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ORIGINAL PAPER

Diamond paste-based electrodes for the determination of sildenafil citrate (Viagra)

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Abstract Three types of monocrystalline diamond: natural diamond 1 µm, synthetic diamond 50 µm (synthetic-1), and synthetic diamond 1 µm (synthetic-2) were used for the design of diamond paste electrodes for the determination of sildenafil citrate (Viagra) using square wave voltammetry. The linear concentration ranges recorded for sildenafil citrate when natural diamond, synthetic-1, and synthetic-2 based electrodes were used were between 10^{-12} and 10^{-8}, 10^{-12} and 10^{-9}, and 10^{-11} and 10^{-9}mol/L, respectively. Low detection limits which lie between 0.1 and 1 pmol/L proves the sensitivity of the electrodes. It was found that sildenafil citrate yielded a peak at about +0.175±0.025 V (versus Ag/AgCl) for all the electrodes. Sildenafil citrate was determined with high reliability from its pharmaceutical formulation.

Keywords Diamond paste electrodes · Monocrystalline diamond · Sildenafil citrate

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Introduction

Chemical and electrochemical properties of diamond such as low background current, wide potential range, and lack of adsorption [1–13] made the electrodes based on diamond paste very special. Explanations regarding the electrical properties (especially conductivity) of diamond were given with several occasions by physicists and are based on the mobilities of electrons and holes, on the inherent structural defects of diamond crystals, as well as on the presence of small amounts of impurities in its structure. Polycrystalline diamond-based electrodes were the first to be used in electrochemical studies, boron-doped diamond being well known in the scientific community [14]. Monocrystalline diamond proved to be a good alternative for polycrystalline material due to its special properties, such as improved holes and electrons mobilities [15, 16]. To date, the monocrystalline diamond paste electrodes showed improved sensitivities, noise, limits of detection, selectivity, and reliability for the analysis of different inorganic [17–21] and organic substances, also when used in enantioanalysis [22–24].

Sildenafil citrate (Viagra), 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate (Fig. 1), is a drug used in the therapy of erectile dysfunction which inhibits the cyclic guanosine monophosphate-specific phosphodiesterase type 5 [25–27]. It has demonstrated effectiveness in men with erectile dysfunction associated with prostatectomy, radiation therapy, diabetes mellitus, certain neurologic disorders, and drug therapy (e.g., selective serotonin reuptake inhibitors) [28]. Studied initially for its use in treatment of hypertension and angina, Viagra was very efficient for the proposed treatment, but for one of its secondary effects that appear during the trials of drug, namely, change in erectile function. As a result, the research

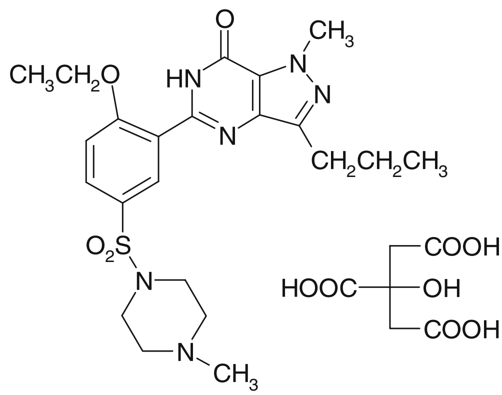

Fig. 1 Sildenafil citrate

team changed the purpose of utilization of the drug on the new direction and proved that it can be used in patients having this deficiency. In the general population, sildenafil is considered to have an acceptable tolerability profile; however, patients with moderate to severe cardiovascular disease or those taking nitrate therapy are at an increased risk for potentially serious cardiovascular adverse effects with sildenafil therapy. In addition, patients taking drugs that inhibit the cytochrome P450 3A4 isozyme, which metabolizes sildenafil, may experience increased drug concentrations and possible toxicity from normal doses of sildenafil [28]. To date, numerous analytical techniques were proposed for the assay of sildenafil citrate: potentiometry [29], voltammetry [30, 31], spectrometry [32], flow injection analysis [33], and chromatography [34, 35].

In this paper, three electrodes based on monocrystalline diamond paste are described for the assay of sildenafil citrate. A diamond paste similar with the carbon paste was preferred for electrodes design. Three types of diamonds were used for the design of the diamond paste: a natural diamond and two types of synthetic diamonds. Square wave voltammetry (SWV) was used for the calibration of the electrodes and for the recovery tests of sildenafil citrate.

Experimental

Diamond paste electrodes design

Each diamond paste electrode was prepared by mixing 0.1 g of diamond powder with 20 µL paraffin oil. A portion of the paste was then filled into a plastic pipette tip. The diameter of the sensing part was 2.3 mm. Electric contact was made by inserting a silver wire into the diamond paste. Before use, the electrode surface was smoothed by polishing with an alumina paper (polishing strips 30144-001, Orion). When not in use, the diamond paste electrode was stored dry at room temperature.

Reagents and materials

All chemicals were of analytical reagent grade. All solutions were prepared by using doubly distilled water. $HClO_4$ and $NaClO_4$ were purchased from Merck. High-purity monocrystalline diamond powder: natural diamond 1 µm, synthetic diamond 50 µm (synthetic-1), and synthetic diamond 1 µm (synthetic-2) were purchased from Aldrich, while the paraffin oil was purchased from Fluka (Buchs, Switzerland). All solutions were deoxygenated prior to use by thorough degassing with high-purity N_2.

Preparation of pharmaceutical for analysis

Each of the five tablets of Viagra (sildenafil citrate 50 mg/tablet) was dissolved separately in 100 mL doubly distilled water. SWV was recorded for the solutions containing different portions of aqueous solutions in 20 mL of a 0.01-mol/L $HClO_4$ and $NaClO_4$ (pH 2.00).

Direct SWV assay

The technique used for the direct voltammetric assay was SWV. All measurements were performed at 25 °C. The diamond paste electrode together with the reference and auxiliary electrodes were dipped into a cell containing a solution of 0.01 mol/L $HClO_4$ and $NaClO_4$ (pH 2.00). All solutions were deoxygenated before the measurements with N_2. The peak height measured at 175 mV versus Ag/AgCl was plotted versus the concentration of sildenafil citrate. The unknown concentrations of sildenafil citrate were determined from the calibration graphs.

Apparatus

Square wave voltammograms were recorded using a 663 VA Stand (Metrohm, Herisau, Switzerland) connected to a PGSTAT 100 and an Ecochemie Software Version 4.9. A platinum electrode and a Ag/AgCl (0.1 mol/l KCl) electrode served as counter and reference electrode in the cell, respectively. The operating conditions were: potential range, −0.4 to +0.4 V (versus Ag/AgCl); equilibration time 5 s.

Result and discussion

Calibration equations

The relation between the peak height and the concentration of sildenafil citrate was linear over a wide concentration range and can be read from the following equations of calibration: (a) natural diamond, (b) synthetic-1, and (c) synthetic-2:

(a) $H = 1.9 \times 10^{-5} + 778.6\,C; r = 0.9956; < C >= \mu\text{mol/L},$
(b) $H = 1.7 \times 10^{-5} + 15.9\,C; r = 0.9949; < C >= \text{nmol/L},$
(c) $H = 4.1 \times 10^{-6} + 8886.3\,C; r = 0.9969; < C >= \text{nmol/L}$

where H is the height of the peak (in microamperes), C is the concentration of sildenafil citrate, and r is the regression coefficient. For natural diamond, the linear concentration range was between 10^{-12} and 10^{-8}mol/L with a detection limit of 10^{-13}mol/L; for synthetic-1, between 10^{-12} and 10^{-9}mol/L with a detection limit of 10^{-13}mol/L; and for synthetic-2, between 10^{-11} and 10^{-9}mol/L with a detection limit of 10^{-12}mol/L. The reproducibility of the reduction peak (at C=O group) currents were good (RSD less than 1%, n=10). The advantages of using such electrodes over the hanging mercury drop electrode proposed by Berzas et al. [31] are nontoxicity, increased sensitivity, extension of the linear concentration range to a very low concentration (up to picomoles per liter magnitude order), and decrease of the limit of detection.

The best electrode accordingly with its sensitivity is the one based on synthetic-2 diamond paste although its linear concentration range is very small. Overall, the best behavior was achieved by the natural diamond paste-based electrode in terms of shape (Fig. 2) and linear concentration range, although it is not as sensitive as the one based on synthetic-2 diamond paste, but more sensitive than the one based on synthetic-1 diamond paste. Typical square wave voltammograms of sildenafil citrate obtained using the natural diamond paste-based electrode are shown in Fig. 3.

The reason of selection of natural and synthetic diamonds for electrodes design is to determine if they behave similarly or differently as electrode materials; the comparison between the designed electrodes was possible by selection the same particle size (1 µm) for both types of diamonds. The influence of the particle size on the response characteristics of the electrodes was determined by utilization of a synthetic diamond with a higher particle size (50 µm). Regarding the differences in the structures of natural and synthetic diamonds, the best behavior of natural diamond-based electrode proved that, due to the uncontrolled development of the monocrystals, it presents more structural defects than the synthetic diamonds made using a well-known controlled synthesis.

An analysis of the electrochemical noise was performed for all the diamond paste electrodes, and the results were compared with those obtained for glassy carbon- and carbon paste-based electrodes. This analysis proved that, by using the diamond as electrode material, the noise is decreased 100 times for natural diamond and 10 times for both synthetic diamonds.

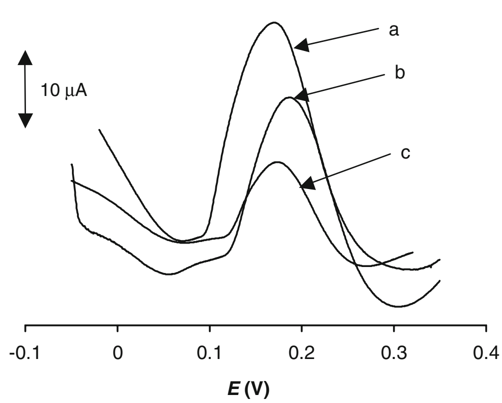

Fig. 2 Typical comparative square wave voltammograms of 1×10^{-9} mol/L sildenafil citrate at electrodes based on *a* natural diamond, *b* synthetic-1, and *c* synthetic-2. All measurements were done in a solution containing $HClO_4$ and 0.01 mol/L $NaClO_4$; pH 2

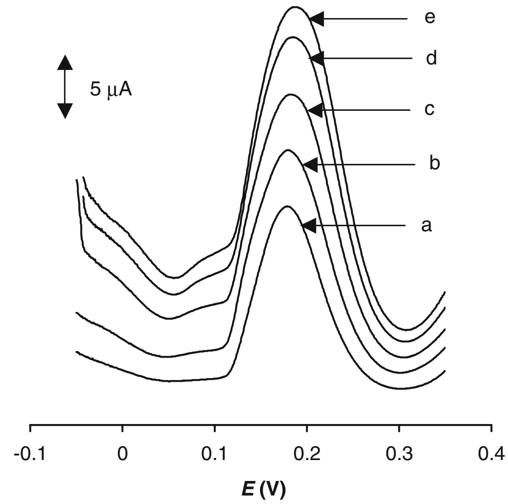

Fig. 3 Typical square wave voltammograms of *a* 1×10^{-12}, *b* 1×10^{-11}, *c* 1×10^{-10}, *d* 1×10^{-9}, and *e* 1×10^{-8}mol/L sildenafil citrate at natural diamond paste electrode. All measurements were done in a solution containing $HClO_4$ and 0.01 mol/L $NaClO_4$; pH 2

Table 1 Determination of sildenafil citrate in Viagra® tablets (50 mg sildenafil citrate per tablet)

Tablet	Recovery of sildenafil (mg)		
	ND	SD-1	SD-2
1	48.76±1.43	48.61±1.44	47.72±1.40
2	47.84±1.38	47.53±1.31	47.44±1.50
3	48.21±1.33	47.90±1.36	47.46±1.53
4	48.56±1.30	48.10±1.38	47.50±1.45
5	47.91±1.41	47.95±1.39	47.49±1.51

All measurements were made at 25 °C; all values are averages of ten determinations

Selectivity studies

Polyvinylpyrrolidone was tested as possible interfering species in the determination of sildenafil citrate using the mixed solutions method. The ratio between it and sildenafil citrate was 10:1. The choice of this substance was due to the fact that it can be used in the formulation of sildenafil citrate. Amperometric selectivity coefficients of 1.12×10^{-3}, 1.09×10^{-3}, and 2.52×10^{-3} were obtained for the electrodes based on natural, synthetic-1, and synthetic-2 diamond paste-based electrodes, respectively. These values proved that polyvinylpyrolidone did not interfere in the determination of sildenafil citrate.

Analytical applications

The high sensitivity and wide concentration range of the proposed electrodes made their utilization possible for the determination of sildenafil citrate in pharmaceutical products and biological samples. The SWV method was used for the recovery of sildenafil citrate in its pharmaceutical formulation. Table 1 shows that the values obtained for the average recoveries of sildenafil citrate in its pharmaceutical formulation are comparable when using different diamond electrodes.

Conclusion

The design of the monocrystalline diamond paste-based electrode is simple and reliable ensuring a high reliability of analytical information. The advantages of using these electrodes over mercury and glassy carbon electrodes for the determination of sildenafil citrate are higher sensitivity, wider linear concentration range, and lower limit of detection. The best of the three electrodes is the one based on natural diamond paste. One of the features of the proposed electrodes is their utilization for the in vivo assay of sildenafil citrate in biological samples, diamond paste being one of the most biocompatible materials.

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