

Disposable potentiometric citrate sensor based on polypyrrole-doped films for indirect determination of sildenafil in pharmaceutical formulations

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ABSTRACT: A new sensitive and selective disposable potentiometric sensor based on polypyrrole (PPy) films for determination of sildenafil citrate (SC) was proposed. The pyrrole polymerization was performed in presence of citrate ions under galvanostatic conditions which resulted in a membrane of PPy doped with citrate anion at graphite pencil electrode surface. Experimental conditions (e.g., pH and conditioning time) and instrumental parameters (e.g., current density and electrical charge) were evaluated in order to reach the best potentiometric response for the proposed sensor. Under optimized conditions, the device presented a linear dynamic range (LDR) for citrate ions concentrations varying from 0.034 to 1.7 mmol L⁻¹ with a Nernstian slope of 57.2 mV dec⁻¹ and a limit of detection (LOD) of 30 μmol L⁻¹. The developed potentiometric sensor was applied for sildenafil citrate (SC) determination (pharmaceutical formulations) and results compared with an official spectrophotometric method indicating a good agreement for a confidence level of 95%. Effect of concomitants species on the potentiometric response of the proposed device and morphologic characterization using microscopy of atomic force (AFM) were realized. The surface roughness of PPy films (synthesized in citrate solution and chloride) showed poorly affected by changing the doping anion, probably because the polypyrrole nodules grow three-dimensionally simultaneously. © 2016 Wiley Periodicals, Inc. *J. Appl. Polym. Sci.* **2016**, *133*, 43762.

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INTRODUCTION

Sildenafil citrate (Figure 1 - SC) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)—specific phosphodiesterase type 5 (PDE5) used by men with erectile dysfunction.¹ Since its approval by US Food and Drug Administration (FDA) in 1998, SC has been used by more than 27 million of men including young population with erectile dysfunction caused by medical conditions, such as diabetes and spinal cord injuries.² A growing number of studies have reported a significant increasing in the risk of cardiovascular events, particularly fatal arrhythmias, after oral SC administration for patients with cardiovascular disease. Furthermore, the use of SC is contraindicated concomitantly with the use of other pharmaceutical formulations containing nitrate, which have been associated with a prolonged decrease in blood pressure.³

There are no official methods described in Brazilian Pharmacopeia currently available for SC determination.⁴ Quantitative procedures are commonly performed by spectrophotometric^{5,6} and

chromatographic methods.^{7,8} Dinesh *et al.* proposed spectrophotometric methods based on formation of ion-association complexes of sildenafil citrate with bromocresol green (BCG, method A) and with chromoxane cyanine R (CCR, method B) in aqueous acidic buffer.⁶ Ghodsi *et al.* reported the development of the high-performance liquid chromatography (HPLC) method using narrow-bore C18 column with UV detection at 292 nm⁷. Despite of good results presented by cited works, preconcentration and/or separation steps are necessary besides the high instrumental cost are common disadvantages of these methods in comparison with electroanalytical methodologies.⁹ In general, electrochemical approaches have been proposed for determination of sildenafil citrate (SC) based on mainly in voltammetric methodologies such as adsorptive stripping voltammetry,^{9,10} square-wave adsorptive stripping voltammetry^{11,12} and amperometry,^{13,14} but potentiometric methods are few reported for SC determination.^{15,16} Potentiometric sensors could be an interesting alternative for sildenafil citrate determination in pharmaceutical formulations because they are simple and low-cost methodologies with a faster

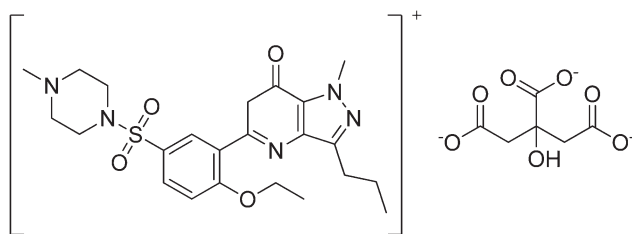


Figure 1. Molecular structure of sildenafil citrate.

response.¹³ Ion-selective electrodes (ISE) constructed using conductive polymers such as polypyrrole in the preparation of selective membranes has been widely explored. The main characteristics of these devices are the high conductivity, fast, and easy incorporation of ionophore on the polymeric matrix and good selectivity.¹⁷

The use of polypyrrole (PPy) membrane in the development of potentiometric sensors is based on its doping by counter-ion (anion) that occurs during the polymerization step yielding a selective response to the dopant ion. The ability of polypyrrole films to incorporate anions has allowed the development of potentiometric sensors not only for inorganic species such as nitrate,¹⁸ phosphate,¹⁹ iodide,²⁰ silver²¹ ions but also for some organic species present in food^{22,23} or pharmaceutical samples.^{24–26} In this way, Bindewald *et al.* reported the development of a sensitive and selective solid-state potentiometric sensor based on doped polypyrrole films (PPy) for dipyrone determination. The sensor has exhibited was a linear dynamic response for dipyrone concentration in a range varying from 1.0×10^{-4} to 4.0×10^{-2} mol L⁻¹ with a slope of 29 mV dec⁻¹ without significant interference of inorganic and/or organic species commonly found in pharmaceutical formulations samples.²⁶ Using a similar approach Oliveira *et al.* have constructed an ISE for determination of Diclofenac which showed excellent analytical results. The response mechanism for the proposed sensor is based on incorporation of Diclofenac anion into polypyrrole film during polymer electrochemical synthesis. Sensor proposed exhibited a linear dynamic response in the concentration range from 3.1×10^{-4} to 1.1×10^{-2} mol L⁻¹ of Diclofenac with a slope 48.2 mV dec⁻¹ and a limit of detection of 1.9×10^{-4} mol L⁻¹. Although the use of PPy in the construction of ISE has been reported, the preparation of these sensors for organics species is still poorly explored.²⁷

The main purpose of this study is the development of an alternative strategy for indirect determination of sildenafil citrate based on a polypyrrole membrane doped with citrate ions which could be useful for quality control of SC in pharmaceutical formulations exhibiting a fast response, high accuracy, and low-cost of analysis.

EXPERIMENTAL

Apparatus

Galvanostatic procedure and potentiometric measurements were carried out using portable potentiostat PalmSens, under computer control. The deposition of polypyrrole films were performed in a three-electrode cell using as working electrode a

graphite pencil electrode (GPE), a counter electrode of platinum and reference electrode Ag/AgCl (3.0 mol L⁻¹ KCl). Chronopotentiometric measurements were performed using PSTrace 3.0 software and recorded 2 min after SC addition.

Morphological and structural characterization were performed using a ITO glass substrate as working electrode, a counter electrode of platinum plate and Ag/AgCl (3.0 mol L⁻¹ KCl) as reference electrode. A high-resolution scanning electron microscopy (FEG/SEM - FEI QUANTA 450) and an energy dispersive X-ray spectroscopy (EDS) were used to examine the surface morphologies and compositions of the deposited films. Roughness and thickness were obtained by atomic force microscopy (AFM - Shimadzu SPM 9700), in the non-contact mode.

Electrochemical impedance spectroscopy measurements were carried out by a PARSTAT 2263A in a similar cell model as the polypyrrole grown conditions.

The spectrophotometric method was performed using a spectrophotometer Shimadzu UV-2401-PC with a quartz cuvette.

Reagents and Solutions

All solutions were prepared using purified water from Millipore (Milli-Q) system. All chemicals used were of analytical grade and used without previous treatment (except pyrrole). Pyrrole was previously distilled (stored at low temperature and protected from light exposure) to insure better reproducibility in the formation of polypyrrole film.

For potentiometric measurements, sodium citrate solutions were prepared daily by dissolving solid standard (Merck) in 10 mL of a 1.0×10^{-2} mol L⁻¹ solution of ammonium sulfate.

Electrochemical Procedures

Graphite pieces of 5.0 cm length were obtained from commercial graphite pencil Faber Castel (soft lead (HB) with 2.0 mm diameter) and manually polishing with an abrasive sheet P200. Afterward, the graphite pencil electrodes were directly connected to the potentiostat by cable and no additional pretreatment was required. For polymerization step, an area of 0.659 cm² (delimited with parafilm[®]) was immersed in the polymerization solution containing 1.0 mol L⁻¹ of pyrrole and 1.0×10^{-1} mol L⁻¹ of sodium citrate.

The preparation of polypyrrole film was performed using a galvanostatic procedure based on controlled current (anodic). Electrochemical parameters were evaluated: electric current densities varying from 0.09 to 0.38 mA cm⁻², electrical charge from 1 to 50 mC and the suitable conditioning time was evaluated ranging from 0 to 24 h.

For SEM and AFM measurements, the pyrrole polymerization was performed on ITO electrode (1.125 cm² of geometric area) under galvanostatic conditions. A solution containing 1.0 mol L⁻¹ of pyrrole was prepared and then added into two different solutions: 10 mL of potassium chloride 0.1 mol L⁻¹ and 10 mL of sodium citrate 0.1 mol L⁻¹. The films were obtained by current density of 0.23 mA cm⁻², electrical charge of 100 mC (PPy: citrate) and 200 mC (PPy: chloride).

Sample Preparation

For analysis of pharmaceutical formulations, the evaluated solutions were obtained by dissolving of commercial samples in

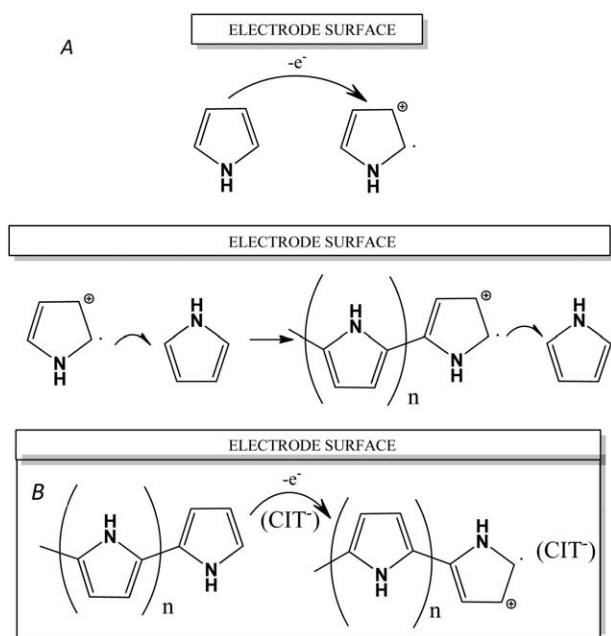


Figure 2. (A) Polymerization process of pyrrole; (B) Polypyrrole doping by citrate anion and membrane formation over the electrode surface.

ammonium sulfate 1.0×10^{-2} mol L $^{-1}$ solution after pulverization using mortar and pestle. No additional pretreatment was required.

The percentage content of SC in these sample was determined by the standard addition method, compared with a spectrophotometric method and also the labeled value provided by the manufacturer.

Comparative Method

For spectrophotometric analysis, commercial samples were dissolved in methanol and a filtration process was required before

the measurements. Twenty SC tablets were weighted and grinded with pestle in a mortar. A mass quantity of SC was weighted and dissolved in methanol, resulting in a solution of concentration 6.0×10^{-5} mol L $^{-1}$. The filtration was performed using a paper filter, a filter and solvent methanol. The measurements were carried out in 291 nm.

RESULTS AND DISCUSSION

Morphological and Structural Characterization of Ppy Films

A galvanostatic procedure for polypyrrole polymerization was adopted. As previously described,²⁶ the mechanism is based on pyrrole oxidation by applied anodic current which promotes formation of a pyrrole radical (with positive charge). Afterward, a sequential radical reaction is performed and the polymer deposited over the graphite pencil electrode with incorporation of citrate anions in order to reach the electro-neutrality of the film. The sequence of events that occur during polymerization step and membrane formation are shown in Figure 2.

SEM/EDS measurements were carried out in order to investigate the characteristics of the electrode surface after polypyrrole doping by citrate anions [Figure 3(a,b)] and chloride anions [Figure 3(d,e)]. On both films, the typical nodular PPy morphology was observed, as previously reported,^{28–30} showing that the PPy doping by citrate anion does not provide significant alterations in the morphological characteristics when compared to PPy:chloride films. EDS spectra showed the presence of elements confirming the qualitative doping of PPy: citrate [Figure 3(b)] and PPy:chloride [Figure 3(e)]. In addition, SEM images also revealed the formation of smaller nodules for PPy: citrate film than PPy:chloride film, confirmed by AFM topography [Figure 3(c,f)], probably affected by applied charge during film formation.³¹ The roughness average (R_a) of polypyrrole synthesized in citrate solution was estimated as 30.02 nm [Figure 3(c)] and as 31.89 nm for chloride solution

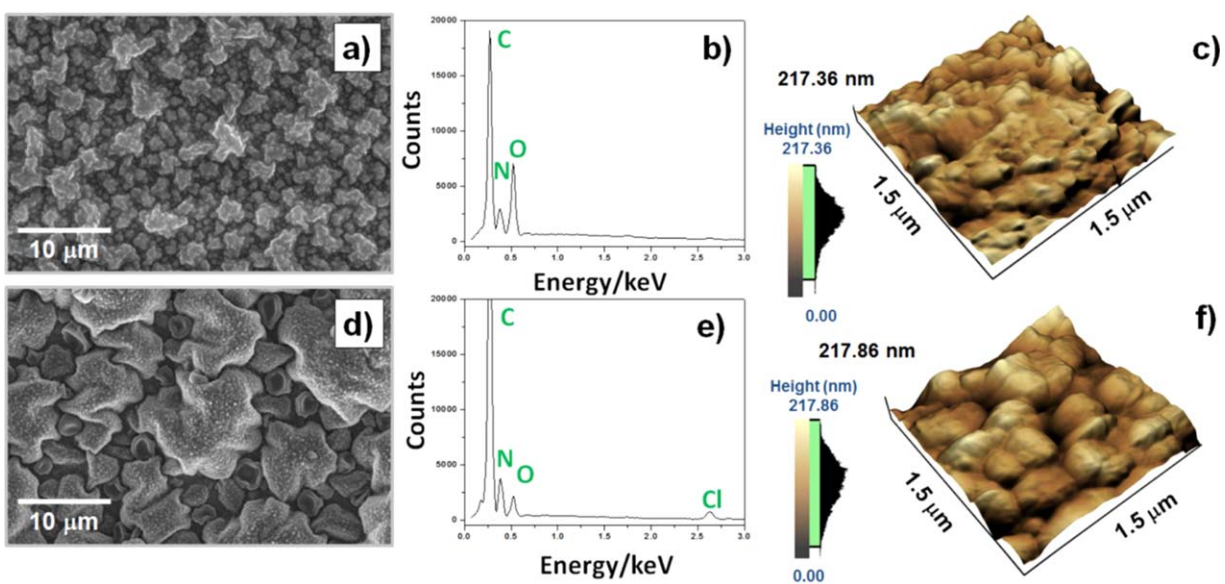


Figure 3. Polypyrrole doping by citrate anion (a,b,c) and by chloride anion (d,e,f). SEM images at the magnification of $\times 5000$ (a,d) and EDS spectrum (b,e). Three-dimensional AFM images in non-contact mode (c,f). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

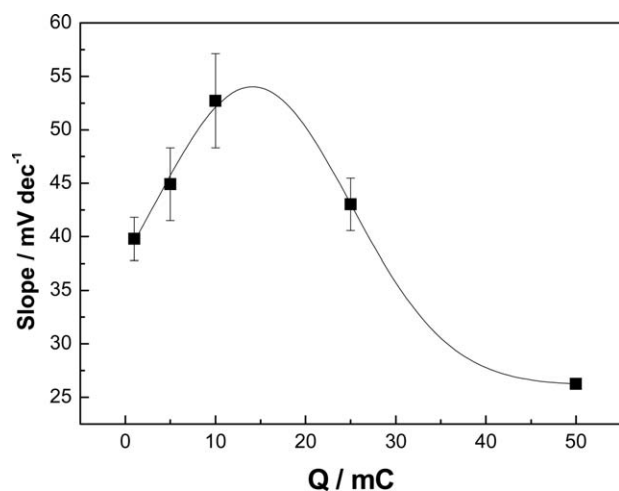


Figure 4. Influence of the electric charge on the potentiometric response of the proposed sensor.

[Figure 3(f)]. The surface roughness of PPy films showed poorly affected by changing the doping anion, probably due to polypyrrole nodules grow three-dimensionally simultaneously.³¹

Effect of Experimental Parameters on the Potentiometric Response of Sensor

In order to obtain the best performance of the proposed sensor some experimental parameters were optimized based on sensitivity values (slope) from potentiometric response for citrate ions. The effect of current density was evaluated for values ranging from 0.09 to 0.38 mA cm⁻². Current density (j) smaller than 0.23 mA cm⁻² yields a non-effective polymerization resulted in a poor potentiometric response. In contrast, for higher values of this current density, the response sensitivity was lower due to the increased diffusion barrier caused by the increased film thickness.^{19,25} For these reasons, best values of sensitivity for SC determination were obtained for a current density of 0.23 mA cm⁻², which was employed for further studies.

The electric charge used for the polymerization step can be related to the thickness of the polypyrrole film. The influence of this parameter was evaluated from 1 to 50 mC, varying the polymerization time used in the sensor preparation (using the optimized value of current density: 0.23 mA cm⁻²). The potentiometric responses for the ISE prepared in different electric charges are shown in Figure 4.

The potentiometric response of the sensor reached a maximum value for an electric charge of 10 mC with a decrease on sensitivity for higher values. Lower electric charges in the film deposition resulted in an inadequate coverage in the graphite

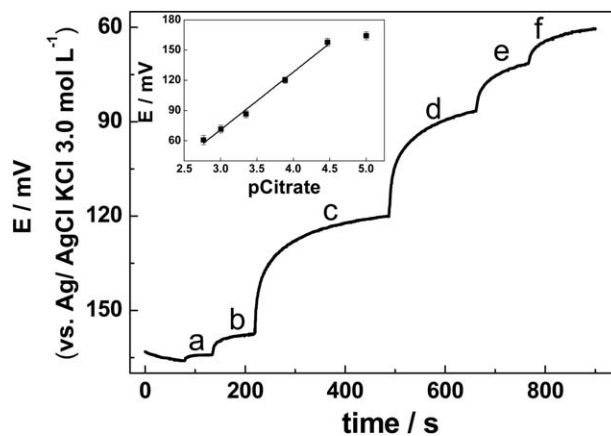


Figure 5. Chronopotentiometric response obtained using GPME/PPy-CIT; Analytical curve (in detail) for reference solutions of sodium citrate of (a) 9.9×10^{-6} , (b) 3.4×10^{-5} , (c) 1.3×10^{-4} , (d) 4.5×10^{-4} , (e) 9.9×10^{-4} , and (f) 1.7×10^{-3} mol L⁻¹.

electrode surface and consequently in an inefficient response of the ISE.^{27,32}

For conditioning time study, the proposed electrode was previously immersed in a conditioning solution of 1.0×10^{-2} mol L⁻¹ sodium citrate and calibration curves were obtained after a period from 0 to 24 h. The ISE response (sensitivity) has shown a slight decrease after 2 h of conditioning time, probably due to the stability of films is weakened after this time. Thus, an adequate potentiometric response for proposed sensor can be obtained keeping the electrode in 1.0×10^{-2} mol L⁻¹ sodium citrate solution for 2 h.

In order to evaluate the effect of pH on the potentiometric response, analytical curves were obtained in different pH values, from 2.0 to 6.0 using ammonium sulfate solution as supporting electrolyte. An increase on the slope of calibration was observed in the pH range from 2.0 to 4.0, which can be explained probably due to the first protonation of sodium citrate ($pK_{a1} = 3.14$). For pH > 4.0 a decrease in slope values was observed which could be related to the second protonation of sodium citrate ($pK_{a2} = 4.76$). Additionally, hydroxyl ions may react with the polymeric chain deposited over the electrode surface for pH values higher than 7.0, resulting in the exchange between the hydroxyl ions and the dopant anion and in the loss of selectivity for the potentiometric response.³⁰ Thus, solutions of (NH₄)₂SO₄ 0.1 mol L⁻¹ adjusted to pH 4.0 were used for potentiometric measurements.

Analytical Performance and Application of the Proposed Sensor

After optimization of experimental parameters, potentiometric measurements were carried out in (NH₄)₂SO₄ 0.1 mol L⁻¹

Table I. Determination of SC in Pharmaceutical Samples Using the Proposed Sensor and Reference Spectrophotometric Method

Sample	Labeled (mg/tablet)	Proposed (mg/tablet)	Reference (mg/tablet)	(E_{r1}) ^a /%	(E_{r2}) ^b /%
EuroFarma [®]	50	49.8 ± 3.8	52.8	-0.4	-5.7
Medley [®]	100	102.7 ± 7.6	100	+2.7	+2.7

^a E_{r1} : labeled value vs. potentiometric method.

^b E_{r2} : spectrophotometric method vs. potentiometric method.

Table II. General Characteristics of the Electrochemical Methods Used for Sildenafil Citrate Determination in Several Samples

Electrode	Technique	LDR (mol L ⁻¹)	LOD (mol L ⁻¹)	Reference
GCE/Bismuth film	AdCSV	1.0 × 10 ⁻⁷ –1.0 × 10 ⁻⁶	1.8 × 10 ⁻⁸	10
BDDE	FIA	6.0 × 10 ⁻⁷ –1.0 × 10 ⁻⁴	1.0 × 10 ⁻⁸	14
SC-PMA	Potentiometry	10 ⁻² –10 ⁻⁵	5.0 × 10 ⁻⁶	33
SC-TPB			6.0 × 10 ⁻⁶	
CPE	Potentiometry	1.0 × 10 ⁻⁷ –1.0 × 10 ⁻²	9.0 × 10 ⁻⁸	34
SPCE		5.3 × 10 ⁻⁷ –1.0 × 10 ⁻²	3.5 × 10 ⁻⁷	
Ppy/Cit/Graphite	Potentiometry	3.4 × 10 ⁻⁵ –1.7 × 10 ⁻³	3.0 × 10 ⁻⁵	This work

AdCSV, adsorptive cathodic stripping voltammetric; BDDE, boron doped diamond electrode; FIA, flow injection analysis with amperometric detector; SC-PMA, complex ion associates of SC with phosphomolybdic acid in poly vinyl chloride membrane (PVC); SC-TPB, complex ion associates of SC with sodium tetraphenylborate in PVC; CPE, carbon paste electrode; SPCE, screen-printed carbon electrode.

solution (pH 4.0). Additions of sodium citrate solutions were performed in a potentiometric cell in order to obtain different concentrations of the compound and analytical curves were constructed by monitoring potential values. The response of the ISE for different concentrations of citrate is illustrated in Figure 5.

The potentiometric response of the GPME follows the equation: $E/mV = -100.8 + 57.2 pC_{\text{citrate}}$ with a linear relationship citrate concentration ranging from 0.034 to 1.7 mmol L⁻¹ with a limit of detection (LOD) of 30 μmol L⁻¹. The reproducibility and repeatability of the proposed method was evaluated ($n = 4$) and standard deviation of 2.1 and 1.4%, respectively, were obtained, indicating there is no significant variability on the potentiometric response of the ISE. The sensor exhibits stable response until 4 h after the growth of polypyrrole film and in 6h the response decreased to 70% of the original sensitivity.

The selectivity of the proposed method was evaluated by potentiometric measurements for solutions containing different inorganic and organic species such as caffeine, sulfate, chloride and nitrate and no significant interference was observed, even for a 10-fold concentration level of the evaluated species. Selectivity coefficients of the sensor for some interfering ions B relative to SC were determined by the separate solutions method (SSM). The selectivity coefficients ($K_{SC, B}^{\text{pot}}$) were determined with the rearranged Nicolsky equation:

$$\log K_{SC, B}^{\text{pot}} = \left(\frac{E_1 - E_2}{S} \right) + \left(1 + \frac{Z_1}{Z_2} \right) \log(a_B)$$

where E_1 is the potential measured in 10⁻³ mol L⁻¹ of SC, E_2 the potential measured in solution content 10⁻³ mol L⁻¹ of the interfering ion (B), Z_1 , and Z_2 are the charges of the SC and interfering species B, respectively; S is slope of the calibration curve. For neutral compounds the charge (Z_2) adopted was equal to zero. The determined selectivity coefficients were: $\log K_{SC, \text{dipyron}}^{\text{pot}} = -7.30$, $\log K_{SC, \text{Sulfate}}^{\text{pot}} = -5.98$, $\log K_{SC, \text{nitrate}}^{\text{pot}} = -7.97$ and $\log K_{SC, \text{chloride}}^{\text{pot}} = -8.00$ which are demonstrating a good selectivity to citrate anions. In addition, PPy films doped with chlorine ions do not exhibit a selective potentiometric response for citrate anions.

Under optimized conditions, the proposed sensor was applied for determination of SC in two different commercial samples.

The obtained results were compared with a spectrophotometric method, as shown in Table I.

Recoveries values of 99.6% and 102.7% were obtained using the ISE confirming the accuracy and the applicability of the proposed procedure. Furthermore, statistical calculations using the *t*-student test (with confidence level of 95%, for $n = 4$) showed no statistical difference between the results from the proposed method and the results from the spectrophotometric method.

CONCLUSIONS

This study reports the use of anion citrate as counter-ion on polypyrrole films resulted in a simple, effective and disposable potentiometric sensor for indirect determination of sildenafil in pharmaceutical formulations with a concentration ranging from 0.034 to 1.7 mmol L⁻¹ and LOD of 30 μmol L⁻¹. Experimental conditions used in the polymerization and measurement steps showed a significant influence on the potentiometric response of the developed ISE. The proposed low cost potentiometric sensor could be easily applied with good sensitivity, 57.2 mV dec⁻¹ (Nernstian), and accuracy exhibiting deviations in the order of 2%, in comparison with literature (Table II), resulting in a promising method of determination of this compound with low cost.

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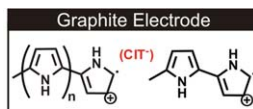
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Potentiometric Measurements

