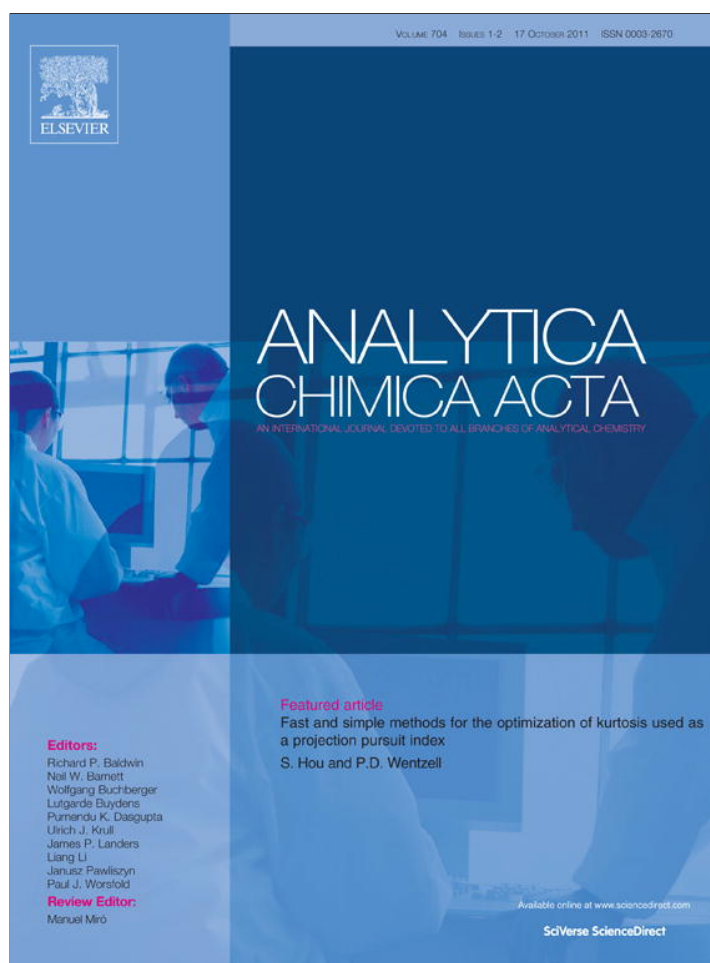


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Electrochemical quantification of 2,6-diisopropylphenol (propofol)

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ABSTRACT

2,6-Diisopropylphenol (propofol) is a potent anesthetic drug with fast onset of the anesthetic effect and short recovery time for the patients. Outside of the United States, propofol is widely used in performing target controlled infusion anesthesia. With the long term vision of an electrochemical sensor for *in vivo* monitoring and feedback controlled dosing of propofol in blood, different alternatives for the electrochemical quantification of propofol using diverse working electrodes and experimental conditions are presented in this contribution.

When the electrochemical oxidation of propofol takes place on a glassy carbon working electrode, an electrochemically active film grows on the electrode surface. The reduction current of the film is proportional to the propofol concentration and the accumulation time. Based on these findings a stripping analytical method was developed for the detection of propofol in acidic solutions between 0 and 30 μM , with a detection limit of $5.5 \pm 0.4 \mu\text{M}$.

By restricting the scanned potential window between 0.5 V and 1.0 V in cyclic voltammetric experiments, the formation of the electrochemically active polymer can be prevented. This allowed the development of a direct voltammetric method for assessing propofol in acidic solutions between 0 and 30 μM , with a $3.2 \pm 0.1 \mu\text{M}$ ($n = 3$) detection limit.

The stripping method has a better sensitivity but somewhat worse reproducibility because the electrode surface has to be renewed between each experiment. The direct method does not require the renewal of the electrode surface between measurements but has no adequate selectivity towards the common interfering compounds.

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1. Introduction

2,6-Diisopropylphenol (propofol) is a potent anesthetic drug with fast onset of the anesthetic effect and short recovery time for the patients. It is widely applied in ambulatory anesthesia and intensive care units (ICU) for sedation. Propofol is highly lipid soluble but hardly soluble in water [1]. The therapeutic range of propofol is between 0.25 and 4.0 $\mu\text{g mL}^{-1}$ or between 1.4 and 22.5 μM [2–7].

Real-time *in vivo* measurement of propofol in patients would permit the correlation of serum levels with therapeutic efficacy data and enhance the safety of propofol delivery for target-controlled infusion anesthesia (TCIA) [8–12] in which the infusion rate of the drug is determined by population-based

pharmacokinetic data and individual patient biometrics instead of measured drug levels [8,11,13,14]. However, despite its importance, real-time measurements of propofol concentration in blood and other biological fluids have proved elusive. Current analytical methods are time consuming and require laboratory analysis with complex instrumentation, e.g. head space gas chromatography–mass spectrometry, ion-mobility spectrometry, liquid chromatography–mass spectroscopy [15–21]. Due to the very rapid half-life of the propofol drug, these methods have proven to be inadequate for rapid quantification of serum propofol levels or continuous monitoring in whole blood at the bedside. Recent works towards a real-time assessment and monitoring system have been reported by Miekisch et al. [22]. The authors coupled a solid-phase microextraction system with gas chromatography–mass spectrometry to assess the correlation between breath and blood (arterial and venous) propofol concentrations in patients under anesthesia or sedation using simultaneous sampling in combination with off-line analysis. On the other hand Hornuss et al. [23] coupled their ion-molecule reaction mass spectrometry (IMR–MS) system directly to the endotracheal tube and performed on-line *in vivo*

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determination of exhaled propofol levels. These rather complex approaches indicate the importance of propofol monitoring during anesthesia. Our motivation for this work is to develop a method capable of direct measurement of propofol *in vivo*. We intend to develop voltammetric methods for the quantitative determination of propofol, which ultimately can be implemented for continuous monitoring and eventually for “closed loop” feedback controlled drug delivery. To achieve this goal, first we studied the electrochemical oxidation of propofol using different working electrodes (gold, platinum and glassy carbon disk) under various experimental conditions.

The electrochemistry of phenol derivatives has an extensive literature [24–27]. Unfortunately the oxidation of phenolic compounds at solid electrodes produces phenoxy radicals that usually lead to electrode passivation and fouling [26–32]. Compared to the wealth of papers on the electrochemical quantification of phenolic compounds, very few manuscripts discuss the electrochemical oxidation of propofol. In most of these papers the electrochemical detectors were used in combination with high performance liquid chromatography to assess the propofol concentrations in serum, plasma or whole blood [33–36]. As a consequence, these papers in general, do not discuss the difficulties of the electrochemical determination of propofol (the importance of the electrode material, applied potential, electrode fouling, etc.). However, there is plenty of information on the electrochemistry of a variety of phenolic antioxidants with very similar structures to propofol, e.g. butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and tert-butylhydroquinone. The voltammetric behavior of these antioxidants on glassy carbon [37–39], boron-doped diamond [40,41], carbon composite [42] and platinum [43–47] electrodes was studied in acetonitrile, acetonitrile–water, ethanol–water, and acidic ethanol–benzene mixtures. Due to their importance as preservatives that prevent the oxidative degradation of fats and oils BHA and BHT were determined by voltammetric methods in solid food samples [37,39,42], edible oils [45] as well as in transformer oils [43]. The mechanism of the electrochemical oxidation varies with the background electrolyte in which the experiments are performed. In acidic solutions it is suggested that the oxidation follows an ionic path while in neutral solutions the importance of a radical reaction path is emphasized [43].

Most recently, Thiagarajan et al. [48] demonstrated the advantageous properties of preanodized, screen printed carbon electrode for the determination of propofol in physiological pH range and showed the feasibility of the electrochemical measurement of propofol in a flow injection analysis assay.

2. Experimental

2.1. Reagents, materials and electrodes

2,6-Diisopropylphenol was purchased from Aldrich (St. Louis, MO) and used as received for preparation of a 0.01 M stock solution in 0.1 M NaOH or 0.1 M in 3:7 mixture of water to methanol. All other aqueous solutions were prepared with water purified by Milli-Q Gradient A10 System (Millipore Corp., Billerica, MA).

Voltammetric measurements were performed using the Autolab/PGSTAT12 System equipped with the GPES Version 4.8 (Eco Chemie B.V., Utrecht, NL, <http://www.ecochemie.nl>) in a standard three-electrode cell setup with platinum ($\varnothing = 1.6$ mm), gold ($\varnothing = 1.6$ mm), or glassy carbon (GC) ($\varnothing = 3$ mm) disk working electrodes (all from Bioanalytical Systems (BAS), West Lafayette, IN), platinum wire counter electrode, and an Orion Research Model 90-02 double junction, Ag/AgCl reference electrode (Orion Research, Inc., Beverly, MA) with 10% KNO₃ outer filling solution. The working electrodes were always polished with 0.3 μ m particle size alumina sludge prior to use.

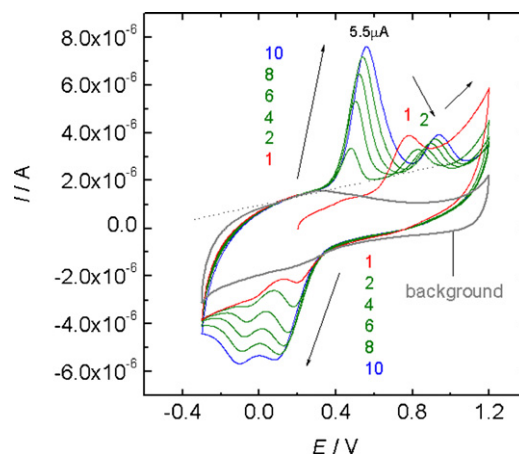


Fig. 1. Cyclic voltammograms recorded with a BAS $\varnothing = 3$ mm glassy carbon electrode in 10^{-4} M propofol solutions in the presence of 10^{-2} M H₂SO₄ at 0.1 V s⁻¹ scan rate. The consecutive scans are labeled 1–10. The arrows show the direction of change for consecutive scans. The traces representing the first and tenth scans are labeled red and blue, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Based on the comments of McBride and Evans [38] and Michalkiewicz et al. [44], that dissolved oxygen does not interfere with the voltammetric determination of BHA and BHT, oxygen was not removed from the propofol standard solutions before the voltammetric experiments reported in this study.

3. Results and discussion

Cyclic voltammetric experiments performed with a platinum working electrode did not show any significant oxidation current signal when the working electrode potential was scanned between -0.3 V and 1.4 V in 4×10^{-4} M propofol solutions with 10^{-2} M H₂SO₄ as background electrolyte. Instead, only indications of electrode passivation were observed around the potential values related to platinum oxide formation. Similarly, the same concentration of propofol in 10^{-2} M NaOH as background electrolyte had no effect on the background current when the potential of the Pt working electrode was scanned in the potential range between -0.7 V and 1.0 V. Conversely, propofol could be oxidized on the gold working electrode however the Au electrode surface became quickly passivated. After only four scans between -0.2 V and 1.0 V in a pH 7.2 phosphate buffer solution, the current at 0.8 V dropped to $\sim 50\%$ of its original value and after 10 scans it was less than 10% of its original value (not shown).

In contrast to the results obtained with the gold electrode, cyclic voltammetric experiments with a glassy carbon (GC) working electrode yielded a gradually growing current signal in 10^{-4} M propofol solutions when the potential was scanned at 0.1 V s⁻¹ scan rate between -0.4 V and 1.2 V, using different concentrations of H₂SO₄ as background electrolyte. As shown in Fig. 1, by starting the potential scan at 0.2 V and scanning the potential towards positive potential values, the first oxidation peak of propofol (monomer) is observed at around 0.7 V. During the reverse scan, two reduction peaks emerged (~ 0.2 V and -0.03 V) that grew with subsequent cycles. Scanning towards positive potential values once more, an additional oxidation peak emerges at 0.4 V, which gradually increases in subsequent cycles. The shape of the cyclic voltammograms, the peak potential and peak current values as well as the capacitive current depend on the pH of the propofol solutions. In this work the measurements were performed in sulfuric acid solutions with H₂SO₄ concentrations ranging between 10^{-3} and 1 M. Similar to other phenolic compounds, increasing pH shifts the oxidation peak of propofol towards lower potential values [33]. In

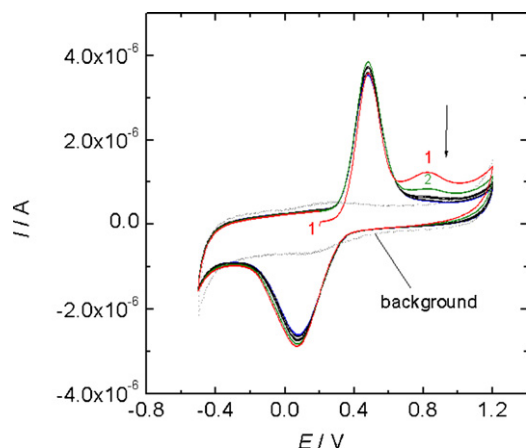


Fig. 2. Ten cyclic voltammograms recorded with a glassy carbon working electrode at 0.1 V s^{-1} scan rate in $10^{-2} \text{ M H}_2\text{SO}_4$ solution without propofol. The GC electrode was placed into the $10^{-2} \text{ M H}_2\text{SO}_4$ background electrolyte immediately after the experiments shown in Fig. 1. The numbers in the figure indicate the 1st and 2nd scans, while the arrow indicates the direction of change for consecutive scans.

accordance with this trend, the oxidation peak at 0.7 V in Fig. 1, that was assigned to the monomer oxidation in $10^{-2} \text{ M H}_2\text{SO}_4$ emerges around 0.2 V in 10^{-2} M NaOH (not shown). In 10^{-2} M NaOH solution of propofol, the peaks assigned to the electrochemical reactions of the polymer also develop at more negative potentials. In summary, despite the similarities, the electrochemical behavior of propofol and the electropolymerized films in acidic and basic solutions were quite different. In basic solutions the oxidation current of propofol decreased with the number of cycles and after 10 scans an insulating passivation layer was formed on the electrode surface. However, this passivation layer could be removed by scanning the electrode potential in 10^{-2} M NaOH solution without propofol.

The growing peaks between 0.4 V and 0.6 V (oxidation) and between -0.1 V and 0.3 V (reduction) are attributed to the deposition of an electrochemically active layer on the GC electrode surface while the peaks between 0.7 and 0.9 V are related to the direct oxidation of propofol (monomer). These statements can be supported by the results shown in Fig. 2. Following 10 scans in 10^{-4} M propofol solution (in $10^{-2} \text{ M H}_2\text{SO}_4$ background electrolyte as shown in Fig. 1) the GC working electrode was placed into $10^{-2} \text{ M H}_2\text{SO}_4$ without propofol and 10 cyclic voltammograms were recorded using the same reference electrode. As it can be seen, during continuous cycling of the electrode potential, only two peaks, corresponding to the oxidation and reduction of the electrochemically active layer remained. This behavior is similar to electrochemically deposited conductive polymer films. The peak at 0.8 V is related to the direct oxidation of traces of adsorbed propofol from the preceding experiment. As shown in Fig. 2 this peak disappeared after the 3rd cycle.

The overall reaction resulting in the electrochemically active layer formed on the surface of glassy carbon is uncertain. However, it is presumed that similar to the electrochemical oxidation of other phenolic compounds the oxidation of propofol generates radical species that polymerize and remain adsorbed at the electrode surface [28]. This polymerization of propofol is expected to yield rather linear polymeric chains since the ortho positions of the monomer are blocked.

Surfactants are commonly used to improve the quality of the electrochemically deposited conductive polymeric films [49–53]. The presence of surfactants in the monomer solutions improves polymer growth and influences the morphology of the deposited films which results in improved electrical properties and mechanical stability. The introduction of surfactants, like Tween 20 or lauryl sulfate, into the propofol solutions did not significantly change the

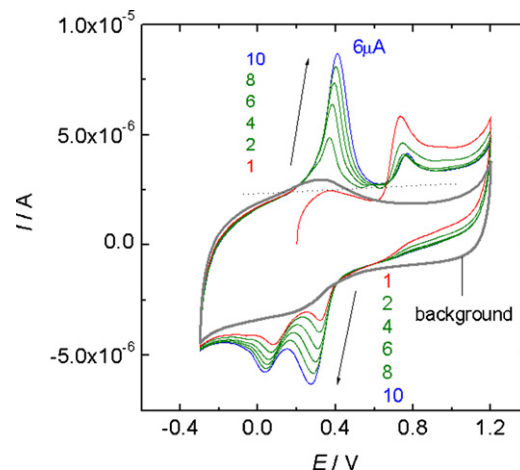


Fig. 3. Cyclic voltammograms recorded with a glassy carbon electrode at 0.1 V s^{-1} scan rate in 10^{-4} M propofol solution containing also $10^{-2} \text{ M H}_2\text{SO}_4$ and 10^{-3} M lauryl sulfate. The consecutive scans are labeled with numbers. Traces of the 1st and 10th scans are labeled red and blue, respectively. The arrows indicate the direction of change for consecutive scans. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

shape of the voltammograms but improved the stability of all peak potentials in consecutive scans. Fig. 3 shows that in the presence of 10^{-3} M lauryl sulfate the peak potential values hardly change from cycle to cycle. In stirred solutions, all peak currents were almost doubled and the reduction peaks merged into a single peak at 0.2 V (Fig. 4).

The peak related to the reduction of the primary product of the propofol oxidation offers an attractive possibility for the quantitative determination of propofol by cathodic stripping voltammetry because it emerges between 0.0 V and 0.3 V where the effect of interferences is expected to be minimal. To evaluate this possibility the potential of the working electrode was kept at the oxidation potential of propofol (0.8 V), to accumulate the electroactive polymer, and then the polymer was reduced by linear sweep cathodic stripping voltammetry. The correlation between the accumulation time and the cathodic stripping response in 10^{-4} M propofol solution in the presence of 10^{-3} M lauryl sulfate and $10^{-2} \text{ M H}_2\text{SO}_4$ is shown in Fig. 5. As shown in the figure, the reduction peak current increases linearly with the accumulation time.

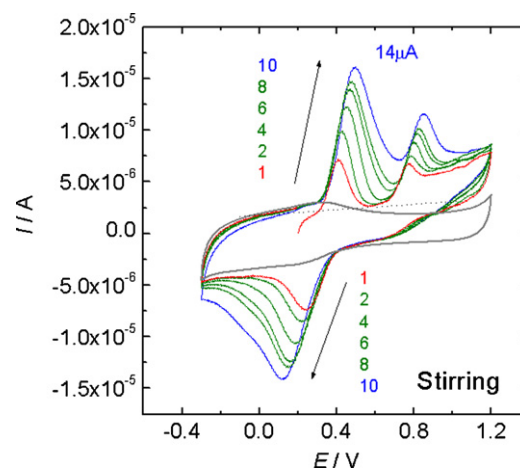


Fig. 4. Cyclic voltammograms recorded with a glassy carbon electrode at 0.1 V s^{-1} scan rate in stirred 10^{-4} M propofol solution containing also 10^{-3} M lauryl sulfate and $10^{-2} \text{ M H}_2\text{SO}_4$. The consecutive scans are indicated with numbers. Traces of the 1st and 10th scans are labeled red and blue, respectively. The arrows indicate the direction of change for consecutive scans. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

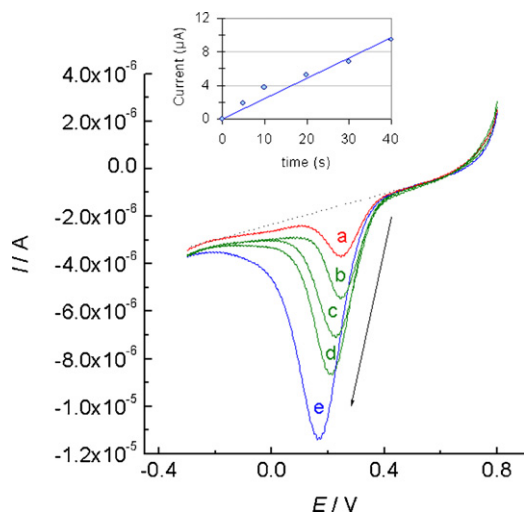


Fig. 5. Cathodic stripping responses of a glassy carbon electrode with propofol accumulated at 0.80 V for (a) 5 s, (b) 10 s, (c) 20 s, (d) 30 s and (e) 40 s. Solutions prepared with 10^{-4} M propofol, 10^{-2} M H_2SO_4 and 10^{-3} M sodium lauryl sulfate. Scan rate = 0.1 V s^{-1} . Inset: correlation between the accumulation time and the cathodic peak current.

The above stripping protocol was applied to solutions with different concentrations of propofol. Fig. 6 shows that the reduction peak increases linearly with the concentration of propofol: $i_p = -(0.080 \pm 0.005)[\mu\text{A}/\mu\text{M}] \times C_{\text{propofol}}[\mu\text{M}] + (0.05 \pm 0.08)[\mu\text{A}]$. The sensitivity can be improved by increasing the accumulation time and the scan rate during the stripping step. The residual mean standard deviation (RMSD) around a fitted regression line in the figure is $0.15 \mu\text{A}$. The detection limit (DL) of the method is calculated as $5.5 \mu\text{M}$ by using the formula: $\text{DL} = 3 \times \text{RMSD}/S$, where S is the slope of the calibration curve.

The strongly adsorbed, electrochemically active film develops on the electrode surface during the reduction of the initial product of propofol oxidation. The prevention of this polymer formation/adsorption on the electrode surface makes the development of a direct voltammetric method for the quantitative assessment of propofol possible. This can be achieved by restricting the scanned potential window between 0.5 V and 1.0 V. Fig. 7 shows a set of cyclic voltammograms recorded in acidic (10^{-2} M H_2SO_4) propofol solutions of different concentrations without renewal of the electrode surface between the individual measurements. The propofol concentration was varied from $1.25 \mu\text{M}$ to $30.3 \mu\text{M}$ by

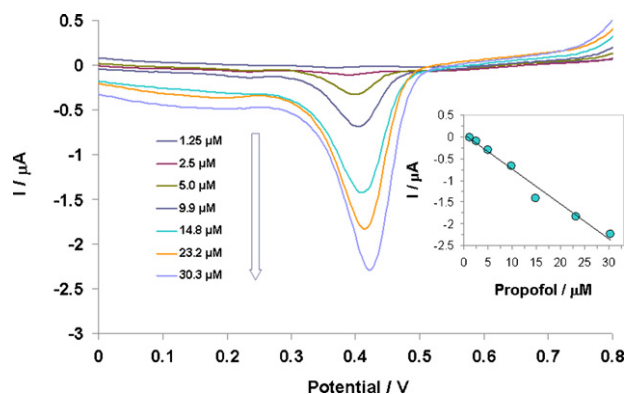


Fig. 6. Cathodic stripping voltammetric profiles recorded with a GC working electrode in different concentrations of propofol solutions of 10^{-2} M H_2SO_4 and 10^{-3} M lauryl sulfate following 40 s accumulation at 0.80 V. The potential was scanned from 0.8 to -0.3 V at 0.1 V s^{-1} (only the section between 0 and 0.8 V is shown). Inset: background current corrected peak current values as a function of the concentration of propofol.

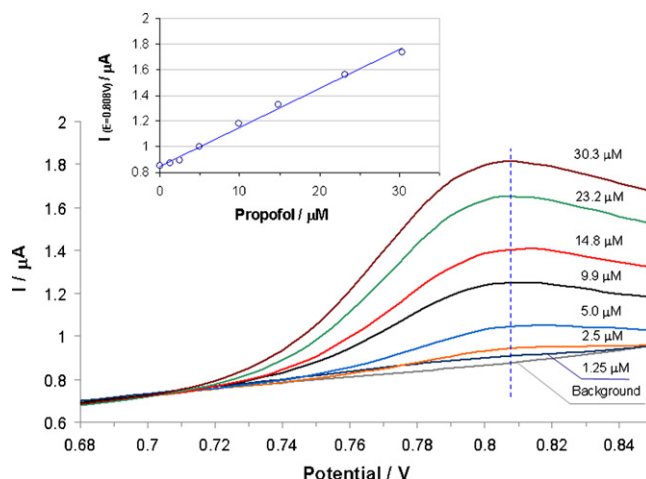


Fig. 7. Cyclic voltammograms recorded at 0.1 V s^{-1} scan rate for solutions with 10^{-2} M H_2SO_4 and different concentrations of propofol. The potential was cycled from 0.5 V to 1.0 V (only the section between 0.68 and 0.85 V is shown). Between the scans the electrode potential was kept at 0.5 V and the solution was stirred at 200 rpm for 15 s. Inset: dependence of the current values measured at $E = 0.805 \text{ V}$ on the propofol concentration.

standard addition. After each addition three cyclic voltammograms were recorded by scanning the GC working electrode potential at 0.1 V s^{-1} from 0.5 V to 1.0 V. Between the scans the electrode potential was kept at 0.5 V and the solution was stirred at 200 rpm for 15 s. The peak current values at a given concentration increase linearly with $\nu^{1/2}$, where ν is the scan rate (not shown), which indicates diffusional control. The inset in Fig. 7 shows a calibration curve constructed from the current values measured at 0.805 V : $i_{E=0.805 \text{ V}} = (0.031 \pm 0.001)[\mu\text{A}/\mu\text{M}] \times C_{\text{propofol}}[\mu\text{M}] + (0.84 \pm 0.02)[\mu\text{A}]$. The residual mean standard deviation (RMSD) around a fitted regression line in the figure is $0.032 \mu\text{A}$. The detection limit (DL) of the method is calculated as $3.2 \pm 0.1 \mu\text{M}$ ($n=3$) by using the formula: $\text{DL} = 3 \times \text{RMSD}/S$, where S is the slope of the calibration curve. Square wave voltammetric analysis in the same potential window provided very similar results. This direct voltammetric method does not require the renewal of the electrode surface between each measurements, thus it has better reproducibility and detection limit than the stripping method.

4. Conclusions

Two voltammetric methods have been developed for the quantitative assessment of propofol in aqueous samples. In both methods glassy carbon electrodes were used as working electrodes because gold and platinum electrodes are fouled in the presence of the analyte.

The first method involves the oxidative accumulation of propofol at the GC electrode surface followed by a cathodic stripping voltammetric scan in which the accumulated product of the propofol oxidation is reduced. The reduction occurs around 0.0 V where the influence of potential interfering species is expected to be minimal. This stripping analytical method has a detection limit of $5.5 \mu\text{M}$, which is within the therapeutic range of propofol [2–7]. During the stripping step of the method a strongly adsorbed, electrochemically active film develops on the electrode surface. As a consequence, each measurement requires a new electrode or a freshly polished surface.

In the second quantification method the possibility of the formation of strongly adsorbed species at the electrode surface has been minimized by limiting the potential window in which the working electrode potential is scanned and by keeping the electrode potential at 0.5 V between the measurements. In this way, the products of

the propofol oxidation are not reduced and do not form the strongly adsorbed film at the electrode surface, which could obstruct the voltammetric signal related to the propofol oxidation. The oxidation current measured at 0.805 V under these conditions can be used for the determination of propofol in aqueous samples with a detection limit of 3.2 μM .

In summary, the stripping method has better sensitivity (larger slope) but somewhat worse reproducibility compared to the direct method. The direct method does not require the renewal of the electrode surface between measurements but has no adequate selectivity towards the common interfering compounds.

Although promising, the protocols described in this contribution cannot be applied to *in vivo* for continuous monitoring and feedback controlled dosing of propofol in a clinical setting. However, it is envisaged that the analytical properties of the voltammetric propofol sensors can be improved by using carbon-based micro-electrodes and by performing the analysis in an organic medium, e.g. in an organic film immobilized onto the electrode surface. These approaches will be discussed in a future publication.

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