) | 1.0×10⁻³ | 9.814×10⁻⁶ | 98.14 | 1.0×10⁻⁵ | 9.953×10⁻⁶ | 98.53 |
|          | 1.0×10⁻⁴ | 9.973×10⁻⁷ | 99.73 | 1.0×10⁻⁵ | 1.0153×10⁻⁶ | 101.53 |
|          | 1.0×10⁻⁵ | 1.0102×10⁻⁷ | 101.02 | 1.0×10⁻⁶ | 9.810×10⁻⁸ | 98.10 |
4.1 Content Uniformity Assay Test:

To study the content uniformity assay test for pharmaceutical preparations of SILC drug, four individual tablets of Vegamax (100 mg) were placed in separate 100-mL beakers and dissolved in 100 mL distilled water to obtain (1.5×10⁻³) M the potential of each solution was recorded using the new coated carbon electrodes (SILC-PMA and SILC-PTA). The mean potential was used to evaluate the content uniformity applying straight line of calibration graph. The results are shown in Table 4.

*Robustness: examined by changing the aqueous solution to acetate buffer pH (3.4).

**Ruggedness: checked by using another model of pH-meter (HANNA, HI 2216).
Table 4: The results of Content uniformity Assay.

| Parameter          | Vegamax (100mg) |          |
|--------------------|-----------------|----------|
|                    | SILC-PTA        | SILC-PMA |
| Taken Conc.        | 1.5×10³         |          |
| Found Conc.*       | 1.494×10⁻³      | 1.498×10⁻³|
| % Recovery ± SD    | 99.62± 0.288    | 99.86± 0.280|
| Variance           | 0.083           | 0.078    |
| %RSD               | 0.289           | 0.280    |
| % RE               | -0.38           | -0.14    |

*mean of 4 determination

5. Conclusion:

The proposed method introduced an ion selective electrodes for the determination of SILC based on PVC matrix and DBP as a plasticizer and using PTA or PMA as active materials. These electrodes showed a successful application with low limit of detection and good recovery. The electrodes also showed long life time, fast response time, good selectivity and reasonable working concentration ranges.

References

[1] Goldstein G. I., Lue T. F., Padma-Nathan H., Rosen R. C., Steers W. D. and Wicker P.A., "Sildenafil study group. Oral sildenafil in the treatment of erectile dysfunction", The New England Journal of Medicine, 338,1397 (1998).

[2] Fabbri A., Aversa A. and Isidori A. "Sildenafil and erectile dysfunction", Journal of Endocrinological Investigation , 22, 486 (1999).

[3] Medina P., Segarra G., Vila J. M., Domenech C., Martinez-Leon J. B. and Lluch S., "Effects of sildenafil on human penile blood vessels", Urology, 56, 539 (2000).

[4] Kloner R.A., Brown M., Prisant L.M. and Collins M., "Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy", American Journal of Hypertension, 14, 3 (2001)
[5] Stuckey B.G., Jadzinsky M.N., Murphy L.J., Montorsi F., Kadioglu A., Fraige F., Manzano P. and Deerochanawong C., "Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: Results of a randomized controlled trial", Diabetes Care, 26, 84 (2003).

[6] Nurnberg H.G., Seidman S.N., Gelenberg A.J., Fava M., Rosen R. and Shabsigh R., "Depression antidepressant therapies and erectile dysfunction Clinical trials of sildenafil citrate (Viagra®) in treated and untreated patients with depression", Urology, 60, 58 (2002).

[7] Morales A. Gingell C. and Collins M., "Clinical safety of oral sildenafil citrate in the treatment of erectile dysfunction", International Journal of Impotence Research, 10, 69 (1998).

[8] Jackson G., Benjamin N., Jackson N. and Allen M.J., "Effects of sildenafil citrate on human homodynamic", American Journal of Cardiology, 83,13 (1999).

[9] Marmor M.F. and Kessler R., "Sildenafil (Viagra) and ophthalmology", Survey of Ophthalmology, 44, 153 (1999).

[10] Tracqui A. and Ludes B., "HPLC-MS for the Determination of Sildenafil Citrate (Viagra | in Biological Fluids. Application to the Salivary Excretion of Sildenafil after Oral Intake", Journal of Analytical Toxicology, 27, 88 (2003).

[11] Liu Y.M., Yang H.C. and Miao J.R., "Reversed-phase HPLC determination of sildenafil citrate tablet", Yaowu-fenxi-zazhi, 20, 61 (2000).

[12] Amir A. S. and Shaza A., "Simple and Sensitive Spectrophotometric Determination of Sildenafil Citrate in Pharmaceutical Formulations", Research Journal of Pharmacy and Technology, 10(12), 1994 (2017).
[13] Taízia D. S., Cibele R. T. and Cristina D. V., "Development and validation of alternative methods by non-aqueous acid-base titration and derivative ultraviolet spectrophotometry for quantification of sildenafil in raw material and tablets", Brazilian Journal of Pharmaceutical Sciences, 53(1), 1 (2017).

[14] Issa Y.M., El-Hawary W.F., Youssef A.F.A. and Senosy A.R., "Spectrophotometric determination of sildenafil citrate in pure form and in pharmaceutical formulations using some chromotropic acid azo dyes", Spectrochimica Acta. Part A, 7, 1297 (2010).

[15] Mohammad A., Mohammad R., Asma R., Ummay N. S. and Mohammad Z. S. "Study of in Vitro Interaction of Sildenafil Citrate with Bovine Serum Albumin by Fluorescence Spectroscopy", Pharmacology& Pharmacy, 6, 94 (2015).

[16] Érica F. B., Elen R. S., Roberta A. M., Romeu C. R. and Orlando F., "Voltammetric method for the determination of sildenafil citrate (Viagra) in pure form and in pharmaceutical formulations", AnalyticalLetters, 43, 1046 (2010).

[17] Hesham S., "Spectrochemical Methods for the Determination of Sildenafil Citrate (Viagra) in Bulk Powder and in Pharmaceutical Dosage Form", Journal of Applied Sciences, 8, 28 (2006).

[18] Segall A.I., Vitzle M.T., Perez V.L., Palacios M.L. and Pizzorno M.T., "Simultaneous assay of sildenafil and desmethylsildenafil in human plasma using liquid chromatography–tandem mass spectrometry on silica column with aqueous–organic mobile phase", Journal of Chromatography B, 768, 277 (2002).

[19] Zhu X., Xiao S., Chen B., Zhang F., Yao S., Wan Z., Yang D. and Han H. "Simultaneous determination of sildenafil, vardenafil and adalafil as forbidden components in natural dietary supplements for male sexual potency by high-performance liquid chromatography–electrospray ionization mass spectrometry", Journal of Chromatography A, 1066, 89 (2005).
[20] Frag E. Y. Z., Zayed M. A., Omar M. M., Elashery S. E. A. and Mohamed G. G., "Electroanalytical determination of sildenafil in Viagra tablets using screen-printed and conventional carbon paste electrodes", Journal of Electroanalytical Chemistry, 7, 650 (2012).

[21] Abu Shawish H. M., Abu Ghalwa N., Saadeh S. M. and El Harazeen H., "Development of novel potentiometric sensors for determination of tartrazine dye concentration in foodstuff products", Food Chemistry, 138, 126 (2013).

[22] Khalil S., "Ion-selective electrode for the determination of trazodone in tablets", Analyst, 124, 139 (1999).

[23] El-Ansary A.L., Issa Y.M. and Tag-Eldin A.S., "Plastic membrane selective electrodes for chlor tetracyclinium ion based onchlorotetracyclinium-phosphotungstate and phosphomolybdate ion-pair associates", Electroanalysis., 13, 1203 (2001).

[24] 24-Cosofret V.V. and Buck R.P., "Pharmaceutical Applications of Membrane Sensors", Pharmaceutical Applications of Membrane Sensors, 1, 50 (1992).

[25] 25-Vytras K., "The use of ion-selective electrodes in the determination of drug substances", Journal of Pharmaceutical and Biomedical Analysis, 7, 789 (1989).