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Short communication

Electrochemistry of pertechnetate on ultramicroelectrode: A new quality control for radiopharmaceuticals manufactured at hospital in nuclear medicine

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ABSTRACT

Every day, thousands of diagnostic tests in nuclear medicine are performed on patients around the world wherein pertechnetate-based solutions are taken internally, requiring time-consuming quality controls. In this paper, we demonstrate the use of platinum ultramicroelectrodes coupled to differential pulse stripping voltammetry as an advantageous alternative to conventional quality control for radiopharmaceuticals using paper or thin-layer chromatography and gamma camera. Detection limits lower than 5 nM have been achieved during fast experiments in few minutes with ready-to-use pertechnetate-based physiological solutions. This method can be generic and transposed to other radiopharmaceuticals having an electrochemical activity at a potential different from each others.

1. Introduction

Radiotracers in nuclear medicine are widely used in scintigraphy, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging, for diagnostic investigations [1]. Among them, metastable technetium (^{99m}Tc) is one of the most attractive radionuclides to nuclear physicians because of its gamma radioactivity, short half-life (about 6 h), and is rapidly eliminated from the body [2]. Another advantage is its easy in-house production and use via a ^{99}Mo/^{99m}Tc generator to produce on demand sodium pertechnetate $Na^{99m}TcO_4$ (noted $NaTcO_4$ thereafter) dissolved in physiological serum [3].

Every day, tens of thousands of radiopharmaceutical injections labeled with $NaTcO_4$ are performed worldwide where $NaTcO_4$ is used in more than 80% cases. Pharmaceuticals are sold lyophilized in sterile kit preparations. Their labeling with $NaTcO_4$ freshly synthesized is made easy and fast via the use of a cold kit containing the pharmaceutical (sealed under nitrogen atmosphere) by adding it with a syringe.

During the labeling, colloidal formation of $^{99m}TcO_2 \cdot xH_2O$ (noted TcO_2 thereafter) can occur due to oxygen trace, limiting the labeling yield. TcO_2 is considered as an impurity in solution because it is not involved in the radiopharmaceutical labeling. Moreover, it is an excess of radioactivity injected to patient which is useless to imaging diagnostic. Only solutions not less than 95% of radiochemical purity (%RCP) are injected according to the European Pharmacopeia. The %RCP is the percent of $NaTcO_4$ bound to a ligand without any impurity.

Consequently, many quality controls estimating the radiochemical purity defined as the ratio between the activity of the labeled radiopharmaceutical and the total recovered activity are needed every day in nuclear medicine departments. Recommended control quality use chromatography technique such as thin-layer (TLC) and paper chromatographies (PC), but are time consuming and operator dependent (almost 2 h per radiopharmaceutical). No faster analytical technique is used nowadays at hospital. The main reason is the very low concentration of $NaTcO_4$ in samples which is a challenge for titration. The second drawback is the complicated speciation of technetium in solution [4,5]. The labeling step requires reducing Tc(VII) to a lower state Tc(IV). This is reached with $SnCl_2 \cdot 2H_2O$ present in cold kits [6]. In addition to impurities such as free ligands and TcO_2, SnO_2 can be present too.

Electrochemical techniques could be useful for quality controls in nuclear medicine as an alternative to time-consuming PC tests for quality control of $NaTcO_4$-based injections. Herein, we demonstrate the relevance of using platinum ultramicroelectrodes (UMEs) coupled to stripping technique for titration of pertechnetate trace in saline isotonic solution.

2. Experimental

Sterile saline infusions were from B. Braun Medical SAS, France, and glass homemade UMEs were rinsed using ultrapure water (Milli-Q,

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Millipore). 3,3-Diphosphono-1,2-propanedicarbonic acid (DPD, also known as Teceos) and Stamicis ligands used as radiopharmaceutical labeled with $NaTcO_4$ are included in the cold kit from BioCis, France. Myoview is from GE Healthcare, France. Methylethylketon (MEK) and acetonitrile are from VWR (France).

The UMEs consist in Pt wires of 5 and 76 μm diameter (Goodfellow, France and Sigma-Aldrich, France respectively), wrapped with fused glass (Pasteur pipette) and polished mechanically. The electrochemical behavior of the UMEs was tested with ferrocenemethanol mediator (Sigma-Aldrich, France). A standard three-electrode electrochemical setup was used and plugged to an e-corder picopotentiostat EA163 (eDAQ, Australia). All potentials are quoted *vs.* an AgCl reference electrode. The optimized parameters for the differential pulse stripping voltammetry (DPSV) method consisted in deposition at −1 V during 30s. Then a series of periodic voltage pulses having 50 ms width and 25 mV height was applied. The DPSV voltammogram is achieved by superimposing this series of pulses to a linear potential sweep from −0.20 to 0.85 V at 25 mV/s. The current is measured just before each potential change (sampling period: 30 ms, rest time: 2 s), and the current difference is plotted versus potential. Titration of solutions by DPSV was repeated with five identical electrodes used one after another.

Paper strips (Whatman Pure Cellulose Chromatography Paper, Grade 3MM Chr., 0.34 mm thick, band of 2 × 6.5 cm^2 for use with MEK and 2x18 cm^2 with water–acetonitrile mixture) were used for paper chromatography (PC). A paper chromatogram is developed in a chromatography glass jar (ascending paper position) for almost 2 h with a freshly $NaTcO_4$-based electrolyte drawn from the generator. Then, the radioactivity distribution is captured by a scintillation camera (Raytest MiniGita radiochromatograph, Isotopenmeβgerate GmBH, Germany).

The $^{99}Mo/^{99m}Tc$ generator stored in the clean room (also known as hot room) is from IBA Company (TEKCIS model, France).

All the measurements (by DPSV and PC techniques) were carried out with freshly prepared solutions before injection to patients under aerated (sterile) atmosphere.

3. Results and discussion

The electrochemistry of the pertechnetate-based aqueous electrolytes is rich. First studies date back to the seventies from the previous century (if we except Pourbaix diagram works) [7], and many have been performed extensively by polarography in alkaline or acidic medium [8,9]. On millimeter size glassy carbon electrode, the two oxidation states Tc(IV) and Tc(VII) are observed [10]. Due to the millimeter size of the electrode, detection of species with concentration lower than 10^{-7} M is impossible for analytical purposes. Carbon fiber electrode could be a solution, but chemistry of this material is manufacturer dependent. Platinum electrode is a good alternative since it is used for microsystem fabrication embedding miniaturized Pt electrodes. It follows that on smooth platinum electrode, the reduction of pertechnetate yields passivation via oxide film formation [11]. Consequently, the formation of technetium oxide (IV) on the electrode surface can be exploited for analytical purposes [12]. At neutral pH, only NaCl, $NaTcO_4$, TcO_2, the free ligand and the radiopharmaceutical can be present in the solution to control. The use of a Pt ultramicroelectrode exhibits excellent signal-to-background characteristic to study the electrochemical behavior of $NaTcO_4$ in physiological serum between −1.15 and 0.85 V vs. AgCl. The transition from 76 μm (Fig. 1a and b) to 5 μm diameter electrode (Fig. 1c and d) improves the signal-to-background (noise) response. The anodic wall starts at about 0.65 V (Fig. 1a) for the saline electrolyte,

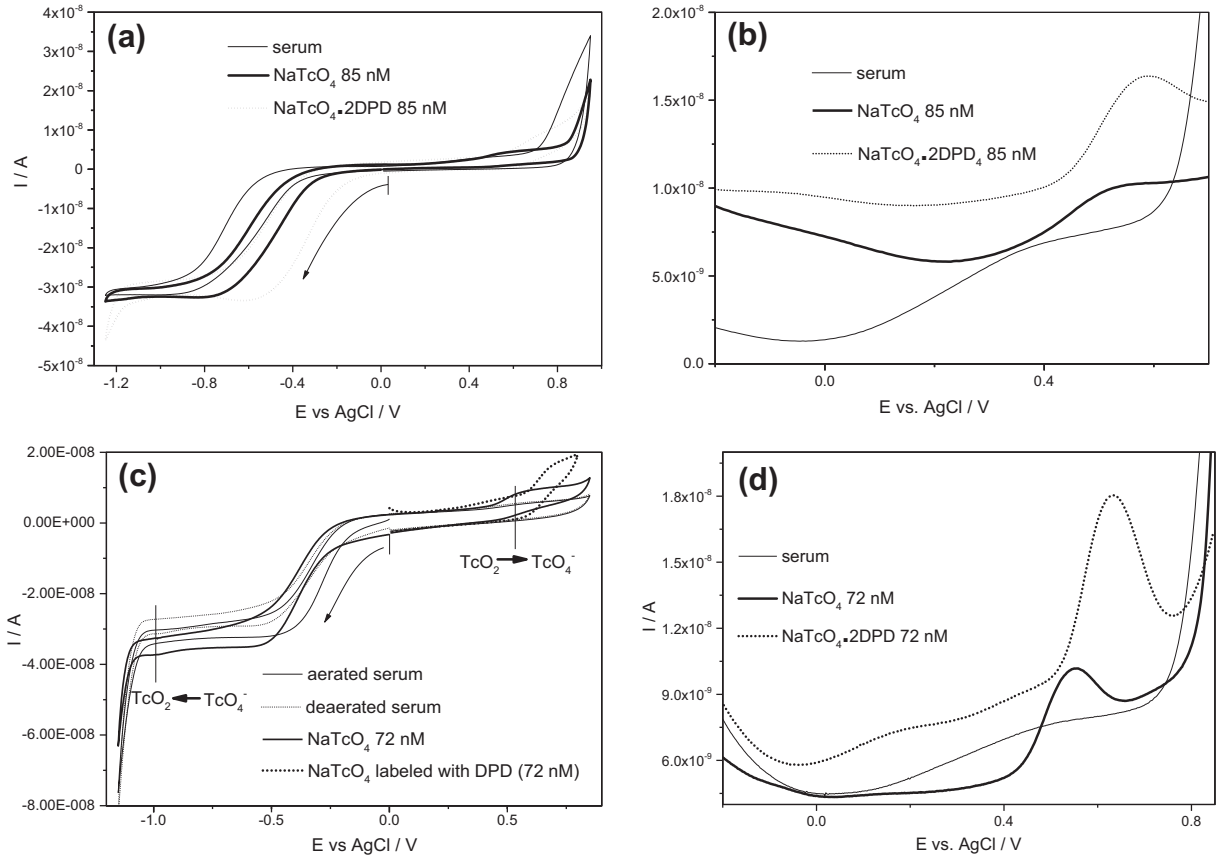

Fig. 1. (a) Cyclic voltammograms of physiological serum, $NaTcO_4$ 72 nM dissolved in physiological serum and $NaTcO_4$•2DPD 72 nM dissolved in physiological serum on Pt 76 μm diameter. (b) DPSV technique applied to physiological serum, $NaTcO_4$ dissolved in physiological serum and $NaTcO_4$•2DPD dissolved in physiological serum on Pt 76 μm diameter. Same experiments on Pt UME 5 μm diameter for (c) cyclic voltammetry and (d) DPSV with $NaTcO_4$ and $NaTcO_4$•2DPD 72 nM. Scan rate: 25 mV/s.