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ORIGINAL ARTICLE

Probing the effectiveness of barrier creams against human skin penetration of nickel powder

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Abstract

Objective: Barrier creams (BCs) are marketed as locally applied medical devices or cosmetic products to protect the skin from exposure to chemicals and irritants. Generally, the mechanism of action of such products is mainly due to the formation of a superficial thin film between the skin and the irritant or sensitizer, thus reducing or totally blocking the cutaneous penetration of such agents. Specifically, studies focusing on the effectiveness of commercial protective creams to prevent nickel cutaneous penetration are extremely scarce. The aim of the current work, therefore, is to evaluate the protective role of a commercially available barrier cream for nickel and compare the results with a simple moisturizing, following exposure to Ni powder.

Methods: Marketed BCs were evaluated and tested. Human skin absorption of Ni was studied in vitro using static Franz diffusion cells.

Results: Our results demonstrate that the application of both formulations caused a reduction of Ni inside the skin ($8.00 \pm 3.35\,\mu g\,cm^{-2}$ for the barrier cream and $22.6 \pm 12.6\,\mu g\,cm^{-2}$ for the general moisturizing product), with the specialized barrier cream being statistically ($p = 0.015$) more efficient on forming a protective barrier, thus evidencing the importance of some ingredients in such formulations on the nickel dermal accumulation.

Conclusions: The composition of the formulations based on film-forming or chelating agents may play an imperative role in reducing the cutaneous penetration of Ni.

KEYWORDS

barrier creams, formulation, Franz cells, Ni exposure, skin barrier

Résumé

Objectif: Les crèmes de barrière (CB) sont commercialisées en tant que dispositifs médicaux ou produits cosmétiques appliqués localement pour protéger

la peau contre l'exposition aux produits chimiques et irritants. En général, le mécanisme d'action de ces produits est principalement dû à la formation d'un film mince superficiel entre la peau et l'irritant ou le sensibilisant, réduisant ainsi ou bloquant totalement la pénétration cutanée de ces agents. Plus précisément, les études portant sur l'efficacité des crèmes protectrices commercialisées pour prévenir la pénétration cutanée du nickel sont extrêmement rares. L'objectif du projet en cours est donc d'évaluer le rôle protecteur d'une crème barrière disponible dans le commerce contre le nickel et de comparer les résultats à un simple hydratant après une exposition à la poudre de Ni.

Méthodes: Des CB commercialisées ont été évaluées et testées. L'absorption cutanée du Ni dans la peau humaine a été étudiée *in vitro* à l'aide de cellules de diffusion statiques de Franz.

Résultats: Nos résultats démontrent que l'application des deux formulations a entraîné une réduction du taux de Ni à l'intérieur de la peau ($8{,}00 \pm 3{,}35\,\mu g \cdot cm^{-2}$ pour la crème barrière et $22{,}6 \pm 12{,}6\,\mu g \cdot cm^{-2}$ pour le produit hydratant ordinaire), la crème barrière spécialisée étant statistiquement ($p = 0{,}015$) plus efficace pour former une barrière protectrice, démontrant ainsi l'importance de certains ingrédients dans ces formulations sur l'accumulation dermique du nickel.

Conclusions: La composition des formulations basées sur des agents de formation de film ou de chélation peut jouer un rôle nécessaire pour réduire la pénétration cutanée du Ni.

INTRODUCTION

Exposure to hazardous agents such as chemicals, metals, and other contaminants can cause their penetration into the skin and thus potentially into the general circulation. Skin absorption of these molecules can decisively induce local effects such as skin sensitization or irritation and potential systemic toxic effects. Nickel (Ni) is recognized as the premier cause of contact allergy (CA), affecting a predominantly female population with a prevalence of sensitization of about 10–20% in women and only 1–3% in men [1–4]. Although it has reduction in the last 20 years [5], the prevalence of nickel allergy in children and adolescents is approximately 8–10% with a strong female predominance [6]. CA is an alteration of the immune response with the readiness to develop an inflammatory reaction against a specific substance of low molecular weight ("hapten") after skin contact [7]. CA may evolve into allergic contact dermatitis (ACD), a T cell-mediated delayed type hypersensitivity reaction that occurs upon hapten challenge in sensitized individuals [8–10]. It is acutely characterized by redness, erythematous macules, papules, oedema, vesicles, or, chronically, by scaling and dry skin [11]. Exposure to Ni is common due to its ubiquitous presence in routine objects such as jewellery and wristwatches (before the EU regulation on Ni), coins, studs, and clothing buckles. Particularly, the sustained high prevalence of Ni allergy is often explained by prolonged skin contact with Ni ions released from metallic items, which may penetrate through the skin and directly activate an immune response in allergic individuals [12], ultimately resulting in ACD [1]. It is well reported in the literature that metals easily penetrate through the skin in their ionized form [13–15], and their percutaneous penetration is closely related to the ability of the sweat to form complexes with metal atoms [16, 17]. However, the study of Hagvall [18] demonstrated higher accumulation into the epidermis of cobalt and chromium (III) species compared to Ni species. This may be dictated by the fact that 50% of chromium was found to be present as stable aqueous ions, while less than 1% of Nil and cobalt ions were found to form aqueous ions in the solutions of nickel sulphate [dominated by $Ni\text{-}(COOH)^2$ ions] and cobalt chloride [dominated by $Co(NH_3)Cl^{2+}$], respectively. Furthermore, higher skin penetration of Cr (III) may be attributed to the metal's binding to skin components such as glycolipids, phospholipids, carboxylate, phosphate groups, and carbonyl groups of sn-2 phospholipid chains. This binding may occur in all layers of the skin with the formation of a depot in the *stratum corneum*, which can reduce metal diffusion [14, 19, 20]. Notably, trivalent ions such as Cr (III) ions show a strong affinity for the skin tissue, forming more stable complexes than divalent ions

such as Ni (II) [18]. Moreover, it has been reported that nickel nanoparticles (NiNPs) are able to penetrate through human skin more readily compared to bulk material due to their characteristics, such as their small size and high surface area. NiNPs were detected in the skin, but metal ions were accumulated in the receptor compartment. Notably, the ionized metal represents the Ni content able to permeate through the skin [21]. Recently, the study of Magnano et al. [22] showed that a higher content of Ni ions permeated through the intact skin compared to other metal ions following exposure to road dust containing multiple metals at a relatively low dose, representing a potential health hazard. Similarly, it was demonstrated that NiNPs dissolved in artificial sweat could produce ions that may penetrate through the skin, directly causing an immune response [12]. Additionally, in our previous paper, it was demonstrated that two commercially available creams (i) one to prevent the dermal absorption of Ni (Nik-L-Block™ containing a chelating agent) and (ii) the other as a moisturizing cream (Ceramol 311 basic cream without a chelating agent) decreased Ni accumulation in the skin compared to the untreated samples after exposure to NiNPs [23]. This positive effect can be attributed to the composition of such formulations, which plays an imperative role in dermal uptake of Ni [23]. Percutaneous permeation of metals is a complex phenomenon affected by several factors such as pH, oxidation state, presence of counter-ions, dose, and solubility. Generally, the transcutaneous passage of a substance is enhanced in cases of wounded skin or skin disorders due to the disruption of the protective layer, the *stratum corneum* [24, 25]. According to the International Agency for Research on Cancer (IARC), Ni compounds are classified as carcinogenic to humans (Group 1), and metallic nickel is classified as possibly carcinogenic to humans (Group 2B) [26]. Further, in order to reduce the amount of allergen in contact with the skin and to avoid the development of nickel allergies, the European Directive 94/27/EC "nickel free" limits the Ni content in items inserted into pierced ears or other parts of the body (limit 0.05%) and the Ni release from objects in direct and prolonged contact with skin (limit $\leq 0.5\,\mu g\,cm^{-2}$ per week) [27, 28]. Then, to prevent or even reduce the penetration of irritants or sensitizers, specific measures of protective equipment such as gloves, moisturizing creams, and skin barrier creams (SBCs) were developed. However, it is reported that low-molecular-weight chemicals may penetrate through various gloves [29]. Notably, it was found that some allergens, including Ni, are soluble in rubber gloves, leading to a lower resistance of the gloves, which may facilitate Ni penetration and induce dermatitis [30–32]. Furthermore, continuous glove-wearing can inhibit skin barrier function and lead to maceration of the skin due to the fact that the hands are continuously sealed inside a glove [33]. For this reason, barrier creams (BC) are preferred compared to gloves, and they are the most common measures adopted for limiting skin contact. Moreover, BC have several advantages, such as (i) the ability to add a lipid mixture to the skin surface (occlusion), which provokes an immediate effect on the epidermis; (ii) they add the lipid mixture to the intercellular spaces, leading to an intermediate effect; and (iii) the addition of lipids to the epidermal cells [34], which can promote the restoration of the natural barrier function of the skin [35], causing a delayed effect on the epidermis. It is important to mention that, due to the ability to build up a physical barrier (thin film) between the skin surface and the agent, BCs should reduce dermal absorption and possible penetration of irritants into the skin [35–37]. Due to these features, in our current study, we selected two commercially available creams as protective tools to reduce skin penetration of Ni powder. In the literature, studies reporting on the effectiveness of BCs have been reported as controversial. Indeed, while in a few studies [38–40] the efficacy of BCs in the prevention of eczema and occupational contact dermatitis has been highlighted, other studies claim that the use of these BCs is not an effective measure. Additionally, it is also important to mention that there are no official methods for testing the efficacy of BCs [41, 42]. To our knowledge, the study of Ni skin deposition and penetration into the *stratum corneum* (SC) after short contact with metallic items is so far not extensive, and a series of questions related to its mode of action remain unanswered. The aim of this work therefore was to study the percutaneous absorption of Ni following exposure to Ni powder and to evaluate and compare the efficacy of two commercially available formulations on Ni human skin penetration.

MATERIALS AND METHODS

Materials

Nickel powder, average particle size (APS) 2.2–3.0 µm, 99.9% (metals basis), C typically <0.1%, was purchased from Alfa Aesar (Karlsruhe, Germany). Urea, sodium chloride, sodium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from Carlo Erba (Milan, Italy); ammonium hydroxide (25% w/v) was bought from J. T. Baker (Deventer, Holland); lactic acid (90% v/v) was obtained from Acros Organics (Geel, Belgium); and nitric acid (67–69% v/v, Normatom) from VWR (Milan, Italy). Water reagent grade was obtained using a Millipore purification pack system (MilliQ water). The physiological solution used as the receptor fluid was prepared by dissolving 2.38 g of Na_2HPO_4, 0.19 g of KH_2PO_4, and 9 g of NaCl into 1 L of MilliQ water (final pH = 7.35). The synthetic sweat solution used as the

donor fluid consisted of 0.5% w/v sodium chloride, 0.1% w/v urea, and 0.1% w/v lactic acid in MilliQ water; and the pH was adjusted with ammonium hydroxide (1 N) to pH 4.5.

Formulation

The two tested commercially available creams are formulation A and formulation B. According to the manufacturer's instructions, the composition of each cream is described in Table 1. Both commercial formulations were used as received.

Preparation of nickel powder in synthetic sweat solution

The Ni powder solution (5% w/v) was freshly prepared by weighing 1.25 g of Ni powder in 25 mL of synthetic sweat at pH 4.5. Before application in the donor chamber, the suspension was sonicated in an ultrasonic bath for 10 min in order to disperse the powder as homogeneously as possible. The total nickel concentration ($1.0\,g\,L^{-1}$) of the donor solution has been confirmed by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP – OES) analyses, as described below in "Analytical measurement".

Skin samples preparation

Human skin membranes

Full-thickness human abdominal skin was obtained as surgical waste and approved by the Trieste Hospital Ethical Committee no 236/2007. The donors were men and women, with ages ranging from 45 to 71 years. Prior to storage in a freezer (−25°C), subcutaneous fat was removed using a scalpel blade, and the hair was shaved from the epidermis. Skin samples were stored in a freezer at −25°C for up to 4 months. Skin samples were prepared to a final thickness of 1.05 ± 0.02 mm with a micrometric calliper (Mitutoyo, Roissy en France, France). On the day of the experiment, skin samples were thawed in a physiological solution at room temperature, and the skin samples were cut into $4\,cm^2$ square sections. Skin integrity was checked by measuring the trans epidermal water loss (TEWL) (Delfin Vapometer, Delfin Technologies, Sweden), which was used in our previous work [43]: the average TEWL values of the skin samples were found to be below $10\,g\,m^{-2}\,h^{-1}$ [44].

In vitro permeation and distribution in skin layers after 24 h exposure

Skin absorption studies were performed in static diffusion cells according to the OECD guidelines [45]. The protocol for testing the skin permeation of Ni after exposure to Ni powder was derived from our previous works [22, 23]. The skin pieces were mounted between the donor and receptor chambers of Franz-type static diffusion cells, with the *stratum corneum* facing the donor chamber. The effective skin area for diffusion was $0.95\,cm^2$. The receptor fluid (RF) was composed of a physiological solution that was continuously stirred using a Teflon-coated magnetic stirrer. The concentration of salt in the receptor fluid is approximately the same as that found in the blood. The receptor compartment had a mean volume of 4.5 mL filled with RF. Mounted Franz cells were maintained at 32 ± 1°C by means of the circulation of thermostated water in the jacket surrounding the cell.

Application of creams

Skin pre-treatment consisted of $25\,mg\,cm^{-2}$ of cream applied as homogenously as possible using a cotton swab with a gloved finger prior to Ni exposure. This quantity

TABLE 1 Composition of the tested formulations.

Formulations	Ingredients
Formulation A	Diethylenetriamine penta-acetic acid (DTPA) 7.5%, Steareth-2, Steareth-21, Cetostearyl alcohol, Chitosan, Glycerol, Light liquid paraffin, Methylparaben, Propylparaben, Sodium hydroxide, Tinogard TT, and Water
Formulation B	Butyrospermum parkii butter, Ceramide 3, Palmitamide MEA, Hydrogenated Polydecene, Glycerin, Ammonium acryloyldimethyltaurate/VP copolymer, Cholesterol, Stearic acid, Squalane, Caprylyl Glycol, Hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, o-cymen-5-ol, Polysorbate 60, Citric Acid, Xanthan Gum, and Water

was chosen according to the study of [46], and recently adopted in our work [23] The choice of this high amount was also dictated to guarantee a reduction in Ni skin penetration. After a complete drying of the deposit (~3 min), cells were closed. The complete drying of the formulations was defined by an ocular inspection, and there were no cracks. The formulations used were formulation A (barrier cream for Ni) and formulation B (moisturizing cream).

Sampling

The skin absorption experiments were carried out as follows:

Exp. 1 Skin pre-treated with creams

Briefly, infinite doses of 1.0 mL of pure, freshly made suspension of Ni (5% w/v) in synthetic sweat at pH 4.5 were applied to the skin surface pre-treated with the two creams. This resulted in a theoretically applied dose of $Q_0 = 52.6\,mg\,cm^{-2}$. The choice of 1.0 mL in the donor compartment was dictated to be in agreement with the protocol of the European Project EDETOX 2000. The donor compartment was closed with parafilm during the experiment. The permeation study was then carried out for 24 h to determine the permeation profile of Ni remaining and permeating through the skin. At selected time points (3, 6, 9, 18, 21, and 24 h), 0.5 mL of each receptor sample was collected and analysed. An equal volume of fresh receptor fluid was immediately replaced in each sample. All experiments were conducted on six independent biological replicates. Skin from two donors was tested.

Exp. 2 Skin without pre-treatment (Controls)

Experiments were performed following the same procedure described above (Exp. 1), but the skin was not pre-treated with creams. All experiments were conducted on six independent biological replicates. Skin from two donors was tested.

Blanks: A skin sample without Ni powder applied to the skin surface and without pre-treatment with creams was used as a blank in each run. In the donor chamber, 1.0 mL of synthetic sweat (pH = 4.5) were added, and the experiment was performed following the procedure described in Exp. 1. All experiments were conducted on four independent biological replicates. Skin from two donors was tested.

The amounts of Ni in the RF as well as in each skin layer after 24 h were quantified by Inductively Coupled Plasma-Mass Spectrometry (ICP – MS), the method described below, in "Analytical measurements".

Collection and treatment of samples

After 24 h of exposure, the cells were dismantled. All the receptor fluid was removed and frozen for subsequent analysis. The non-absorbed fraction was removed from the skin surface by washing the donor chamber thrice with 1.0 mL of MilliQ water for 20 s and gently wiping with a cotton swab. The skin membranes (4 cm^2) were cut in a "little circle" in order to get only the exposed "exposed area" (0.95 cm^2). From the exposed skin area (0.95 cm^2), the skin layers were separated as follows: the viable epidermis (VE) was separated from the dermis (D) by heat treatment (1 min in water at 60°C) before digestion of the tissue (see section below "Skin digestion after the experiment"). The receptor fluid was diluted 1:10 in MilliQ water and acidified with 1% nitric acid before the ICP-MS analysis.

Skin digestion after the experiment

At the time of the analysis, the skin membranes were thawed, and the exposed area was weighted and placed in a Teflon-based sealed vessel with 2.0 mL of HNO_3 (69% v/v); 0.5 mL of H_2O_2; 1.0 mL of MilliQ water. Subsequently, the reaction mixture was heated in a microwave oven (Multiwave-PRO, Anton Paar) at 180°C for 25 min. After the digestion treatment, the solutions were diluted 1:10 in MilliQ water for the ICP-MS analysis.

Analytical measurements

Quantification of nickel by inductively coupled plasma-optical emission spectroscopy

The extent of Ni ions in the donor solutions was determined by Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) using an Optima 8000 ICP-OES Spectrometer (PerkinElmer, USA) equipped with an S10 Autosampler (PerkinElmer, USA). The donor solutions were collected at the end of the experiment, centrifuged (2400 g, 15 min, 20°C), and the supernatant was filtered using 0.45 μm GHP Acrodisc syringe filters (Pall Life Sciences, Ann Arbor, MI) in order to remove metal particles and to evaluate the percentage of ionized metal in the donor phase, according to our previous work [13]. The filtered solutions were recovered, diluted 1:20 in MilliQ water and analysed using ICP-OES at the operative wavelength of 231.604 nm. The analyses were conducted using a calibration curve obtained by dilution (range: 0–10 $mg\,L^{-1}$) of a standard solution (1000 $mg\,L^{-1}$) for ICP analyses (Sigma-Aldrich). The calibration curve was

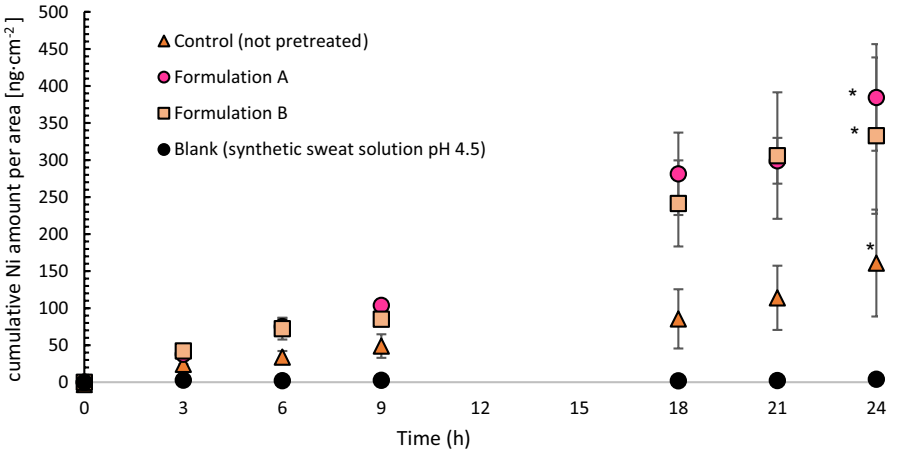

FIGURE 1 Ni concentration that permeated into the receptor fluid at specific extraction times. Values are expressed as mean ± SEM ($n = 6$ exposed skin samples; $n = 4$ blank samples). An asterisk (*) indicates a statistically significant difference obtained between blanks and exposed skin samples to Ni powder ($p < 0.05$).

TABLE 2 Ni amounts found in receptor fluid (RF).

Ni concentration in receptor fluid (ng cm^{-2})				
Time (h)	**Blank**	**Control (not pretreated)**	**Formulation A**	**Formulation B**
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
3	0.15 ± 0.01	24.2 ± 6.54	37.9 ± 13.6	42.2 ± 8.48
6	0.25 ± 0.08	34.0 ± 8.20	75.2 ± 11.4	72.4 ± 14.8
9	0.39 ± 0.14	48.8 ± 15.9	104 ± 4.79	85.1 ± 7.0
18	0.63 ± 0.28	85.5 ± 40.0	281 ± 55.6	241 ± 58.2
21	0.77 ± 0.12	114 ± 43.3	299 ± 30.9	306 ± 85.4
24	0.95 ± 0.05	160 ± 72.1[a]	384 ± 71.9[a]	333 ± 106[a]

Note: Values are expressed as mean ± SEM ($n = 6$ exposed skin samples; $n = 4$ blank samples).
[a]Statistically significant difference obtained between blanks and exposed skin samples to Ni powder ($p < 0.05$).

linear from 0.1 to 10 mg L^{-1} ($R^2 = 0.9999$), and five calibration points from 0 to 10 mg L^{-1} (0; 0.1; 1; 5; 10) were carried out. The limit of detection (LOD) was 0.020 mg L^{-1} by ICP-OES. The precision of the measurements as measured by the relative standard deviation (RSD%) for the analysis was always less than 5%.

Quantification of nickel by Inductively Coupled Plasma-Mass Spectrometry

The Ni of controls and exposed skin samples, together with receptor solutions, were evaluated by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) using a NexION 350X Spectrometer (PerkinElmer, USA) equipped with an ESI SC Autosampler. The analysis was performed in KED mode (Kinetic Energy Discrimination) using ultra-high purity helium (flow rate of 4.8 mL min^{-1}) to control and minimize cell-formed polyatomic ion interference. The ICP-MS calibration curve was linear ($R^2 = 0.999$; ion mass selected: 60 u.m.a.) in the concentration range of 0.1–100 µg L^{-1} according to the dilution of a multistandard solution of 10 mg L^{-1} for ICP analysis (Periodic Table MIX 1, TraceCERT Sigma-Aldrich). Six calibration points from 0 to 100 µg L^{-1} (0; 0.1; 1; 5; 10; 100) were used. The limit of detection (LOD) was 0.05 µg L^{-1} for Ni. The coefficient of variation of repeatability (RSD %) was <3%. Moreover, the analysis was performed using Sc (45 u.m.a.; spike of 100 µg L^{-1}, prepared by dilution from a standard solution at 1000 mg L^{-1}, Scandium Standard for ICP, TraceCERT Sigma-Aldrich) as an internal standard to minimize the potential matrix effects. Additional quality control was performed by the analysis of laboratory-fortified samples prepared by spiking 1 or 5 µg L^{-1} (depending on Ni concentrations in the investigated samples) of Ni into actual samples to calculate the recovery percentage. These laboratory-fortified samples were prepared for each matrix (solutions from skin digestion, and receptor fluid) to obtain a robust method for the analysis. Acceptable recoveries from spiked samples were obtained (ranging between 90 and 110%).

Statistical analysis

The results are expressed as the quantity penetrated per skin surface unit (µg cm^{-2}) or as the quantity permeated

per skin surface unit (ng cm^{-2}). Data from skin absorption experiments were expressed as the mean ± SD. Data from skin permeation experiments were expressed as the mean ± SEM. Statistical analysis of differences between two groups was performed by Student *t*-test, and those between multiple groups were performed using the analysis of variance (ANOVA, one-way) The significance level was set at $p < 0.05$. Data were treated and analysed using Excel for Windows (release 2010) and Stata Software (version 17.0; StataCorp LP, College Station, TX, USA).

RESULTS

Nickel quantification in donor solutions

The concentration of solubilized Ni in donor solutions (DS) at time 0 and after 24 h of exposure was quantified using an ICP-OES after the removal of Ni powder by centrifugation and filtration. The analysis revealed that the effective dose of Ni ions, expressed in mg cm^{-2}, were 0.07 mg cm^{-2} at time 0 and 0.12 mg cm^{-2} after 24 h. The ionized metal represents the effective dose (Ni ions able to cross the skin barrier and reach the receiving phase) [21, 47].

Skin permeation of nickel

The Ni concentrations in the receptor fluid expressed in ng cm^{-2} are represented in Figure 1 and Table 2. In the experimental condition, the mean amounts of Ni measured in RF at 24 h in exposed skin samples increased over time, to a higher extent for samples pretreated with formulation A (384 ± 71.9 ng cm^{-2}) and with formulation B (333 ± 105 ng cm^{-2}) compared to the samples without pre-treatment (161 ± 72.1 ng cm^{-2}). As expected, the total amount of Ni was 0.95 ± 0.05 ng cm^{-2} in blank samples. A statistically significant difference between blanks and exposed skin samples was therefore found.

In vitro skin penetration of nickel

The amount of Ni retained by the different skin layers was quantified and is reported in Figure 2 and Table 3. The results show that samples pre-treated with creams showed lower skin penetration of Ni compared to control samples (not pretreated), indicating the positive effect of the two tested formulations. As it can be reported in Figure 2, after 24 h of contact, the total content of Ni retained in epidermis and dermis by applying the formulation B was significantly lower (22.6 ± 12.6 µg cm^{-2}) compared to the not pretreated samples (36.5 ± 9.51 µg cm^{-2}). Additionally, the lowest total amounts of metal penetrated in exposed human skin layers were observed for samples pretreated with formulation A (8.0 ± 3.35 µg cm^{-2}). Moreover, both tested products exhibited a significantly reduced Ni in deeper skin layers compared to the untreated samples. Importantly, the epidermis, dermis, and total skin (*E* + *D*) data of Ni content obtained by the two formulations are statistically different (epidermis $p = 0.010$, dermis $p = 0.020$; total skin $p = 0.015$). As expected, the total quantity of Ni measured in the epidermis and dermis (*E* + *D*) was detectable at a very low level in blank samples (without Ni exposure). A statistically significant difference between blank samples and exposed skin samples was found ($p < 0.05$).

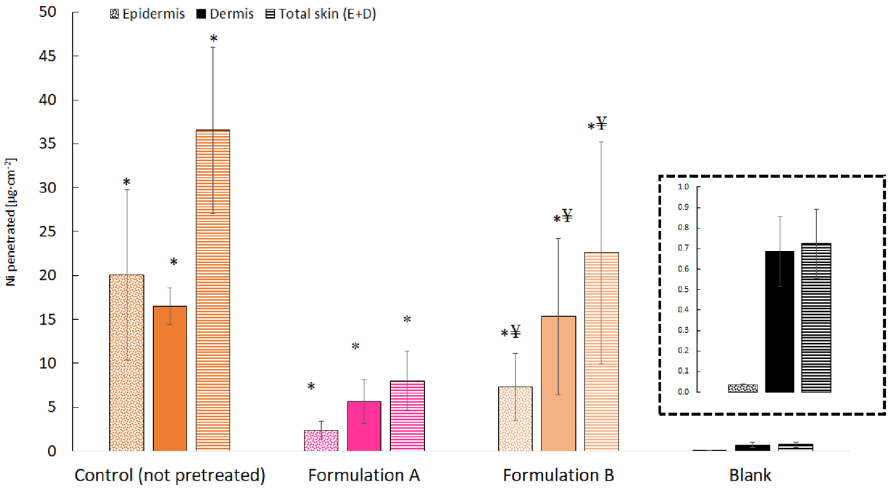

FIGURE 2 Ni concentration found in skin layers (*E* and *D*) after 24 h exposure to Ni powder. The applied dose was 52.6 mg cm^{-2}. Data is given as mean ± SD ($n = 6$ exposed skin samples; $n = 4$ blank samples). (*) shows the statistically significant differences obtained between blanks and exposed skin samples to Ni powder ($p < 0.05$). (¥) shows the statistically significant differences obtained between samples pre-treated with Formulation A and skin samples pre-treated with Formulation B in the Student's *t*-test ($p < 0.05$).

TABLE 3 Ni amount found in skin layers in blanks and exposed skin after 24 h exposure.

	Epidermis (*E*) ($\mu g\,cm^{-2}$)	Dermis (*D*) ($\mu g\,cm^{-2}$)	Total skin (*E* + *D*) ($\mu g\,cm^{-2}$)
Blank	0.04 ± 0.00	0.69 ± 0.17	0.72 ± 0.17
Control (not pretreated)	20.0 ± 9.70[a]	16.5 ± 2.09[a]	36.5 ± 9.51[a]
Formulation A	2.34 ± 1.06[a,b]	5.66 ± 2.47[a,b]	8.00 ± 3.35[a,b]
Formulation B	7.31 ± 3.84[a,b]	15.3 ± 8.93[a,b]	22.6 ± 12.6[a,b]

Note: The applied dose was 52.6 $mg\,cm^{-2}$. Data are given as mean ± SD.

[a]Statistically significant difference obtained between blanks and exposed skin samples to Ni powder ($p < 0.05$).

[b]Statistically significant differences obtained between samples pre-treated with Formulation A and skin samples pre-treated with Formulation B in the Student's *t*-test ($p < 0.05$).

Calculation of full absorbed amount recovered

Finally, the full absorbed recovered amount (Q_{abs}) was calculated utilizing Equation 1.

$$Q_{abs} = E + D + RF \quad (1)$$

where *E* is the sum of the recovered amounts of Ni in the epidermis, *D* is the sum of the recovered amounts of Ni in the dermis, and RF is the sum of the recovered amounts of Ni in the receptor fluid. Q_{abs} of Ni values obtained from samples pretreated with formulation A were lower compared to samples pretreated with formulation B, reaching values of 8.38 ± 3.28 $\mu g\,cm^{-2}$ and 23.0 ± 12.9 $\mu g\,cm^{-2}$, respectively. On the contrary, Q_{abs} of Ni values observed from not pretreated samples was 36.7 ± 9.37 $\mu g\,cm^{-2}$. A statistically significant difference was found between the two creams ($p = 0.016$).

DISCUSSION

In the current study, the skin was pretreated with two commercially available creams: (i) one specialized barrier cream containing chelating agents for Ni and (ii) a general moisturizing cream without chelating agents, and then exposed to Ni powder solubilized in synthetic sweat at pH 4.5. Metallic ions may influence percutaneous absorption because they can diffuse through this cutaneous membrane. Most elements increase their ionized form as acidity increases; in some cases, it becomes approximately 10–100-fold higher for each decreasing pH unit [48]. For this reason, our experiments were performed using a synthetic sweat solution at pH 4.5 in order to reproduce the typical pH of the skin around 4–5.5 and to increase metal release. The results showed that at the selected pH, Ni reaches a concentration of 0.12 $mg\,cm^{-2}$ after 24 h. For the development of a barrier cream, a main requirement is the capability to immobilize potential allergens or irritants by this barrier system in order to prevent the penetration and permeation of such molecules through the skin [29]. As can be seen from our results (Figure 1, Table 2), despite the treatment with the formulations, the Ni content reached the RF was higher compared to the controls (not pretreated samples), but no statistically significant differences between the groups were found. Additionally, these results are also in line with our previous study, where Ni penetration was higher for samples pretreated with the creams than for samples not pretreated [23]. From our data, the higher permeation of Ni observed by the application of formulation A may be due to the presence of two transdermal enhancers such as steareth-2 and steareth-21 (emulsifiers), which are able to facilitate the permeation pathway [49]. On the other hand, formulation B is an oil-in-water (o/w) emulsion containing hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, a polymeric surfactant that does not interfere with the skin structure [50]. Generally, in an o/w emulsion, the penetration of ingredients is higher when they are dissolved in the continuous phase of the emulsion [51]. So, in the case of the o/w emulsion, the ingredients are mainly distributed into the continuous water phase of the emulsion [49], but it is important to point out that in our study the substance tested is hydrophilic, so it may be hypothesized that the affinity of Ni for some ingredients of formulation B in the continuous phase of the emulsion may apparently promote skin permeation. Moreover, it was reported in the literature that after the application of skin barrier creams, higher skin penetrations of toxic molecules were registered compared to the untreated samples. Notably, [52] demonstrated an increase in skin permeation of aniline (ANI) and the human carcinogen o-toluidine (OT) following the application of BCs. This effect may be attributed to ethoxylated emulsifiers or some substances such as glycols and ethers, which act as penetration enhancers, making the upper layers of the *stratum corneum* more permeable and affecting the percutaneous uptake of the compounds [53]. Furthermore, it is important to underline that large amounts in the donor solutions, occlusion, and the water can act as penetration enhancers [49, 54, 55]. However,

occlusive in-use conditions are not an ideal scenario to simulate Ni exposure, representing a limitation of this study but they were only dressed to protect the skin from pollution. The increased skin hydration may have caused an increase in transdermal delivery of both hydrophilic and lipophilic permeants [56]. Then, the Ni distribution in the different skin layers was also assessed post-exposure. Our results demonstrated that the Ni total skin contents of samples pretreated with creams were totally lower than those measured in the not pretreated samples, confirming the capability of these two formulations to act as an "invisible glove" [29], shielding the skin from potentially harmful substances. Moreover, it is important to point out that the degree of protection of the tested creams was variable. From our data, it can be noticed that formulation A significantly showed the lowest skin penetration of Ni (Figure 2, Table 3), which was expected based on the presence of the active ingredient such as the chelator DTPA, intended to complex the metal ions and to block them from penetrating the skin [57]. Similarly, a positive effect was also shown by the application of formulation B, which is an o/w emulsion without chelating agents. The ability of such a formulation to reduce the dermal uptake of Ni can be attributed to some ingredients such as ceramide 3, cholesterol, hydrogenated polydecene, and fatty acids, which are able to form a more resistant lipid film. Moreover, formulation B is a repairing and protective cream for the epidermal barrier, containing a balanced mixture of fundamental lipids of the epidermis such as ceramide 3, cholesterol, and fatty acids able to restore the skin barrier function [58, 59] and palmitamide MEA with soothing activity on irritation and itching [60]. These obtained results concerning the effectiveness of such two products to reduce cutaneous Ni penetration are consistent with our previous study [23]. Further, for samples pretreated with the formulations, the total absorbed amounts (Q_{abs}) of Ni were statistically different, while the highest total skin absorption of Ni was obtained for not pretreated samples (Table 4), which was expected based on the absence of treatment with the formulations. It is important to underline that, considering the risk of ACD from consumer products intended for extended (nonpiercing) dermal contact, the E.U. Directive EN 1811 (EC 2009, ECHA 2014) limits the release of Ni to a weekly equivalent dermal load of $\leq 0.5\,\mu g\,cm^{-2}$. In our study, the amount of Ni in the epidermis and dermis was higher for both tested creams, so the protection against nickel sensitization is not likely considering EU regulation. However, a more recent evaluation [61] suggests that exposure in this range can cause symptoms only in a minority of nickel sensitized subjects. Although, the concentration of Ni inside the skin was higher than $0.5\,\mu g\,cm^{-2}$, overpassing the limit suggested by E.U. Directive EN 1811 (EC 2009, ECHA 2014) to prevent the risk of ACD, our data demonstrated that skin contact with Ni powders may lead to a relevant skin absorption of Ni, but the application of a protective cream is able to reduce the Ni uptake. Then, the results from our study confirm the capability of Ni ions to permeate and accumulate through the skin, and they are in line with the study of Hagvall et al. [18]. Hagvall et al. [18] demonstrated that Ni ions penetrated through the cutaneous barrier, mainly in the *stratum corneum* and to some extent in the upper parts of the epidermis, while in our tests, Ni ions were more retained in the dermis layer than in the epidermis layers for samples pretreated with creams. The higher distribution of Ni ions in the dermis compared to the epidermis was also observed in our previous work [23]. It is well reported that the percutaneous passage of metals through the injured skin is more pronounced as a consequence of the less efficient cutaneous barrier function, due to histological and skin microenvironmental changes. In fact, wounds, scratches, inflammation, disorders of lipid composition and organization, as in the case of atopic dermatitis [62], or epidermal differentiation disorders such as psoriasis, ichthyosis, and skin cancer [63, 64], alter the skin barrier properties. Our study is the first to investigate the protective effect of a barrier cream containing chelating agents for Ni and a moisturizing cream containing a balanced mixture of fundamental lipids of the epidermis (ceramide 3, cholesterol, and fatty acids) to reduce skin absorption of Ni powders, in order to get information that can be helpful for the application of preventive measures in exposed subjects and could

TABLE 4 Full absorbed and recovered amount (Q_{abs}) of Ni after 24 h exposure to Ni powder.

	Total skin ($E+D$) ($\mu g\,cm^{-2}$)	Receptor fluid (RF) ($\mu g\,cm^{-2}$)	Q_{abs} ($E+D+RF$) ($\mu g\,cm^{-2}$)
Control (not pretreated)	36.5 ± 9.51	0.16 ± 0.14	36.7 ± 9.37
Formulation A	8.00 ± 3.35[a]	0.43 ± 0.15	8.43 ± 3.28[a]
Formulation B	22.6 ± 12.6[a]	0.42 ± 0.34	23.0 ± 12.9[a]

Note: The applied dose was $52.6\,mg\,cm^{-2}$. Data are given as mean ± SD.

[a]Statistically significant difference obtained between samples pre-treated with Formulation A and skin samples pre-treated with Formulation B in the Student's *t*-test ($p < 0.05$).

therefore help to find better protective devices. Finally, the Franz cells method adopted in our current study has some limitations: firstly, it is an in vitro method used to investigate the percutaneous absorption of molecules, which may not reproduce the real scenario. The obtained results can underestimate the in vivo conditions because only passive diffusion is evaluated, while in vivo skin absorption can be enhanced by active mechanisms. Moreover, it is important to underline that only diffusion cell results are reported in this work. Secondly, to mimic sweat, the *stratum corneum* was exposed for 24 h, but the excessive hydration may promote the transcutaneous passage of many compounds. Thirdly, our conditions do not reflect those recommended for the use of the product; for example, the application of formulation A should be reapplied after contact with water or in cases of heavy sweating.

CONCLUSION

The current study aimed to evaluate and compare the efficacy of two marked creams to reduce Ni skin penetration after exposure to Ni powder. Our results showed that both tested formulations decreased Ni accumulation in the skin layers, compared to the not pretreated samples, with a higher efficacy in the case of the specialized barrier cream that contains a chelating agent. Interestingly, also the general moisturizing product (an o/w emulsion without chelating agents) showed protection for dermal uptake of Ni, possibly related to the presence in the formulation of a balanced mixture of fundamental lipids (ceramide 3, cholesterol, and fatty acids), which can form a resistant lipid film able to prevent the dermal uptake of the metal. The level of Ni inside the skin, however, resulted in all cases exceeding the EU suggested protective limit for allergic patients, suggesting a limited protective effect. Finally, based on the data of our study, we showed that the composition of the formulations based on film forming or chelating agents may play an imperative role in reducing the cutaneous penetration of Ni.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interests to disclose.

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