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Cleaning strategy for carbon-based electrodes: Long-term propofol monitoring in human serum

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ABSTRACT

In this work, we present a novel electrochemical cleaning procedure for long-term electrochemical monitoring of propofol by using *boron-doped diamond* (BDD) and *pencil graphite electrode* (PGE). Propofol is an anesthetic that is widely used for long-lasting medical operations. Therefore, it is of great importance to be able to develop a sensor for long-term detection of propofol in the therapeutic range. Up to now, this aim could not be achieved due to loss of sensor sensitivity caused by the fouling phenomenon from propofol oxidation mechanism. We have developed intermittent cleaning steps to be able to ensure sensitive detection of propofol for more than 4 h. In addition to long-term monitoring, we also managed to detect the drug inside human serum by using PGE for *differential pulse voltammetry* (DPV) measurements achieving a *limit of detection* (LOD) of 0.82 ± 0.08 μM, which is even lower that the physiological concentration usually used range of propofol ([1–60] μM).

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1. Introduction

Propofol (2,6-diisopropylphenol) is a very well-known intravenous anesthetic drug widely used in surgical operations and in critical care settings. Its large popularity stems from its favorable properties: a short duration of action and a consequent rapid recovery [1]. In order to obtain a suitable *depth of anesthesia* (DOA) of the patient, an effective and appropriate concentration of propofol, which ranges among 0.25–10 μg/L (1–60 μM), is injected in the patient's veins. The infusion rate is chosen depending on patient's physical characteristics (e.g. age, sex, weight, etc.) and on the type of surgical operation [2]. To this purpose, *target controlled infusion* (TCI) pumps are largely adopted to drive the anesthetic infusion to achieve and maintain a specific target concentration [3]. Mathematical models are implemented on the TCI to statistically predict the plasma drug concentration in the patient to balance the dosage accordingly [4]. Nevertheless, these mathematical models are not able to reproduce the inter-patient variability in terms of drug metabolism and tolerance [5]. All in all, this variability among patients and clinical conditions may affect the efficiency of the infusion process leading to over- or under-dosages [6]. To overcome these limitations and to avoid risk of wrong dosage, a continuous *therapeutic drug monitoring* (TDM) [7] system has to be integrated with the TCI to keep the concentration levels of drugs under control during anesthesia.

Up to now, various technologies have been developed to determine the propofol concentration in human body fluids. Most of the studies are focused on chromatographic techniques based on *high performance liquid chromatography* (HPLC) [8], and *chromatography-tandem mass spectrometer* (C-MS) [9]. Although their high sensitivity, this techniques are based on bulky instrumentation difficult to be integrated in portable systems. In addition to these techniques, detection of propofol by breath analysis has been proposed [10,11], but the correlation between blood and breath propofol concentrations is still not clear. For this reason, serum samples are preferred as convenient media for propofol concentration monitoring [12].

A common surgical operation normally lasts for up to several hours (~4 h), therefore a system for propofol monitoring should ensure a reliable and accurate response over this period of time. Electrochemical sensors are good candidates for drug monitoring [13] and they have been already investigated for propofol [14–16]. From these studies it emerges that propofol, that is a phenolic compound, can be easily oxidized and sensed electrochemically, but free radicals produced by phenolic oxidation result

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in electro-polymerization. This reaction causes electrode fouling that decreases the sensor sensitivity upon subsequent measurements [17,18].

To address this undesirable phenomenon, in a recent study, a polymeric membrane-coated electrochemical sensor has been developed [14]. It is capable of detecting propofol inside serum-like media with a detection limit of 0.012 ± 0.004 μM. The proposed electrode is highly promising in terms of detection limit and resistance to fouling, but the deposition of the membrane on the electrode surface is a critical step to obtain a proper thickness and uniformity, and, moreover, the major problem of PVC membrane sensors is their low physical and mechanical resistance for long-term usage [19]. However, difficulties in the fabrication process makes the reproducibility of the electrodes uncertain and this may result in over- or under-estimation of the propofol concentration in patient's plasma. More recent studies have reported propofol detection by adopting *molecular imprinted polymer* (MIP) biosensors [20]. Although there has been promising results, the possibility of having heterogeneous pore size distribution might result in sluggish mass transport which is not appropriate for long-term monitoring during surgery [21].

Therefore, in this work we have validated a ready-to-use and robust point-of-care sensor for long-term monitoring of propofol to be adopted during anesthesia practices. BDD electrodes and PGEs were tested in terms of change in their sensitivity and surface characteristics upon long-term monitoring. Moreover, the effect of these two electrode materials on propofol electro-oxidation and fouling was widely analyzed to fully understand the reaction mechanism.

We have proved that BDD is more resistant to fouling and deactivation of the surface with respect to PGE, thanks to the lower adsorption capabilities [22]. This is due to the fact that undoped diamond is normally electrically insulating because of its large bandgap, but it is made conducting by doping it with boron [23,24]. On the other hand, PGEs exhibit a better sensitivity. Two surface cleaning methods: in *phosphate buffer saline* (PBS) and in sodium hydroxide (NaOH) have been developed. Thanks to optimized electrochemical cleaning procedure introduced after the sixth measurement of propofol, a sensitive and reproducible detection for 4 h has been successfully achieved. Finally, experimental results with PGE show that the detection of propofol is possible even in presence of interfering compounds, e.g. *p-acetamidophenol* (APAP).

2. Experimental section

2.1. Chemicals

2,6-Diisopropylphenol (propofol) was purchased from TCI chemical and dissolved in 0.1 M NaOH to prepare the stock solution of 5.4 mM. Subsequent dilutions of propofol stock solution were done inside PBS (10 mM, pH 7.4) or serum to obtain concentra-

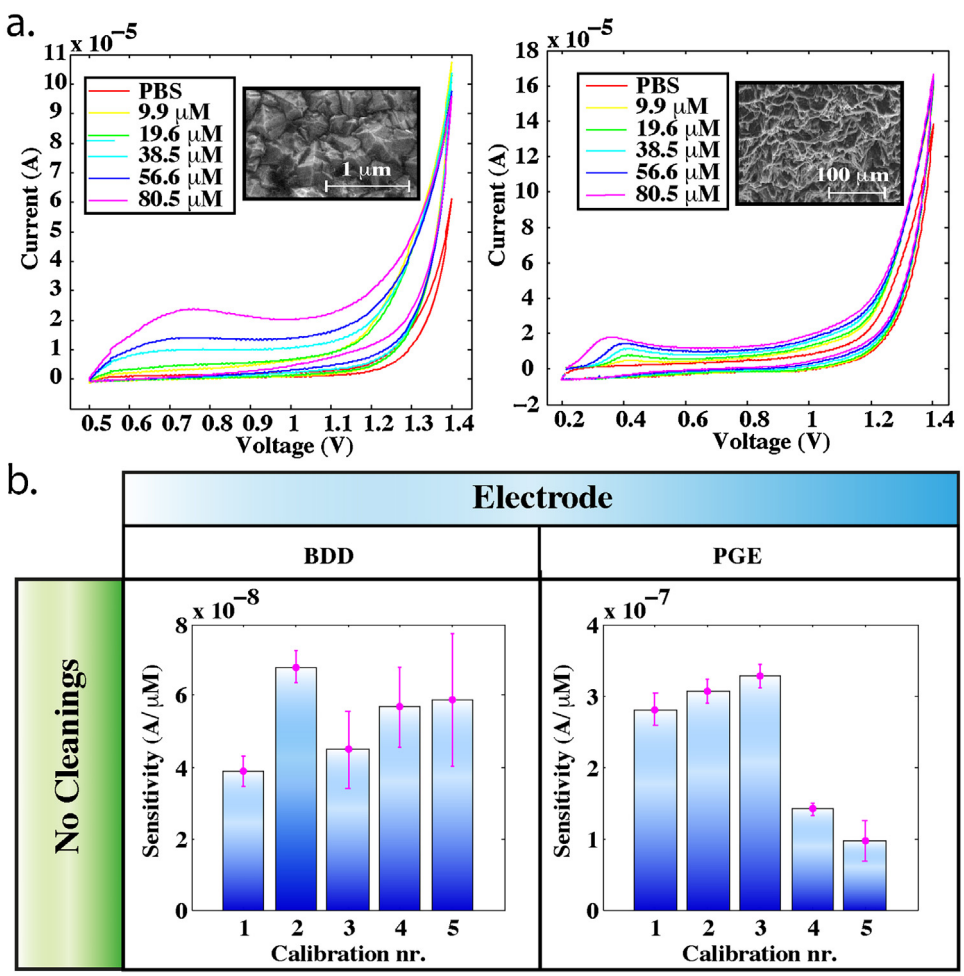

Fig. 1. a) Typical CV of propofol with PGE and BDD for various propofol concentrations [9.9–80.5] μM. (b) Change in sensitivity of BDD and PGE with respect to different number of calibrations performed consecutively in PBS (pH:7.4). Error bars represent the standard deviation from the linear regression analysis performed for *S* evaluation ($n = 5$, points in each calibration).

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