Journal of Applied Electrochemistry (2006) 36:139–146
DOI 10.1007/s10800-005-9041-7

Continuous potentiometric monitoring of viagra (sildenafil) in pharmaceutical preparations using novel membrane sensors

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Received 1 March 2005; accepted in revised form 28 July 2005

Key words: determination of viagra, flow injection analysis, pharmaceutical analysis, potentiometry, reineckate, sildenafil citrate, tungstophosphate

Abstract

Two potentiometric sensors responsive to sildenafil citrate (SC) drug (the active component of viagra) are described, characterized, compared and used for drug assessment. The sensors are based on the use of the ion-association complexes of (SC) cation with tungstophosphate (TP) and reineckate (Re) anions as electroactive materials in plasticized poly(vinyl chloride) membranes. The sensors demonstrate fast near-Nernstian response for SC over the concentration ranges 1.0×10^{-2}–7.9×10^{-7} and 1.0×10^{-2}–1.0×10^{-6} M with detection limits of 0.53 and 0.67 μg ml^{-1} over pH 3–6 for TP and Re based membrane sensors, respectively. The sensors display good selectivity for SC drug over many nitrogeneous compounds, some inorganic cations and excipients and diluents commonly used in drug formulations. Validation of the assay methods with both sensors by measuring the lower detection limit, range, accuracy, precision, repeatability and between-day-variability reveals good performance characteristics confirming applicability for continuous determination of SC in pharmaceutical formulations and in spiked human serum. A membrane incorporating SC–TP complex in a tubular flow detector is used in a two channel flow injection set up for continuous monitoring of the drug at a frequency of 25–30 samples h^{-1}. The results obtained with drugs containing 50–100 mg SC tablet^{-1} show a mean standard deviation of $\pm2\%$ of the nominal which agree fairly well with data obtained by spectrophotometry.

1. Introduction

Viagra, sildenafil citrate (SC) (Figure 1), a selective inhibitor of cyclic guarosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), is a well-tolerated and highly effective treatment for erectile dysfunction. The mechanism of action of sildenafil depends on activation of the nitric oxide (NO)-cGMP pathway during sexual stimulation, which results in corpus cavernosal smooth muscle relaxation and penile erection. Endogenously derived NO is also involved in blood pressure regulation through its effect on basal rescular tone, which is mediated by cGMP levels. Organic nitrates and NO donors exert their therapeutic effects on blood pressure and vascular smooth muscle by the same mechanism as endogenous NO [1].

Few reports have been suggested for quantification and stability assessment of SC. These include electrochemical oxidation on carbon electrodes [2], square-wave and adsorptive stripping square-wave voltammetry [3, 4], flow injection analysis using UV-detection [5], extractive spectrophotometry based on the formation of ion-pair complexes of SC with bromocresol green and chromoxane cyanine-R dyes [6], liquid chromatography with detection at 230 nm [7], high performance liquid chromatography (HPLC) [8], and gas chromatography/mass spectrometry [9]. Most of these methods, however, utilize expensive instrumentation, suffer from lack of selectivity, involve careful control of the reaction conditions or derivatization reactions, and require time-consuming pretreatment steps which affect their usefulness for routine analysis. On the other hand, application of potentiometric sensors in the field of pharmaceutical and biomedical analysis have been advocated [10]. The approach provides simple, fast, and selective technique for determination of various drugs [10–17]. However, as far as the available literature is concerned, very little is known about the use of this technique for viagra quantification [18].

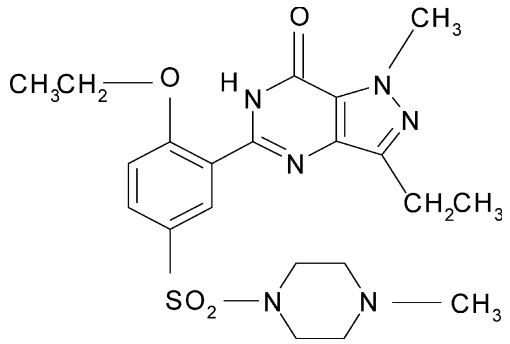

Fig. 1. Structure of sildenafil (viagra).

The present work describes preparation, characterization and application of two potentiometric tubular membrane sensors for continuous determination of sildenafil in pharmaceutical preparations. These sensors incorporate ion association complexes of sildenafil–tungstophosphate (SC–TP) and sildenafil–reineckate (SC–Re) embedded in plasticized PVC matrix membranes. Performance characteristics of both sensors reveal low detection limit, high sensitivity, good selectivity, fast response, long life span and application for accurate determination of viagra in pharmaceutical preparations under static and hydrodynamic (FIA) modes of operation.

2. Experimental

2.1. *Apparatus*

All potential measurements were made at 25 ± 1 °C with an Orion (Cambridge, MA, USA) Model 720 SA pH/mV meter using an Orion Ag/AgCl double-junction reference electrode (Orion 90-02) and tungstophosphate–sildenafil or reineckate–sildenafil poly(vinyl chloride) (PVC) membrane sensors. An Orion Ross pH electrode (Model 80-02) was used for pH adjustment. The components of the FI system were similar to those used previously [15, 19, 20]. The flow injection analysis (FIA) system manifold (Figure 2) consisted of a two-channel Ismatech MS-REGLO model peristaltic pump polyethylene tubing (0.71'' i.d.) and an Omnifit injection valve (Omnifit, Cambridge, UK) with sample loop of 100 μl volume. The potential signals were recorded using a home-made high-impedance data acquisition 8-channel box connected to a PC through the interface ADC 16 (Pico Tech., UK) and PicoLOG for windows (version 5.07) software. A computer-controlled spectrophotometer (Shimadzu, Model 1601) was used for the spectrophotometric measurements under the recommended conditions [6].

2.2. *Reagents and chemicals*

All chemicals were of analytical reagent grade and double distilled water was used throughout unless specified otherwise. *o*-Nitrophenyloctyl ether (*o*-NPOE), tetrahydrofuran (THF), and tungstophosphoric acid (TPA) were obtained from Sigma (St. Louis, MO) Reinecke salt (ammonium Reineckate) was purchased from Aldrich (Milwaukee, W.I). A stock solution (10^{-2} M) of SC at pH 5 was prepared by dissolving 0.667 g of the drug salt in 100 ml H_2O adjusted with phosphate buffer to pH 5. Dilute solutions of (1×10^{-3}–10^{-7} M) were freshly prepared by diluting the stock solution with doubly distilled water and phosphate buffer of pH 5. Pure viagra powder was obtained from Pfizer (USA). Drugs containing viagra were obtained from the local drug stores.

2.3. *Sensors construction*

Sildenafil–tungstophosphate and reineckate ion pair complexes were prepared by slow addition of 10 ml of 10^{-2} M tungstophosphoric acid and ammonium reineckate solutions to 10 ml aliquots of 10^{-2} M aqueous

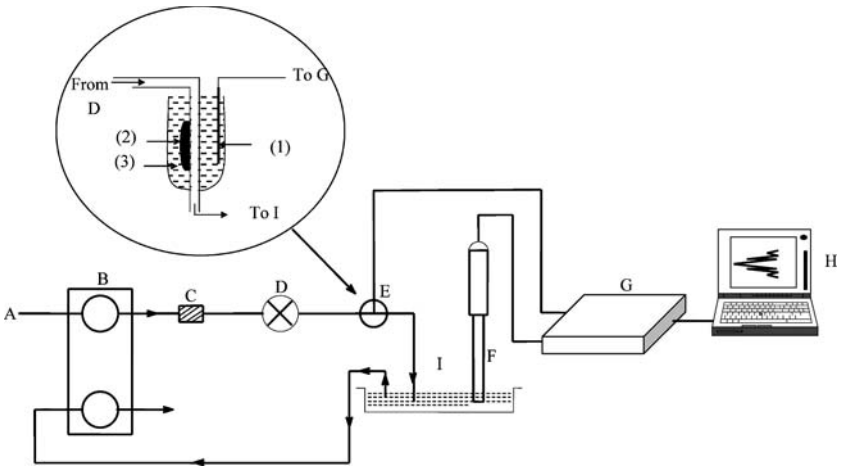

Fig. 2. Manifold for the two channel FIA set up used for the determination of sildenafil: A, carrier phosphate buffer solution pH 5; B, peristaltic pump; C, pulse damper; D, sample injection valve; E, flow injection detector; [(1) Ag/AgCl internal reference electrode, (2) membrane; (3) internal reference solution]; F, reference electrode; G, data acquisition system; H, laptop computer; I, Petri dish.

solution of SC. The mixtures were stirred for 10 min, the precipitates were filtered off through Whattman filter paper No. 42, washed with doubly distilled water, dried at room temperature and finely grounded to fine powders. Elemental analysis revealed the formation of 1:1drug-reagent ion pair complexes.

A 3 mg portion of SC–TP or SC–Re ion pair complex was thoroughly mixed with 124 mg of *o*-NPOE, 68 mg of PVC and 7 ml THF in a glass Petri dish (5 cm diameter) covered with filter paper and left to stand overnight to allow slow evaporation of THF at room temperature. The master membrane was sectioned with a cork borer (10 mm diameter) and glued to a PVC tubing (~3 cm length, 8 mm; id) using THF. The sensor body consisted of a glass tube attached to PVC tubing. The internal reference solution was a mixture of equal volumes of 10^{-3} M SC and 10^{-3} M NaCl. An Ag/AgCl internal reference electrode (1.0 mm diameter) was immersed in the internal reference solution. The sensors were conditioned by soaking in 1×10^{-3}M SC aqueous solution for 4 h and were stored in the same solution when not in use.

The sensors were calibrated under static mode of operation by transferring 1.0 ml aliquots of 1×10^{-2}–1×10^{-6} M aqueous solution of SC to 20 ml beaker containing 9.0 ml of 10^{-2} M NaCl or phosphate buffer of pH 5. The sensor is immersed in the solution in conjunction with a double junction Ag/AgCl reference electrode. The potential readings were recorded after stabilization to ±0.2 mV and emf was plotted as a function of logarithm SC concentration. The calibration graphs were used for subsequent determination of unknown SC concentrations.

2.4. *Tubular detector construction*

The tubular sensors were constructed as described previously [21]. A coating solutions were prepared by dissolving 67 mg of PVC in 7 ml THF followed by addition of 124 mg of *o*-NPOE and 2 mg of SC–TP ion pair. This solution was deposited, using a micro dropper, 3–4 times in a hole (3 mm wide×5 mm length) made in the middle of a 15 cm Tygon tube (ALKEM, P/N A003494 red/red 0.071 i.d). The tube was inserted and sealed with Araldite in 100 μl pipette tip (7 cm long, 0.4 cm diameter) (Figure 2). The tubular sensor was inserted into the flow injection system as schematically shown in Figure 2. A 10^{-2} M phosphate buffer was used as a carrier solution at a flow rate of 4 ml min^{-1}.

All injection tubes were red/red (0.071 inch i.d) and waste tube was blue/blue (0.065 inch. i.d). The tubular detector was located at a distance of 50 cm from the injection valve and at a distance of 20 cm from the waste receiving Petri dish. The detector was calibrated at 25 °C under hydrodynamic mode of operation by injection of SC samples through a valve loop of 100 μl in the carrier stream. After a steady-state, the baseline was reached, the potential signals were recorded using a home made high-impedance data acquisition 8-channel box connected to a PC through the interface ADC 16 (Pico Tech., UK) and PicoLog for windows (version 5.07) software. An Orion Ag/AgCl double junction reference electrode was placed in a Petri-dish down stream from the indicator sensor just before the solution went to waste.

2.5. *Determination of sildenafil in pharmaceutical preparations*

Three tablets of viagra were reduced to a homogeneous fine powder in an agate mortar, accurately weighed, transferred to a 50-ml calibrated flask and completed to the mark with water. The contents of the flask were sonicated for 10 min to ensure complete dissolution. A 1.0 ml aliquot of the clear supernatant was diluted with phosphate buffer of pH 5 in 100-ml measuring flask. For drug measurements under static mode of operation, a 10-ml aliquot of the drug solution was potentiometrically measured. For continuous measurements (FIA), a 100 μl aliquot of the drug test solution was injected in triplicate as described above and the average potential reading was compared with the calibration plot.

2.6. *Determination of sildenafil in spiked serum*

Aliquots of human serum (3.0 ml) were transferred to 15 ml polypropylene sample tubes. A 9 ml portion of ice-cold acetonitrile solution was added, thoroughly mixed and left for 5 min before being centrifuged at 1000 rpm. The supernatant liquid was transferred, without removal of any particulate matter, to a 25 ml beaker and then evaporated on a water bath at 50 °C to a volume less than 3 ml. A 9 ml of 10^{-2} M phosphate buffer solution of pH 5 was added, the mixture was thoroughly mixed and used for both batch and continuous drug measurements. For batch assessment, the drug sensor and reference electrode were immersed in the solution, and the potential readings were recorded after reaching the equilibrium response (10–20 s). The concentration of sildenafil was calculated using a calibration graph.

For continuous measurements (FIA), a flow stream of 10^{-2} M phosphate buffer of pH 5 carrier solution was allowed to pass through the flow-cell at a flow rate 4 ml min^{-1}. Successive 100 μl aliquots of the standard sildenafil and unknown test sample solutions were injected into the flowing stream. The corresponding potential change was measured and recorded vs time. A typical calibration plot was made and used to determine the concentration of the unknown samples.

3. Results and discussion

3.1. *Characteristics of the sensors*

Sildenafil cation reacts with tungstophosphate (TP) and reineckate (Re) anions to form water insoluble 1:1 ion association complexes as confirmed by elemental

analysis data. This indicates that sildenafil (Figure 1) though contains 6 basic nitrogen atoms, behaves as a monovalent species. The complexes were prepared, characterized, and incorporated with a suitable solvent mediator in poly(vinyl chloride) matrix membranes. The membranes were prepared using the optimum standard casting solution [22] of the composition 2:34:64 wt. % ion pair complex, PVC and *o*-NPOE plasticizer, respectively.

The response characteristics of the sensors were systematically evaluated according to IUPAC recommendations [23] using data collected over a period of 4 weeks for five sensor assemblies with membrane incorporating the two ion pairs under static conditions (Table 1).Calibrations were made in 10^{-2} M phosphate buffer solution of pH 5 as a background. Results from five replicate studies gave near-Nernstian slopes of 55.1–51.8 and 44.8–41.4 mV decade^{-1} over the concentration ranges of 1×10^{-6}–1×10^{-2} and 2×10^{-6}–1×10^{-2} M, with detection limits of 7.9×10^{-7} and 1×10^{-6} M (0.53–0.67 μg ml^{-1}) for SC–TP and SC–Re based membrane sensors, respectively (Figure 3).

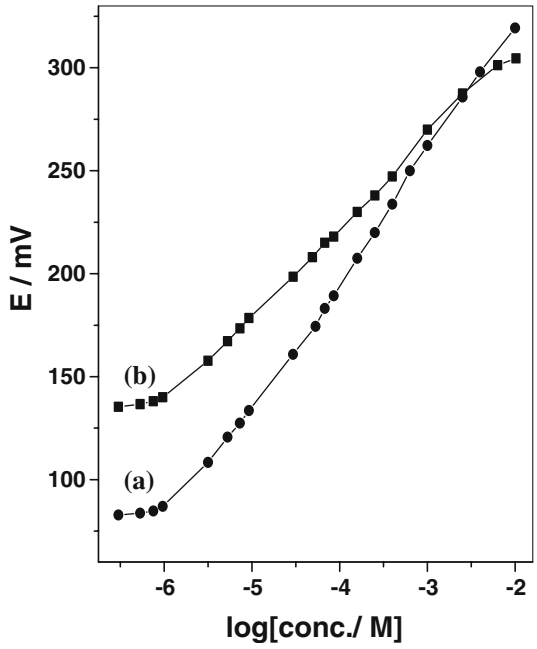

Fig. 3. Potentiometric response of: (A) SC–TP; and (B) SC–Re PVC membrane based sensors.

3.1.1. *Effect of pH and response time*

The influence of pH on the potentiometric response of SC–TP and SC–Re based membrane sensors was examined with standard 10^{-5}, 10^{-4} and 10^{-3} M SC solutions over a pH range of 2–8 (Figure 4). The pH of the solution was adjusted with either hydrochloric acid and/or sodium hydroxide solutions. Figure 4 shows that the variation of solution pH over the range 3–6 has no significant effect on the sensor response for drug concentrations $\geq10^{-4}$ M and over pH 4–6 for concentrations $\leq 10^{-5}$ M. The potentials of both sensors considerably declined with negative drift at higher pH values due to progressive precipitation of the free sildenafil base. At pH < 3, the sensor responses are severely influenced by H_3O^+.

Table 1. Response characteristics of *o*-NPOE plasticized SC–TP and SC-reineckate PVC membrane sensors under static (batch) mode of operation

Parameter	SC–TP*	SC–Re*
Slope (mV decade^{-1})	55.1	44.8
Intercept (mV)	411.17	373.3
Correlation coefficient (r)	0.9988	0.9993
Lower limit of linear range (M)	1.0×10^{-6}	2.0×10^{-6}
Response time (s)	< 10	< 10
Working pH range	3–6	3–6
Detection limit (M)	7.9×10^{-7}	1.0×10^{-6}
Life span (week)	10	10
Accuracy (%)	99.1	98.8
Repeatability (CV_w%)	0.6	0.7
Between day-variability (CV_b%)	1.1	0.8
Standard deviation (%)	1.2	1.1

*Average of six measurements.

The dynamic response times of the SC–TP and SC–Re based membrane sensors were examined by recording the potential readings at time intervals of 10 s over 3 min. The relation between potential reading and response time was plotted for 10^{-6}–10^{-2} M SC. The time required to attain 95% of the equilibrium by both sensors was less than 10 s. These results indicate that both sensors are amenable for use with automated systems.

3.1.2. *Sensor selectivity*

Selectivity coefficients ($K^{pot}_{SC,B}$), of the TP and Re based membrane sensors for some interfering ions B relative to SC were determined by the separate solutions method (SSM) [21]. In this method, the selectivity coefficients of SC sensors were evaluated with a fixed concentration of the interferent (1×10^{-3} M) adjusted to pH 5 with 10^{-2} M phosphate buffer solution. The selectivity coefficients ($K^{pot}_{SC,B}$) were determined with the rearranged Nicolsky equation [21]:

$$\log K^{pot}_{SC,B} = \left(\frac{E_1 - E_2}{S}\right) + \left(1 + \frac{Z_1}{Z_2}\right)\log(a) \qquad (1)$$

where, E_1 is the potential measured in 10^{-3} M SC, E_2 the potential measured in 10^{-3} M of the interfering ion, Z_1

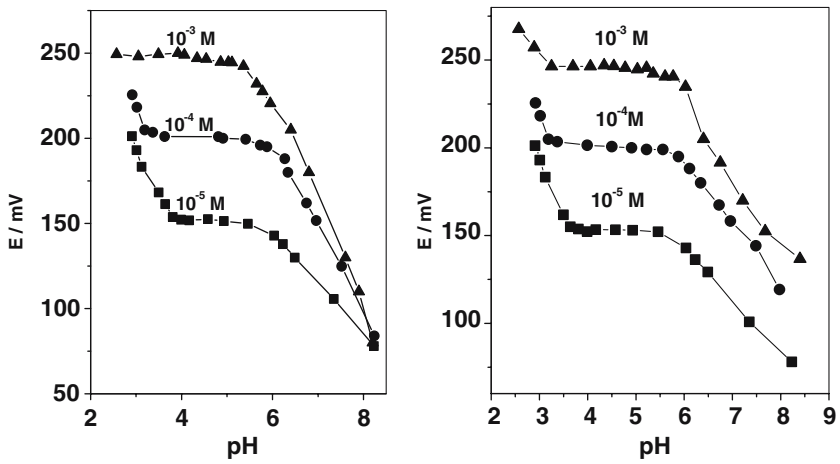

Fig. 4. Influence of pH on the potentiometric response of: (A) SC–TP; and (B) SC–Re PVC membrane based sensors.

and Z_2 are the charges of the SC and interfering species B, respectively and S is slope of the calibration plot. With neutral compounds where the charge (Z_2) equals zero, Equation (1) was simplified by canceling out the term $(1 + Z_1/Z_2)\log(a)$.

Potentiometric selectivities of the proposed sensors are related to the preferential interaction of the membrane electroactive materials with (SC) over many organic nitrogeneous compounds, inorganic cations, and additives used in the drug formulations (e.g. glucose, lactose, maltose, Tween-80 and starch). A typical selectivty of SC–TP based membrane sensor is in the order: SC > > Ca^{2+} > Mg^{2+} > tartrate > citrate > oxalate > thiourea > alanine > glucose > glycine > urea > NH_4^+ > benzamide = maltose > fructose > Na^+ > K^+ > Ba^{2+}. For SC–Re based membrane sensor, the selectivity order is: SC > > Mg^{2+} > Ca^{2+} > Ba^{2+} > urea > thiourea > oxalate > tartrate > alanine > glycine > glucose > NH_4^+ > maltose > benzamide > fructose > K^+ > Na^+. Thus, a sensor based on SC–TP is less affected by glycine, alanine, urea, thiourea, maltose, fructose, oxalate, benzamide, Mg^{2+}, Ba^{2+} and NH_4^+ than sensor based on SC–Re. A sensor incorporating SC–Re is less affected by glucose, tartrate, citrate and Ca^{2+} ions. Generally, the sensor based on SC–TP is recommended for general use (Table 2).

Table 2. Potentiometric selectivity coefficients of *o*-NPOE plasticized SC–TP and SC-reineckate PVC membrane sensors

Interfering ion, B	$K^{pot}_{SC,B}$	
	SC–PT	SC–Re
Glycine	−3.5	−3.1
Alanine	−3.2	−3.0
Urea	−3.6	−2.6
Thiourea	−3.1	−2.7
Maltose	−3.9	−3.7
Fructose	−4.0	−3.9
Glucose	−3.3	−3.4
Oxalate	−2.9	−2.8
Tartrate	−2.7	−2.9
Citrate	−2.8	−3.6
Benzamide	−3.9	−3.8
Ca^{2+}	−2.0	−2.2
Mg^{2+}	−2.2	−2.1
Ba^{2+}	−4.2	−2.4
NH_4^+	−3.6	−3.5
Na^+	−4.1	−4.1
K^+	−4.2	−4.0

3.2. *Batch monitoring of viagra*

Potentiometric determination of sildenafile citrate in drug formulations in triplicate under static mode of operation using the standard addition method showed results with an average recovery of 98.8% and a mean standard deviation of ±1.2% with no interfering effect due to the drug additives (Table 3). These data were compared with results obtained by measuring the absorbance at 292 nm using UV-spectrophotometry [5]. An *F*-test reveals that there is no significant difference between the means and variances of the two sets of results. Quality control/quality assurance (QC/QA) of the method was tested by daily drug analysis running in duplicates over one month, and using the data for construction of R and X control charts [24]. The distribution of measurements and range of determination under investigation indicate that the results are under statistical control.

Validation of the proposed potentiometric methods for determining SC was made by measuring the range (R), lower limit of detection (LOD), accuracy (recovery), precision (σ), repeatability (CV_w), between day-variability (CV_b), linearity (correlation coefficient) and sensitivity (slope). Results obtained on six batches (six determinations each) using the quality assurance standards [25] are depicted in Table 1. These data support the application of the proposed potentiometric methods for quality control assessment of drug formulations.

Comparison of the results with those obtained by some previously suggested methods reveals that the lower detection limit of the proposed sensors is similar

Table 3. Potentiomeric determination of sildenafil in pharmaceutical preparations using SC–TP based membrane sensor

Commercial products	Label (mg tablet^{-1})	Found (mg tablet^{-1})		
		Potentiometry*		Spectrophotometry*,[5]
		Batch	FIA	
Viagra, (Pfizer, USA)	100	99.4 ± 0.6	102.3 ± 0.3	98.2 ± 0.3
	50	49.3 ± 0.1	51.2 ± 0.5	45.2 ± 0.2
Peenagra, (Candila Healthcare Limited, India)	100	99.2 ± 0.3	101.2 ± 0.2	97.3 ± 0.4
Vega, (Asia Co.,Syria)	50	48.8 ± 0.2	51.5 ± 0.5	46.7 ± 0.6

*Average of six measurements.

to those obtained by voltammetry [2] and spectrophotometry [5, 6]. Furthermore, the present methods cover at least 4 orders of magnitude of SC concentration compared to only half-[5, 6] to two-[2, 8] decades of concentration obtained by voltammetry, spectrophotometry and HPLC [2–6, 8]. On the other hand, the previously described potentiometric methods [18] suffers from narrower linear measurement range (10^{-2}–10^{-5} M), detection limit (5×10^{-6} M), longer response time (40 s), shorter life span (5 weeks) and significant interference by ions (Na^+, K^+, Mg^{2+}, NH_4^+) commonly present in high concentrations in biological fluids.

3.3. *Continuous monitoring (FIA) of viagra*

A tubular-type detector incorporating a SC–TP based membrane sensor was prepared and used under hydrodynamic mode of operation for continuous SC quantification. The general intrinsic response characteristics of the detector revealed that the dependency of the peak height, peak width, and time to recover the base line depend on the flow rate of the carrier buffer solution. Continuous injection of 100 μg ml^{-1} SC standard solution with different carrier flow (i.e. 0.5–10 ml min^{-1}) revealed that as the flow rate increased the response peaks width decreased with a decrease in the peak height (Figure 5). A plateau in the potential response was obtained at a flow rate of about 4 ml min^{-1}. Consequently, the recommended optimal flow rate was chosen to be 4 ml min^{-1}. With a flow rates less than 2 ml min^{-1}, the tubular sensor showed slight memory effect and required long washing time, to recover the base line leading to a decrease in the number of sample outputs. At flow rates higher than 4 ml min^{-1}, the peak height declined. Variation or fluctuation of the base line did not exceed ± 5% of the peak height.

A linear relationship between SC concentrations and FIA signals was obtained over the range 5–100 μg ml^{-1} (Figure 6). The slope of the calibration plot was super-Nernstian (75.1 ± 0.3 mV decade^{-1}). The lower detection limit was 0.9 μg ml^{-1} at a signal/noise (S/N) ratio

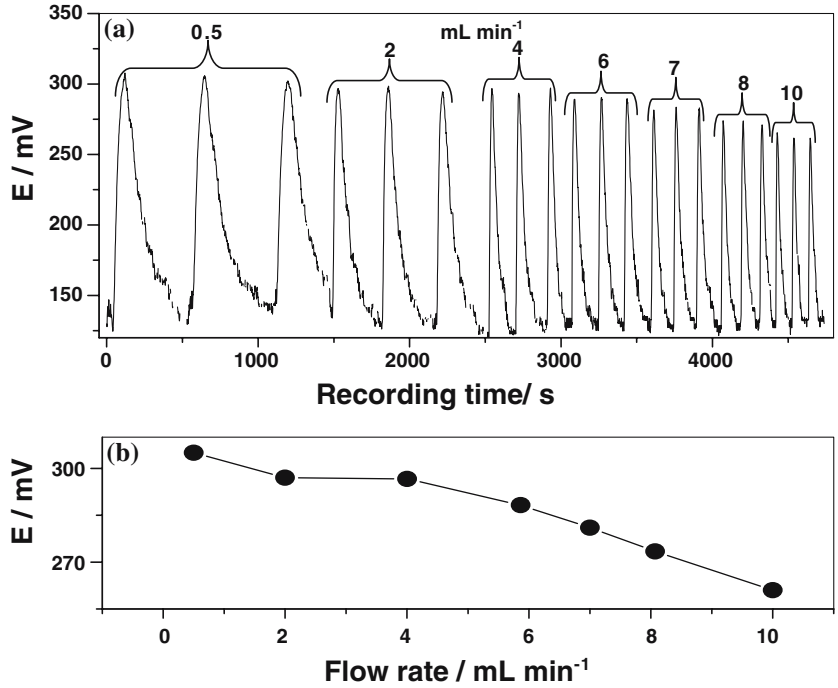

Fig. 5. Influence of flow rate on the potentiometric response (mV decade^{-1}) for 100 μg ml^{-1} of SC solution.

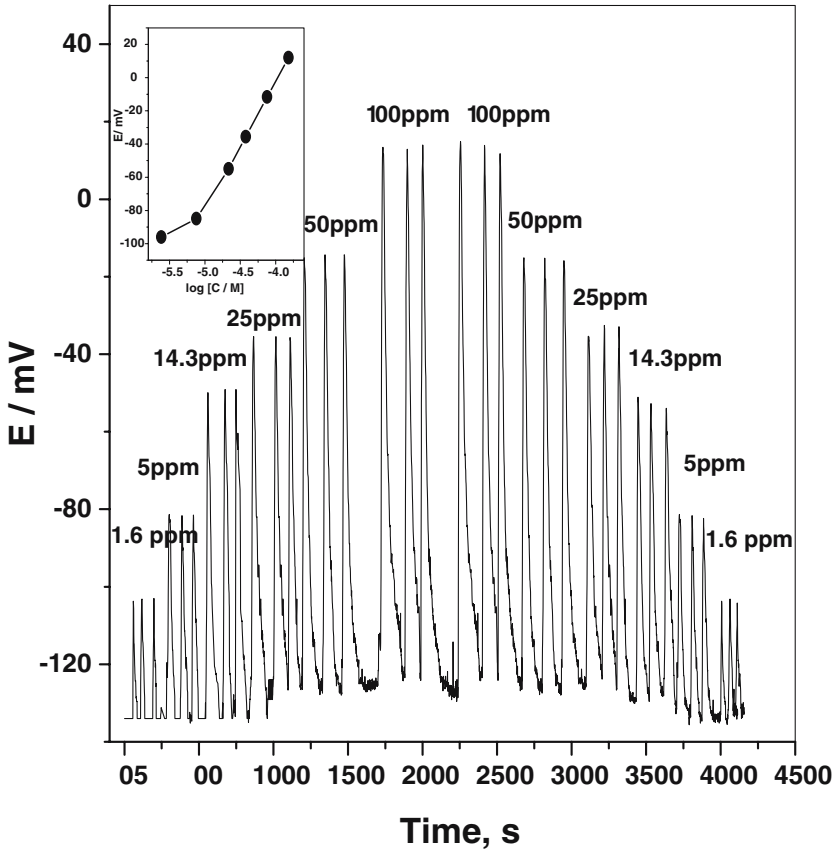

Fig. 6. Typical (FIA) peaks produced by injection of 100 μL aqueous solutions of standard sildenafil into a stream of 10^{-2} M phosphate buffer pH 5 using the SC–TP PVC membrane based sensor.

Table 4. Response characteristics of tubular SC–TP based PVC membrane detector under hydrodynamic (FIA) mode of operation

Parameter	SC–TP*
Slope (mV decade^{-1})	75 ± 0.3
Correlation coefficient (r)	0.9998
Intercept (mV)	297.9
Lower limit of detection (μg ml^{-1})	0.9
Optimum flow rate (ml min^{-1})	4
Carrier phosphate buffer (pH)	5
Sampling rate (sample h^{-1})	25–30
Response time for 10^{-3} M (s)	10
Recovery time for 10^{-3} M (s)	50

*Based on six measurements.

of ≥3. The relative standard deviation of FIA potential signals was better than ±2% for samples containing 100 μg ml^{-1}SC. The sampling frequency is 25–30 samples per hour. Table 4 shows the general response characteristics of the tubular SC–TP based PVC membrane detector under FIA mode of operation. The results obtained for determining SC in drug formulations using FIA are shown in Table 3.

3.4. *Determination of viagra in spiked human serum*

Application of the method for determining sildenafil in biological fluids was tested by spiking aliquots of serum samples with a known standard of SC. The results yield an average recovery of 99.1% with a relative standard deviation of ±0.8%. Results obtained for determination of SC in spiked human serum samples using batch and FIA are listed in Table 5.

Table 5. Batch and flow injection potentiometric determination of sildenafil in spiked human serum samples using SC–TP based membrane sensor

Sample no.	Added (μg ml^{-1})	Found (μg ml^{-1})	
		Batch	FIA*
1	1.5	1.40 ± 0.2	1.15 ± 0.4
2	12.0	11.4 ± 0.1	12.8 ± 0.3
3	50.0	48.1 ± 0.4	47.2 ± 0.5
4	100.0	96.3 ± 0.3	95.5 ± 0.8

*Average of six measurements.

4. Conclusions

Potentiometric sensors for SC (viagra) are prepared, characterized and used for continuous drug determination. Sensors based on the use of plasticized PVC matrix membranes incorporating SC–TP and SC–Re ion exchangers are prepared and used for quantitative determination of sildenafil at concentration level down

to 10^{-6} M with an accuracy of $99.1 \pm 1.3\%$. The drug is determined in pure powders and in dosage forms. The sensors offer the advantages of fast response, reasonable selectivity, elimination of drug pre-treatment or separation steps, low cost and possible interfacings with computerized and automated systems. Advantages offered by using (SC–TP) based membrane sensor are the low limit of detection (7.9×10^{-7} M), long life span (8 weeks), extending working concentration range 10^{-2}–10^{-6} M and wide pH working range (pH 3–6). The use of SC–TP based membrane sensor as a detector for continuous monitoring of SC offers the advantages of simple design, ease of construction and possible applications to small volumes of pharmaceutical drug solutions and biological fluids with little manipulation and without pre-treatment. The detector displays a wide dynamic measurement range of the drug (1.6–100 mg ml^{-1}) under continuous mode of operation with a flow rate of 3.5 ml min^{-1} and sample output of 25–30 sample h^{-1}.

References

1. D.J. Webb, S. Freestone, M.J. Allen and G.J. Murihead, *Am. J. Cardiol.* **83** (1999) 4.
2. S.A. Özkan, B. Uslo and P. Zuman, *Anal. Chim. Acta* **501** (2004) 227.
3. J. Rodriguez, J.J. Berzas, G. Castaneda and N. Rodriguez, *Talanta* **62** (2004) 427.
4. J.J. Berzas, J. Rodriguez, G. Castaneda and M.J. Villasenor, *Anal. Chim. Acta* **417** (2000) 143.
5. G. Altiokka, Z. Atkosar, E. Sener and M. Tuncel, *J. Pharm. Biomed. Anal.* **25** (2001) 339.
6. N.D. Dinesh, P. Nagaraja, N.M.M. Gowda and K.S. Rangappa, *Talanta* **57** (2002) 757.
7. J.D.H. Cooper, D.C. Muirhead, J.E. Taylor and P.R. Baker, *J. Chromatogr. B.* **701** (1997) 87.
8. N. Daraghmeh, M. Al-Omari, A.A. Badwan and A.M.Y. Jaber, *J. Pharm. Biomed. Anal.* **25** (2001) 483.
9. R.J. Lewis and R.D. Johnson, *National Technical Information Service* (Springfield, Virginia, 2000).
10. V.V. Cosofret and R.P. Buck, *Pharmaceutical Applications of Membrane Sensors* (CRC Press, Florida, 1992).
11. K. Vytras, *J. Pharm. Biomed. Anal.* **7** (1989) 789.
12. T.S. Ma and S.S.M. Hassan, *Organic Analysis Using Ion Selective Electrodes* (Academic Press, London, 1982).
13. S.S.M. Hassan, M.M. Abou-Sekkina, M.A. El-Ries and A.A. Wassel, *J. Pharm. Biomed. Anal.* **32** (2003) 175.
14. S.S.M. Hassan and N.M.H. Rizk, *Analyst* **122** (1997) 815.
15. S.S.M. Hassan, M.M. Amer, S.A. Abd El-Fatah and A.M. El-Kosasy, *Anal. Chim. Acta* **363** (1998) 81.
16. K. Vytras, *Ion Sel. Elec. Rev.* **7** (1985) 77.
17. S.S.M. Hassan, M.M. Amer, S.A. AbdEl-Fatah and A.M. El-Kosasy, *Talanta* **46** (1998) 1395.
18. A.M. Othman, N.M.H. Rizk and M.S. El-shahawi, *Anal. Chim. Acta* **515** (2004) 303.
19. S.S.M. Hassan, F.M. El Zawawy, S.A.M. Marzouk and E.M. Elnemma, *Analyst* **117** (1992) 1683.
20. S.S.M. Hassan and M.A. Ahmed, *J. Assoc. Off. Anal. Chem.* **74** (1991) 900.
21. S.S.M. Hassan, I.H. Badr and H.S.M. Abd-Rabboh, *Mikrochim. Acta* **144** (2004) 363.
22. E. Bakker, P. Buhlmann and E. Pretsch, *Chem. Rev.* **97** (1997) 3083.
23. IUPAC Analytical Chemistry Division Commission on Analytical Nomenclature, *Pure Appl. Chem.* **72** (2000) 1851.
24. W. Funk, V. Dammann and G. Donnevert, *Quality Assurance in Analytical Chemistry* (VCH, New York, 1995).
25. J.K. Taylor, *Quality Assurance of Chemical Measurements* (CRC Press, Florida, 1987).