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Palladium nanoparticles exposure: Evaluation of permeation through damaged and intact human skin☆

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ABSTRACT

The intensified use of palladium nanoparticles (PdNPs) in many chemical reactions, jewellery, electronic devices, in car catalytic converters and in biomedical applications lead to a significant increase in palladium exposure. Pd can cause allergic contact dermatitis when in contact with the skin. However, there is still a lack of toxicological data related to nano-structured palladium and information on human cutaneous absorption. In fact, PdNPs, can be absorbed through the skin in higher amounts than bulk Pd because NPs can release more ions. In our study, we evaluated the absorption of PdNPs, with a size of 10.7 ± 2.8 nm, using intact and damaged human skin in Franz cells. 0.60 mg cm^{-2} of PdNPs were applied on skin surface for 24 h. Pd concentrations in the receiving solutions at the end of experiments were 0.098 ± 0.067 μg cm^{-2} and 1.06 ± 0.44 μg cm^{-2} in intact skin and damaged skin, respectively. Pd flux permeation after 24 h was 0.005 ± 0.003 μg cm^{-2} h^{-1} and 0.057 ± 0.030 μg cm^{-2} h^{-1} and lag time 4.8 ± 1.7 and 4.2 ± 3.6 h, for intact and damaged skin respectively.

This study indicates that Pd can penetrate human skin.

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1. Introduction

Palladium nanoparticles (PdNPs) production and use are increasing due to the high catalytic activity that permits many promising industrial applications, including oxidation and coupling reactions, electrocatalysis and fuel cell technology. PdNPs principal use is in automobile catalytic converters and is present in airborne particulate matter (Ravinda et al., 2004; Zereini F. et al., 2004; Kalavrouziotis and Koukoulakis, 2009).

PdNPs are also successfully used in end-of-pipe technologies to control emissions of pollutants, such as halogenated compounds and drugs (Mackenzie K. et al., 2006; Kim et al., 2004; Long et al., 2013).

Its increasing use in jewellery (replacing nickel following EU Directive), dental alloys, and electronics suggests attention to this metal as a main potential allergen of the 21st century (Faurschou et al., 2011). Pd in contact with the skin can induce sensitization and can cause allergic contact dermatitis (Faurschou et al., 2011, Muris et al., 2015a,b). Increased sensitization to Pd was reported by Larese in 2003 in a long term survey on patch tested patients. In general, Pd allergy is associated to Ni allergy, probably due to a cress reaction between Pd and Ni.

Respiratory symptoms as asthma and rhinitis were associated with exposure to Pd salts only (Daenen et al., 1999).

The higher surface/mass of the PdNPs can lead to higher biological activities respect to bulk palladium, as well as an easy release of reactive metal ions (Larese et al., 2004; Ponti et al., 2009), with great potential skin permeation compared to bulk material.

Preliminary studies on PdNPs cell lines, indicated that the risk correlated to metallic palladium (De Windt et al., 2006), Pd ions (Frazzoli et al., 2007) or palladium/magnetite is rather low for particles 60–100 nm sized (Hildebrand et al., 2010). However, Speranza et al. (2010) showed that Pd-nanoparticles (5–10 nm) can effectively modify kiwifruit pollen entering inside the grains in higher and quicker amounts than soluble Pd(II). Wilkinson in 2011 carefully evaluated the toxicity of Pd nanoparticles (10.4 ± 2.7 nm).

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They demonstrated that the PdNPs cellular uptake occurs in human primary bronchial epithelial cells, with a dose-dependent effect on release of cytokines. PdNPs caused a lower responsiveness of human epithelial cells to TNF-α, and an induced apoptosis in human primary bronchial epithelial cells. Remarkably, these particles caused in lung epithelial cells a decrease in PGE2 secretion, when administered at non-cytotoxic doses. This could suggest an enhancement of airway inflammation. Furthermore, Boscolo in 2004 demonstrated that Pd salts inhibit cytokines' release in primary human peripheral blood mononuclear cells, whereas PdNPs enhanced the release of IFN-gamma with immunomodulatory effect. Reale et al. (2011) demonstrated that palladium ions and PdNPs exert different effects in vitro on the expression and release of cytokines from peripheral blood mononuclear cells on Pd-sensitized vs non-sensitized women. In a very recent work, Petrarca et al. (2014) proved that PdNPs modified the cell cycle in peripheral blood mononuclear cells, suggesting that ions, per se or released by NPs, could be the inducers of Pd toxicity.

With the aim to a better investigation on the potential in-vitro PdNPs skin absorption, permeation experiments with human skin were carried out using the Franz cell method (Franz, 1975). We investigated the total amount of Pd permeating through human skin during a 24-h period. We used the protocol defined during the European project EDETOX (Evaluations and predictions of DErmal absorption of TOXic chemicals, 2001–2004) and used for other experiments to investigate the skin absorption of other metal nanoparticles such as silver, gold and cobalt (Larese et al., 2009, 2011, 2013).

2. Materials and methods

2.1. Chemicals

We purchased palladium (II) chlorite, ammonium hydroxide (25% w/v), sodium hydroxide, sodium chloride, ethanol, hydrochloric acid (37% v/v), polyvinylpyrrolidone PVP (K30, average Mw 40,000) from Sigma Aldrich (Milan, Italy); lactic acid (90%) from Acros Organics (Geel Belgium); hydrogen peroxide (30% v/v), disodium hydrogen phosphate, potassium dihydrogen phosphate from Carlo Erba (Milan Italy). We prepared synthetic sweat using 0.5% sodium chloride, 0.1% lactic acid, 0.1% urea in milliQ water (using a Millipore purification pack system). pH was adjusted at 4.5 with ammonia. We prepared physiological solution with 9.00 g of NaCl, 2.38 g of Na_2HPO_4 and 0.19 g of KH_2PO_4 into 1.00 L of milliQ water to obtain a final pH of 7.35. All reagents used were analytical grade.

2.2. Nanoparticles synthesis and characterization

We synthetized PdNPs in vinylpyrrolidone (PVP) as suggested by Peng Choo et al. (2002) to obtain a molar ratio of 1:20 between Pd and. In detail, we dissolved 166.23 mg of $PdCl_2$ in 0.36 mL of HCl 37% under sonication and 4.163 g of PVP into 35 mL of water. We added Pd solution to PVP solution with 35 mL of ethanol. The suspension was refluxed for 3 h, than evaporated to remove ethanol. We dissolved the final product in 30 mL of H_2O and we adjusted to pH 5.5 by addition of NaOH 1 M. We added 50 mL of water to obtain a nominal metal concentration of 2.0 g/L.

To verify the presence of Pd in ionic form in the PdNPs suspension we purified 4.00 mL of NPs suspensions by ultrafiltration with Centrifugal Filters Amicon® Ultra-4, MWCO 10 kDa (Millipore) (Marassi et al, 2015). The recovered suspension was diluted to the original 4.00 mL with milliQ water. We monitored total metal concentration during the whole process by ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectroscopy).

To evaluate NPs shape and size and aggregation/agglomeration in donor solutions we used a Dynamic Light Scattering (DLS) and a Transmission Electron Microscopy (TEM) before and at the end of the experiment.

2.3. Preparation of skin membranes

Human skin pieces obtained as surgical waste (Ethical Committee authorization n. 236/2007), were cut in 4×4 cm^2 pieces and, after the subcutaneous fat removal and hair shaved, were mounted on the Franz diffusion cells, previously treated with Aqua Regia, second with nitric acid and finally rinsed for 3 times with milliQ water to avoid metallic contamination. The mean exposed skin area was 3.29 cm^2 and the average membranes thickness was 0.9 mm. Four different donors, male and female, (50–70 years-old) were used. To evaluate skin integrity we use a conductometer (Metrohm, 660, Metrohm AG Oberdorfstr. 68 CH-9100 Herisau) at 300 Hz using two stainless steel electrodes (Fasano et al., 2002). In accord with Davies et al. (2004), we rejected cells with a resistance lower than 3.95 ± 0.27 kΩ cm^{-2}.

2.4. In vitro diffusion system

We used Franz static diffusion cells (Franz, 1975) with a receptor compartment with a mean volume of 14 mL thermostated at 32 °C to mimic hand temperature.

In Experiment 1 the donor chambers of 4 Franz cells were filled with 3.0 mL of freshly prepared donor solution (0.60 mg cm^{-2} of PdNPs) After 2, 4, 8, 12, 20 and 24 h, 1.5 mL of the receiving solutions was collected for the analysis and replaced with an equal volume of physiological solution.

At the end of experiment donor and receiving solutions were collected and ultrafiltered using Amicon® Ultra-4 to evaluate Pd ionization in 24 h.

In Experiment 2 we mounted 4 Franz cells with skin pieces that were marked 20 times in one direction and 20 perpendicular with 19-gauge hypodermic needle as suggested by Bronaugh and Steward (1985) to mimic damaged skin. In each experiment, we added a blank cell that was treated as the others without the use of PdNPs.

We repeated each experiment twice using four different donors to obtain 8 cells with intact skin, 8 cells with damaged skin and 4 blank cells.

2.5. Skin digestion

At the end of the experiment, we removed skin samples from the Franz cells. We immersed intact skin in water at 60 °C for 1 min to separate epidermis and dermis. We stored all skin samples in freezer at −25 °C until the day of the analysis. Skin samples were dried for 2 h at room temperature, weighted and digested using a solution with 10.0 mL of HNO_3 69% v/v and 2.0 mL of H_2O_2 (30%), agitated for 24 h and heated at the boiling point to obtain 2.0 mL that was used diluted to a volume of 10.0 mL for chemical analysis.

2.6. Analytical measurements

We used an Inductively Coupled Plasma-Mass Spectrometry (ICP-MS 7500 CE Agilent Technologies Inc., Santa Clara, CA, USA) to measure the total palladium concentration in the skin and in the receiver solutions. The instrument was calibrated against standard solution from 0 to 10 μg L^{-1}, ion mass selected: 105 and 108 u.m.a. and the limit of detection was 0.05 μg L^{-1}.

We used an Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES, Spectroflame Modula E optical plasma

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