Penetration of Metals Through the Skin Barrier

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7.1 Introduction

The skin is a route of entry for substances that come in contact with the stratum corneum and has an important role for the penetration of haptens, which can induce contact sensitization and allergic contact dermatitis. In addition, toxic substances (detergents, acid, soaps, etc.) can act as irritant factors on skin layers, increasing skin permeation of other products, such as haptens. Other substances can pass through the skin, reaching the dermis and, from there, the general circulation, inducing the potential for systemic intoxication.

Skin exposure to metals can happen during contact with metal objects, jewels, coins, or leather that can release metals such as nickel, chromium, cobalt, or palladium, particularly when in contact with sweat [1, 2]. New tissues have been made using silver nanoparticles and silver can also penetrate the skin [3], although urinary levels of silver in one study did not increase after exposure [4], meaning that the applied dose was not sufficient to cause systemic involvement.

Many workers, such as mechanics, solderers, electroplaters, miners, etc., are exposed to different kinds of metals or metal salts. Moreover, an environmental exposure exists to platinum group metals (platinum, rhodium, and palladium) which are released into the atmosphere by vehicle exhaust catalysts [5].

Metals in contact with the skin can be absorbed, reaching the viable layers of the epidermis and sometimes the dermis and general circulation. In general, skin permeation of metals has been underestimated, and much attention has focused only on local effects, as some metals are the principal cause of allergic contact dermatitis, such as nickel, chromium, palladium, and cobalt. Contact with metal objects and jewelry causes metallic ions to be released, which is enhanced by synthetic sweat [2, 6]. Metallic ions or their salts pass through the stratum corneum and reach the viable epidermis, where "antigen-presenting cells" are present and can initiate the type 4 Gell and Coombs sensitization process. Subsequently, metals can penetrate to the dermis and reach the systemic circulation in very low amounts. While sensitization can happen with extremely low doses, systemic intoxication requires high metal concentrations that are unlikely to occur with exposure to intact skin.

In skin penetration, a crucial aspect is the integrity of the skin barrier. Damaged skin, characterized by fissures, scaling, or desquamation, can increase metal skin absorption more than

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100–1000 times, and, for that reason, irritant contact dermatitis must often be considered the first step toward allergic contact dermatitis.

Finally, we consider the term "penetration" when the applied substance reaches the skin and "permeation" when a substance passes through the skin.

7.2 Route of Skin Permeation

Chemicals can be absorbed through the skin via different pathways [7, 8]:

1. The intercellular route, with partitioning into the lipid matrix
2. The intracellular route, for substances that can enter the cells
3. Through sweat glands and hair follicles [9]

Hair follicles can act as a shunt, increasing the penetration and absorption of topically applied substances [10–12] and nanoparticles (NPs) [13]. Hair follicles can also be considered a reservoir for penetrating chemicals and nanoparticles, since substances stored there can diffuse to the surrounding spaces, cross the capillary walls, and even reach the circulatory system [14].

Skin diseases, such as irritant contact dermatitis and atopic eczema, can increase the risk of hapten penetration, leading to a possible sensitization [15, 16].

Skin exposure to irritant compounds can enhance penetration likely due to disruption of the stratum corneum, either by means of protein denaturation agents, such as detergents, or through lipid extraction from the stratum corneum by means of solvent agents [17, 18].

7.3 Factors Involved in Skin Permeation

The skin can be considered a barrier membrane in which Fick's laws of diffusion are applicable and factors involved are summarized in Table 7.1. The involved area, time of contact, gender, differences in skin thickness, hair follicle density, blood flow, age, mechanical flexions for nanoparticles [27, 30], and systemic diseases may all influence the skin barrier function [31, 32].

7.4 Skin Absorption Studies

7.4.1 In Vitro Data on Animals and Human Skin

The approach to studying metal skin absorption can be in vitro, using Franz cells [33] with human or animal skin, that permits the definition of flux through the skin and the lag time (time in which the flux starts to be constant). These studies are widely used to evaluate drug permeation through the skin, and results can assist understanding of the skin absorption of chemicals [34] but need to be conducted following guidelines, i.e., using at least two donors to reduce variability, which is considerable between donors. However, the permeability coefficient measurements have a mean intraindividual coefficient of variation of approximately 40% [35], and an interindividual variation of about 70% [36]. Hostýnek [29] and Loth [37] suggested that these variations are related to differences in the lipid domain of the stratum corneum and that these in vitro studies reflected in vivo conditions.

Despite the wide variability, Franz cell results permit us to determine the amount of permeation of a substance, the time needed for permeation, and the amount of metals inside the skin. In Table 7.2, some results related to metal penetration studies performed using metal powders in micron or nanosize ranges are summarized. Many other data are available for metal salts that have an increased potential for skin penetration due to their chemical characteristics [23, 44–47].

A flux through the skin has been demonstrated for all metals tested (Ni, Co, Pd), except for chromium which is probably strongly bound to skin proteins [48]. In general, flux is very low and in the range of ng/cm^2/h and has been shown to

Table 7.1 Factors involved in skin absorption

Dose
The applied dose can influence skin absorption in variable ways. In some cases, an increased dose can result in increased permeation, but under other conditions, skin absorption can be negatively influenced. For example, chromium skin levels in the skin increased with increasing concentrations of applied chromium salt up to 0.034 M Cr [19]. Conversely, mercuric chloride skin absorption was shown in the guinea pig to reach a maximum at 16 mg hg/ml and decreased to non-detectable levels with increasing concentrations [20].
Ions released (counter ion)
Sweat can increase ion release from metal objects, thus increasing skin permeation [21]. Different nickel salts penetrate the skin in different amounts, and the phenomenon is influenced by occlusion [22].
Area of the skin contaminated
Anatomical site
Skin penetration varies markedly at different body areas. Hostýnek in 2001 [22] suggested a decreasing trend of penetration from scrotum-forehead-postauricular-abdomen-forearm-leg-back. Differences are related to skin thickness and to intercellular lipid composition.
Thickness of the skin reduces skin absorption
Duration of skin contact increases permeation and penetration
Vehicles
Solvents and detergents can increase permeation due to their irritant effects, and different formulations can change skin absorption [23, 24].
Temperature can increase skin permeation
Humidity can increase sweating that, in general, increases permeation
Blood flow can increase skin permeation
Physical activity can increase skin permeation
Gender and race affect skin penetration and permeation as, in general, female skin is thinner and stratum corneum impairment more frequent
Age affects skin penetration, which is inversely related to age
Hair follicle and sweat gland density
This route of entry is extremely important because it is faster than intercellular and intracellular routes. For nickel salts, 25–46% of the dose can be inside follicles [25]. The "follicular route" can be considered the most efficient [13] for nanoparticles. Moreover, electrolytes can also be excreted through hair follicles, and for some elements such as iron (II), zinc(II) and copper (II), sweat can be considered an important pathway [26].
Mechanical flexion of the skin can increase penetration and permeation of nanoparticles [27]
Skin condition
Skin barrier impairment increases metal penetration. Nielsen et al. [28] demonstrated that nickel hypersensitivity develops quickly on nickel exposure of irritated skin compared to application on intact skin.
Characteristics of the substance
Molecular weight is inversely related to permeation.
Valence: Trivalent chromium is less permeable than hexavalent chromium, and cream containing iron sulfate can reduce chromium skin penetration, changing the valence of chromium [29]. This aspect is probably due to the strong binding of trivalent chromium to epidermal proteins.
Octanol/water partition influences skin absorption.
pH can modify the skin absorption.
Storage inside the skin
Nanoparticles in contact with the skin can be stored inside follicles, and from there ions can diffuse into the dermis [13]. Some metals can be bound to skin proteins, such as chromium (III), silver (I), mercury (II), aluminum (III), and nickel (II), as well as the metalloid arsenic (III) [23, 29].

increase 10–100 times in skin damaged with a needle. Particle size influences absorption, and metal NPs represent a higher potential for penetration and permeation than metals in micron size, considering the lower dose applied in nano-form [49, 50]. Lag time ranges between 1 and 14 h and is generally lower for NPs (Pd and Ni), with the exception of cobalt [51].

The application of chromium in metal powders did not cause a permeation flux through

Table 7.2 Permeation studies of sensitizing metals

Metal	Flux μg/cm²/h (mean ± SD)	Lag time (h)	Donor dose mg/cm²	Metal into the skin (μg/cm²)	Skin	Reference
Ni 2.3–3 μm	0.0165 ± 0.00036	14.56 ± 0.56	15.2	–	Human intact	Larese et al. [6]
Ni 2.3–3 μm	–	–	23	82.3	Human intact	Larese et al. [38, 39]
Ni 2.3–3 μm	–	–	23	131	Human damaged	Larese et al. [38, 39]
Ni NPs 77 nm	0.0017 ± 0.0006	6.0 ± 1.4	0.6	9.67 ± 2.70	Human intact	Crosera et al. [40]
Ni NPs 77 nm	0.30 ± 0.12	6.6 ± 0.8	0.6	29.2 ± 11.2	Human damaged	Crosera et al. [40]
Pd NPs 10.7 nm	0.005 ± 0.003	4.8 ± 1.7	0.6	0.69 ± 0.36	Human intact	Larese et al. [41]
Pd NPs 10.7 nm	0.057 ± 0.030	4.2 ± 1.6	0.6	0.93 ± 0.41	Human damaged	Larese et al. [41]
CoO4NPs 17 nm	Nd		0.6	16.8 ± 10.98	Human intact	Mauro et al. [42]
CoO4NPs 17 nm	0.002 ± 0.002	4.3 ± 2.1	0.6	12.3 ± 6.18	Human damaged	Mauro et al. [42]
CoNPS 80 nm	Nd	Nd	1	4.35 ± 1.36	Human intact	Larese et al. [43]
CoNPS 80 nm	0.076 ± 0.049	2.8 ± 2.1	1	12.8 ± 3.8	Human damaged	Larese et al. [43]
Co 2 μm	0.123 ± 0.0054	1.5 ± 5 0.71	15.2	–	Human intact	Larese et al. [6]
Co 2 μm	–	–	23.9	29.6 (median)	Human intact	Larese et al. [38, 39]
Co 2 μm		–	23.9	48.7 (median)	Human damaged	Larese et al. [38, 39]
Co 2 μm	0.55 ± 0.33	–	15.9	12.3 ± 5.4	Human intact	Larese et al. [21]
Co 2 μm	76 ± 49.3	–	15.9	Nd	Human damaged	Larese et al. [21]
Cr	Nd	–	15.2	Nd	Human intact	Larese et al. [6]
Cr < 10 μm	Nd	–	23	14.4 (median)	Human intact	Larese et al. [38, 39]
Cr < 10 μm	Nd	–	23	62.1 (median)	Human damaged	Larese et al. [38, 39]

Studies were performed using Franz cells with the application of metal powders or nanoparticles to full-thickness skin
Nd not detected, – data not available

the skin, but this metal can be found inside the skin in higher amounts when the skin is damaged [6]. The application of $K_2Cr_2O_7$ instead resulted in the significant permeation of this metal, reaching a flux of 7.29 μg/cm²/h and confirming that a metal's salts can pass in higher amounts through the skin. The lag time was around 12 h [6].

7.5 "Disappearance Measurements"

This method, which involves the application of radiolabeled metals followed by evaluation for the disappearance of radioactivity on the skin, demonstrated many years ago that metals can pass through the skin [52–54].

7.6 In Vivo Data on Humans

Feldmann and Maibach [55] studied radiolabeled hydrocortisone applied onto the skin of human volunteers, looking for radioactivity excreted in urine, and obtained important information regarding skin absorption and excretion. Contact with 0.1–0.5 ml of dimethylmercury caused the death of a scientist [56, 57]. There was an increase of mercury concentration in blood, despite the skin having been covered by latex gloves.

The use of tape stripping methods permits verification of the amount and penetration depth of metals applied on the skin of volunteers. This technique involves the standardized application of a fixed pressure during the tape stripping and permits evaluation of the penetration into the skin of nickel sulfate [22]. The same method has also been used to study nickel sulfate skin permeation using full-thickness skin under ex vivo conditions [58, 59]. The authors demonstrated that nickel was detectable in the deepest layers of the stratum corneum, the epidermis, and the dermis, with a decreasing trend. However, 42.2% of the applied dose was removed with the first two tape strips, confirming that only very small amounts of the applied metal penetrated into the viable skin. Nickel penetrating the skin can be bound by filaggrin inside the stratum corneum, as demonstrated by Ross-Hansen et al. [60].

7.7 Lag Time for Metal Penetration

In general, metals are slowly absorbed compared to solvents that can reach the steady state after less than 1 h. Experiments performed using Franz cells demonstrated a lag time of hours (Table 7.2), while experiments in vivo suggested longer periods to reach the flux steady state (70 h in [19]). A recent study demonstrated that, after the in vivo application of a patch test containing nickel sulfate 5% w/v in water in mice, maximum Ni penetration occurred after 24 h. The Ni content was high in the epidermis and spread into the dermis beyond the basal layer [61]. This experimental result confirms the penetration pattern of nickel sulfate after patch test application.

7.8 Skin Metabolism

Metals can be modified by the skin metabolism: hexavalent chromium is reduced to Cr (III) by tissue proteins, and Samitz and Katz in an old paper [62] estimated that 1 g of skin can reduce approximately 1 mg of dichromate to trivalent chromium. Arsenic accumulates in the skin, binding to proteins containing sulfhydryl groups and causing hyperpigmentation, keratoses, and skin cancer. Silver deposits inside the dermis cause a graying of the skin called argyria, and application of mercurial products causes an accumulation of metallic mercury in the skin called hydrargyrosis cutis.

7.9 Conclusion

Contact with metallic objects or with products containing metals, such as leather treated with chromium or cement containing chromium and cobalt, may result in the penetration of metals into the skin. This can cause delayed-type sensitization. The time needed for penetration in general is high, requiring hours to arrive into the dermis or pass through the skin. Sweat can increase ion release from metallic objects or substances, thereby increasing overall penetration and permeation of metals. The amount of skin permeation is generally low (ranging around ng/cm^2/h). Thus, the amount of metal that can reach the general circulation is also low and, in general, not likely to cause systemic intoxication (except for in the case of organic mercury, arsenic, and potentially lead). The presence of metals in the skin, higher in the epidermis than in the dermis, as well as the storage of metal nanoparticles inside hair follicles, can elicit local sensitization with the onset of allergic contact dermatitis. Alteration of the skin barrier, as happens in irritant dermatitis, in atopic eczema patients, and in "wet work," enhances metal penetration and permeation of the skin, increasing the risk of sensitization.

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