International Journal of Pharmaceutics 402 (2010) 44–49

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Skin contamination by radiopharmaceuticals and decontamination strategies

M.A. Bolzinger[a,b,c], C. Bolot[d], G. Galy[d], A. Chabanel[d], J. Pelletier[a,b,c], S. Briançon[a,b,c,*]

[a] Université de Lyon, F-69008, Lyon, France
[b] Université Lyon 1, Institut des Sciences Pharmaceutiques et Biologiques, Laboratoire de Dermopharmacie et Cosmétologie, F-69008, Lyon, France
[c] UMR CNRS 5007, Laboratoire d'Automatique et de Génie des Procédés (LAGEP), F-69622, Villeurbanne, France
[d] Groupement Hospitalier Est, Radiopharmacie, Service Pharmaceutique, 59 bd Pinel, 69677 Bron cedex, France

ARTICLE INFO

Article history:
Received 6 June 2010
Received in revised form
21 September 2010
Accepted 22 September 2010
Available online 1 October 2010

Keywords:
Radiopharmaceuticals
Hofmeister series
Percutaneous absorption
Franz cells
Skin decontamination

ABSTRACT

The aim of the present study was to evaluate the percutaneous penetration of five common radiopharmaceuticals (^{99m}Tc, ^{67}Ga, ^{125}I, ^{111}In and ^{51}Cr) and to evaluate the effect of decontamination by a detergent solution dedicated to hospital institutions for that purpose. The skin kinetic profiles were established by using the *in vitro* Franz cell method over 24 h. The skin distribution in each skin layer was quantified after 6 h exposure time and the efficacy of the detergent solution to remove radionuclides was evaluated also after 6 h. The most striking result was the repartition into two classes of kinetic profiles: ^{125}I and ^{99m}Tc permeated quickly (~60% of applied activity after 24 h) while the 3 other radionuclides permeated slowly (from ~2.75% for ^{67}Ga to ~10% of applied activity for ^{111}In). The lag times, i.e. the time necessary to cross the skin varied from 20 min for ^{99m}Tc to 5 h for ^{51}Cr, which accumulated in skin compartments. Skin washings with the detergent solution were particularly efficient for this radionuclide, contrary to the others for which the washing procedure should be applied earlier. The permeation of ions was dependent on their chemical and physical forms and on their salting-in or salting-out effects (coordination state and Hofmeister series).

1. Introduction

Because of the rapid and continuous advances in molecular biology and genetic engineering a variety of radiopharmaceuticals has been developed for determining organ function or assessing disease status by imaging methods. Diagnostic radiopharmaceuticals are labelled with gamma-emitting isotope because imaging modalities widely used in nuclear medicine include γ scintigraphy, positon emission tomography (PET) and single photoemission computed tomography (SPECT) (Anderson and Welch, 1999). The choice of radionuclides for diagnosis purposes depends on their half life, type of radiation, energy, and presence or lack of other particulate radiation emissions. This choice also depends on their biodistribution characteristics. The most widely used radionuclides are ^{99m}Tc, ^{67}Ga, ^{111}In, ^{131}I and ^{51}Cr. They are intended to detect diseases in the heart, brain, bone, lung and thyroid (Clarke, 2006; Davis et al., 1992; Jurisson and Lydon, 1999; Magill and Galy, 2005; Reinhardt and Moser, 1996; Schibli and Schubiger, 2002; Verbruggen, 1990). For diagnostic imaging the desired half life is dependent upon the time necessary for the radionuclide to localize in the target tissue but must be short enough to limit the radiation dose to the patient. The limitation of the dose is the occupational risk in nuclear medicine departments. Gamma rays are highly penetrating radiations and can result in considerable organic damages. Therefore, gamma emitting sources such as ^{99m}Tc, ^{67}Ga, ^{111}In, ^{131}I and ^{51}Cr which emit Auger electrons and have some IC (internal conversion) effects require heavy shielding and remote handling (Buchegger et al., 2006; Gardin et al., 1999). These radiopharmaceuticals are prepared in nuclear medicine departments in a shielded cell by radiopharmacists wearing double gloves. They are then administered *via* intravenous injection by nurses and practitioners wearing a single pair of gloves to collect clinically useful images. Repeated exposure of personnel members who handle radionuclides everyday should be considered. Actually surface or skin contamination may occur accidentally. The most frequently contaminated areas are the hands and the most likely source of this contamination is the bench top and/or laboratory coat (Nishiyama et al., 1980a,b). In general, diagnostic radiopharmaceuticals are used at very low concentrations and are not intended to have any pharmacological effect (Liu, 2004) but accidental contamination may occur and could have side effects especially in the case of radioisotopes with long decay period as ^{131}I. At present more than 20,000 gamma cameras are used through the world in some 8500 nuclear medicine departments (Magill and Galy, 2005) raising the possibility of accidental contamination. Surprisingly skin contamination studies by commonly used medical radionuclides are little scarce (Moore and Mettler, 1980). The uptake of radionuclides through intact skin may

* Corresponding author at: LAGEP UMR-CNRS 5007, Bat 308G, 43 Bd du 11 Novembre, 69622 Villeurbanne, France. Tel.: +33 4 72 43 18 64; fax: +33 4 72 43 18 64.
E-mail address: briancon@lagep.univ-lyon1.fr (S. Briançon).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.09.027

cause unmanageable side effects especially for radionuclides with a long decay period. The critical site of radiation resulting from contamination is the *stratum germinativum*, where proliferative cells are located. The radiation dose reaching the basal cell layer of the epidermis involves predominantly beta and gamma radiation (Bauerova et al., 2001; Koprda et al., 2000). In this context, the aim of the present study was to evaluate the permeation kinetics profiles of the five diagnostic radiopharmaceuticals cited above over 24 h exposure time *in vitro* by using the Franz cell method in order to evaluate the better timing for skin decontamination. There is an extensive literature on the biokinetics of diagnostic radiopharmaceuticals but the diffusion of radionuclides through the skin after contamination has received little attention except for uranium uptake or derivatives (Bauerova et al., 2001; Koprda et al., 2000; Houpert et al., 2001, 2004; Ilyin et al., 1975; Kassai et al., 1999, 2003; Koprda et al., 1998; Osanov et al., 1971; Petitot et al., 2006, 2007; Tymen et al., 2000; Xu et al., 2008; Yang et al., 2005).

The skin distribution in each skin layer was evaluated after 6 h exposure time (mean time spent by a personnel member before checking a possible contamination) and compared to the skin distribution after removal of radionuclides from the skin surface samples by consecutive washings with a saline solution (0.9%) and a diluted detergent solution. The decontamination effect of washings on radionuclide distribution was therefore evaluated. The radionuclide distribution in the skin is an important task because depending on this radionuclide distribution (dead cells of the *stratum corneum* (SC), living cells of the deeper layers (viable epidermis or VE, dermis or D and receptor fluid or RF)) the absorbable dose from the skin is different.

2. Material and methods

2.1. Materials

Table 1 shows the gamma emitting radionuclides used in this study. Their half-life and energy characteristics are indicated. ^{125}I was chosen because it is less hazardous than ^{131}I. Actually, ^{125}I emits only gamma radiation whereas ^{131}I emits both gamma and beta radiations. Beta radiation is moderately penetrating but can penetrate human skin to the basal layer and may cause skin injury by damaging stem cells. The doses used in this study are far from those used for therapeutic purpose (1000 times lower) or for diagnosis purposes (30–500 times lower).

The formulations used for skin absorption studies were distilled water solutions and are reported in Table 2.

2.2. Methods

2.2.1. In vitro skin absorption studies

Full-thickness pig female or male skins (1.70 ± 0.09 mm; mean ± SE) were obtained from young animals sacrificed at the Laboratoire de Physiologie, Université de Lyon, France. The skin flanks of 3 donor animals (25 kg) were washed and excised, the subcutaneous fatty tissue was carefully removed, and the skin pieces were stored flat at −20 °C until use. On the day of use, the skin was thawed and then cleaned up with tap water. The hairs were cut with an electric cutter. The skin was shortly washed with 1% sodium dodecyl sulfate aqueous solution and rinsed with tap water. Integrity of skin samples was examined by measuring the Trans Epidermal Water Loss (TEWL) (Tewameter TM210, Monaderm, Monaco). The TEWL was measured for 1 min and skin samples with TEWL values larger than 15 g h^{-1} m^{-2} were discarded. The thickness of each skin piece was measured with a micrometer (Mitutoyo). The skin was mounted in two-chamber glass diffusion cells. The effective penetration area was 2.54 cm^2 and the receptor compartment contained 10 ml of 0.9% NaCl aqueous solution. The cells were placed in a water bath at 37 °C providing a skin surface temperature of 32 °C because of heat loss. 1 ml of freshly prepared formulation was deposited on the skin surface.

2.2.1.1. Permeation studies. The permeation experiment was carried out for 24 h in static Franz cells. The replication for each experiment was $n = 6$. During the experiment, the receptor fluid (RF) was completely emptied at, 30 min, 1 h, 1.5 h, 2 h, 2.5 h, 4 h, 5 h, 6 h, 7 h, 8 h, 15 h, 18 h, 21 h, and 24 h exposure times and replaced with fresh medium. The collected samples were count. The percentages of applied activity were plotted against time.

2.2.1.2. Skin distribution after 6 h. The percutaneous experiment was carried out over 6 h. At the end of the experiment the cells were dismantled and the percentage of applied activity evaluated in the donor compartment, the receptor fluid and the different skin layers. The radionuclide solution remaining in the donor compartment and the skin surface were washed 10 times with 2 ml of 0.9% sodium chloride aqueous solution each time. The final volume was adjusted to 50 ml and the radioactivity of samples was measured. The epidermis was separated from the dermis by heat treatment (45 s in water at 60 °C). After separation, the radioactivity of each layer (epidermis and dermis) was measured separately.

In some cases, the skin stripping method was performed. The *stratum corneum* was separated into 19 layers using an adhesive tape D-Squame® (Monaderm, Monaco). The first strip was discarded and added to the washing and the 18 following stripes pooled three by three and count. The viable epidermis (VE) was then separated from the dermis (D) by heat treatment as described above and the radioactivity was measured in each layer. Q_{abs} corresponds to the absorbed dose i.e. the percentage of applied activity recovered in VE + D + RF.

2.2.1.3. Decontamination of the skin. Decontamination of the skin was performed by using a detergent aqueous solution containing a mixture of anionic and amphoteric surfactants and alkanolamide derivatives (Anios® savon doux). This detergent solution is dedicated for hand washing and decontamination procedure in hospital institutions. The applied protocol was meant to mimic *in vitro* the decontamination procedure used in the hospital *in vivo*. The permeation study for each radionuclide was conducted over 6 h which roughly represents the time spent by a personnel member before checking a possible contamination. After this time the remaining solution was removed and the skin surface washed 5 times with 2 ml of 0.9% NaCl aqueous solution each time. Then, the skin surface was mechanically rubbed with a cotton bud impregnated with the diluted detergent solution (50% dilution) for 30 s by applying circular movements. This procedure was repeated once with a second cotton bud before rinsing off 5 times with 2 ml of 0.9% NaCl aqueous solution. The cotton bud was supposed to mimic hands rubbing during the decontamination procedure. The volume of the rinsing saline solution was limited by the volume of the donor compartment. After applying this procedure the *stratum corneum* was stripped and the viable epidermis separated from the dermis as previously described. After separation, the radioactivity was mea-

Table 1
Characteristics of the radionuclides.

Isotope	$E\gamma$ (keV)	$T_{1/2}$ (h or d)
^{99m}Tc	140	6 h
^{111}In	171 and 245	2.8 d
^{67}Ga	185 and 300	3.26 d
^{51}Cr	320	27.7 d
^{125}I	27 and 35	59.9 d

Table 2
Description of radionuclide properties.

Radionuclide solutions	Skin deposition	Supplier
Sodium pertechnetate $^{99m}TcO_4^-Na^+$	1 ml containing 0.3 MBq of ^{99m}Tc (1 pg)	^{99}Mo/^{99m}Tc Generator from IBA Cis Bio Gif/Yvette, France
Indium chloride $^{111}InCl_3$	1 ml containing 0.3 MBq of ^{111}In (19 pg)	Covidien Elancourt, France
Gallium citrate	1 ml containing 0.3 MBq of ^{67}Ga (14 pg)	IBA Cis Bio Gif/Yvette, France
Sodium iodide ^{125}INa	1 ml containing 0.1 MBq of ^{125}I (156 pg)	Perkin Elmer Boston, USA
Sodium chromate $^{51}CrNa_2O_4$	1 ml containing 0.2 MBq of ^{51}Cr (59 pg)	GE Healthcare Velizy, France

sured in each layer. The cotton buds were also count and taken into account in the calculations.

2.2.2. Analysis of radionuclide content

The radioactivity of ^{99m}Tc was measured using a γ counter Packard Cobra II N°2. For ^{111}In, ^{67}Ga, ^{125}I and ^{51}Cr a Perkin Elmer Wizard 1470 Automatic Gamma counter was used.

2.2.3. Data analysis

Results were expressed as percentage of applied activity. The mean and standard error of the mean (S.E.) of $n = 6$ determinations were calculated. Statistical comparisons were made using the Student's *t*-test (two-sample assuming equal variances) and analysis of variance (ANOVA, single factor) with the level of significance at $p \leq 0.05$.

3. Results and discussion

This study was aimed at evaluating the skin absorption of five routinely used radionuclides differing by their half-life in order to estimate the time available to treat the contaminated area before systemic uptake. Fig. 1 shows the skin permeation profiles of the 5 radionuclides over 24 h in percentage of applied activity. The extrapolation of the linear part to the time axis gave the lag time and the slope yielded the pseudo steady-state flux J_{SS} (% of applied activity h^{-1}). The most striking result is the repartition into two classes: ^{125}I and ^{99m}Tc permeates quickly (~60% of applied activity after 24 h) while the 3 other radionuclides permeate slowly (from ~2.75% for ^{67}Ga to ~10% of applied activity for ^{111}In). Pseudo steady-state fluxes are reported in Table 3. For Technetium only the initial part of the curve between 0 and 6 h was considered for the flux calculation because of its specific behavior. Actually after 8 h a plateau was observed. ^{99m}Tc permeates quickly and the donor compartment was partially depleted after 8 h, resulting in a slowing down of the radiopharmaceutical diffusion through the skin as it can be observed in skin permeation experiments conducted with finite dose. A factor of 10–100 is observed in flux values between both groups (0.098% $h^{-1} \pm 0.023$ for ^{67}Ga to 5.63% $h^{-1} \pm 0.36$ for ^{99m}Tc). This result is quite surprising regarding Fick's laws. Actually, the skin's barrier function represented by the *stratum corneum* has been widely studied in the literature and predictive models of percutaneous absorption developed (Förster et al., 2009). The simplest way to model the process of skin transport is to consider the skin as a membrane through which a compound has to pass. The diffusion of the compound through the skin is described by Fick's Laws. This law says that the flux (mass m^{-2} s^{-1}), which is the rate of transfer per unit area, of a compound at a given time and position is proportional to the differential concentration change ∂C over the differential distance ∂x. The flux of the compound through the skin at steady state (i.e. when the flux is constant) is given by:

$$J_{ss} = \frac{D(C_1 - C_2)}{L} \quad (1)$$

where L is the length of the diffusion pathway of the penetrating molecule (layer thickness) (m), C_1 and C_2 are the mass concentrations (kg m^{-3}) of the drug in the membrane at the two faces (at $x = 0$ and $x = L$) and D is the diffusion coefficient (m^2 s^{-1}). The diffusion coefficient is difficult to estimate and is related to the permeability coefficient P expressed mathematically by Eq. (2):

$$P = \frac{K_m D}{L} \quad (2)$$

where K_m is the partition coefficient experimentally determined by the octanol/water partition coefficient $K_{oct/w}$, D the diffusion coefficient (m^2 s^{-1}) and L the membrane thickness.

The dependence of P on the physicochemical properties of the compound has been demonstrated; Potts and Guy (1992) have postulated the dependence of P upon the molar mass and the lipophilic properties of the chemical considered. More generally, physicochemical properties of the active ingredient, which determine the penetration profile, include the molecular size, lipophilicity, hydrophilic–lipophilic balance and distribution of polar and nonpolar parts in the molecule and the extent of the ionized state. These factors play a large part in determining the solubility and the partition coefficient of the ingredient and have been extensively studied in the last decades (Hadgraft and Lane, 2005; Hadgraft and Valenta, 2000; Mitragotri, 2003; Pugh et al., 2000). However, all these studies refer to the penetration of more or less large organic molecules and little is reported on ions penetration through the skin. For ions and molecular species of small size, other criteria should be provided. The penetration of ions in the skin could be

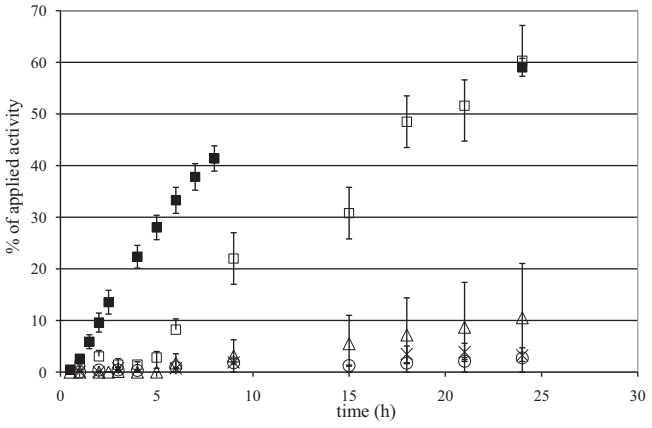

Fig. 1. Permeation profiles of the five radionuclides through the skin over 24 h ($n = 6$): (■) ^{99m}Tc; (□) ^{125}I; (△) ^{111}In; (○) ^{67}Ga; (×) ^{51}Cr.

Table 3
Pseudo steady-state fluxes of radionuclides through pig skin (mean and SD of $n = 6$ determinations).

	Flux (% of applied activity)	Lag time (h)
Sodium iodide	2.64 ± 0.051	4.83 ± 0.47
Sodium pertechnetate	5.63 ± 0.36	0.34 ± 0.12
Indium chloride	0.49 ± 0.12	3.63 ± 0.78
Gallium citrate	0.098 ± 0.023	2.86 ± 1.15
Sodium chromate	0.18 ± 0.022	5.04 ± 1.92

preferentially related to the Hofmeister effect. Hofmeister effects or sequences refer to the relative effectiveness of anions or cations to bind to micelles, proteins and membranes. Consequently these effects intervene on a wide range of phenomena such as transport across membranes, colloid stability, solubility of salts, pH measurements, zeta potentials, buffers, critical micellar concentrations, cloud points of non-ionic surfactants. These effects remain unexplained by present theories of physical chemistry (for review, see Kunz et al., 2004) but allow classifying anions and cations in two ranges: ions with marked salting-in or salting-out effects. According to Hofmeister's theory the ions belonging to the cosmotropic series (salting-out effect) could bind water around them ("water-structure makers") and allow the formation of hydrophilic structures reducing the solubility of compounds with low polarity. UO_2^+, is a strong structure maker which have consequently a salting-out effect (Marcus, 2009). This cation is hydrophilic and does not reach easily the receptor fluid as demonstrated by Petitot and Tymen (Petitot et al., 2007; Tymen et al., 2000). Conversely chaotropic ions are less hydrated ("water-structure breakers") and could interact with apolar substances making them more soluble in water. I^- is a "salting in" anion in the chaotropic range of the Hofmeister series (Cacace et al., 1997). It is a large anion highly polarisable and hydrophobic. Therefore the iodide anion is less hydrated, and is able to interact with apolar substances making these molecules more soluble in aqueous systems. Actually, chaotropic ions favour the swelling of lipids and proteins by disrupting water in the first hydration shell leading to a better protein solubility and lipid hydration. Chaotropic ions are also able to destabilize the lipid bilayer structure of cell membranes by reducing the energy required to expose the non-polar groups within the membrane to the environment (Cacace et al., 1997). Thus, I^- has a good affinity for the lipid skin barrier of *stratum corneum* explaining its longer lag time (~4.8 h versus only 20 min for ^{99m}Tc) but swells membrane promoting thereafter a higher flux through the skin. This explanation is in accordance with Ko et al. who investigated the effects of sodium salts of various monovalent inorganic anions in the Hofmeister series on the transdermal permeation of salicylic acid. Their work was conducted *in vitro* on Franz diffusion cells (Ko et al., 1995). These authors showed that the permeation-enhancing activities of the sodium salts of inorganic anions were roughly proportional to lyotropic Hofmeister swelling abilities of the anions; $F^- < SO_4^{2-} < Cl^- < ClO_4^- < NO_3^- < SCN^- < Br^- < I^-$. In their study I^-, Br^- and SCN^- increased the flux of drugs through the mouse skin, while F^-, SO_4^{2-}, Cl^-, ClO_4^- and NO_3^- decreased or did not affect the flux. In our work in the first group defined by the highest fluxes ^{99m}Tc and ^{125}I behave similarly. It should be noticed that the first application of ^{99m}Tc for medical imaging involved the use of ^{99m}Tc for diagnosis of thyroid disease on the assumption that the ^{99m}Tc would behave similarly to iodide, known to be taken up by thyroid (Liu, 2004). One of the characteristics of technetium is its diverse redox chemistry, consequence of the range of available oxidation states (−1 to +7), a wide number of coordination geometries, and its ability to bind to a large range of donor ligands to fulfil its coordination requirements (Reichert et al., 1999). There is no effective chemistry to attach ^{99m}Tc to biomolecules under this oxidation state (VII). In general, coordination is accomplished upon reduction of pertechnetate in the presence of a good complexing agent. In the absence of reducing agents, pertechnetate ion is quite stable in aqueous solution and permeates well because no chelators with high affinity for the pertechnetate ion are located in the skin (Liu, 2008).

The second group defined by lower permeation profiles comprises ^{111}In, ^{67}Ga and ^{51}Cr. ^{67}Ga and ^{111}In are transition metals reported in the same column of the Mendeleev periodic table (Group IIIB). Transition elements generally exhibit high density, high melting point, magnetic properties, variable valence, and the formation of stable coordination complexes. The complexation of gallium is dominated by ligands containing oxygen, nitrogen and sulphur donor atoms all present in the skin (Reichert et al., 1999). Ga(III) is only stable under acidic conditions. In aqueous solution Ga(III) forms complexes with OH^- with the formation of insoluble $Ga(OH)_3$ when the pH raises above 3. Citric acid is often added to prevent hydrolysis of ^{67}Ga(III) (Liu, 2008). The skin pH is around 5.5 and these conditions do not favour Ga(III) permeation which therefore accumulates at the skin surface. The chemistry of indium is very similar to that of gallium. Both metals are only stable in the +3 oxidation state in aqueous solution. In(III) also hydrolyses easily forming insoluble hydroxides at pH > 3.4. In the same way In(III) is mainly located at the skin surface because skin pH does not favour its permeation in a free form (Reichert et al., 1999). ^{51}Cr is the radioisotope of chromium (VI) (hexavalent oxidation state). It does not permeate well through the skin but accumulates in skin strata as illustrated in Fig. 2 (Kimbrough et al., 1999; Wahlberg, 1965a,b). This cation forms covalent bonds with the side chain polar groups

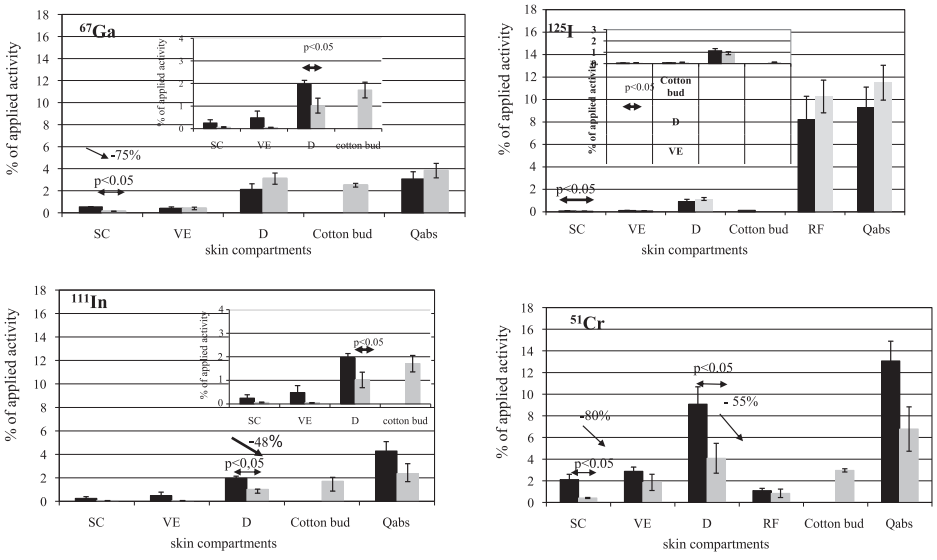

Fig. 2. Distribution of radiopharmaceuticals into skin layers as percentage of applied activity after 6 h ($n = 6$): (■) without any skin treatment and (□) after cleansing the skin.

–COOH, $–NH_2$ and –OH of skin components as well as with peptides and forms insoluble chelates (Koprda et al., 2000; Hostynek, 2003). Chromium applied onto the skin as chromate is reduced to chromic ions (Cr^{3+}) by tissue proteins containing sulfhydryl groups such as cystine, methionine, gluthatione or by ascorbyl acid (Hostynek, 2003; Samitz and Katz, 1969). Cr(VI) as chromate or dichromate is seen to cross the skin unchanged showing however that the skin has a limited capacity to reduce the chromate ion. Samitz and Katz (1969) estimated that one gram of skin can reduce 1 mg of dichromate to Cr^{3+}.

Skin permeation studies were first undertaken to estimate the radionuclide absorbed dose as a function of time. The distribution in each skin layer was also measured after 6 h in the horny layer dead cells but also in viable skin (i.e. viable epidermis obtained after stripping and dermis) to evaluate the dislogeable amount from the skin after this time. In skin absorption studies for toxicological risk assessment the dislogeable dose, considered as the unabsorbed dose, corresponds to the amount of the compound recovered in the *stratum corneum* contrary to quantities recovered in the viable epidermis and the dermis considered as absorbable dose. The *stratum corneum* is made up of two sublayers: the compact layer, where the corneocytes are linked one to another with corneodesmosomes, and the outer sloughing layer, where the breakdown of these corneodesmosomes provokes the phenomenon of desquamation. The corneocytes are thus continually eliminated by this natural phenomenon or following external aggression such as rubbing, washing, or detergents. Consequently the role of *stratum corneum* after skin contamination is complex. It may play a reservoir role or not depending on the properties of the invader. Some studies have demonstrated the reservoir role of the *stratum corneum* for the delivery of substances to the other parts of the skin (Potard et al., 2000; Rougier et al., 1983). For example, Rougier et al. (1983) have noticed a relationship between *stratum corneum* reservoir function and percutaneous absorption. The washing or even mechanical rubbing of the skin surface after contamination could be an interesting strategy to eliminate the radionuclide from the skin (the dislogeable dose) if it did not promote its penetration (no "washing in" effect). In the present work the washing in effect was not evaluated. We proceed consecutive washings before applying the detergent solution because Nishiyama et al. have demonstrated the benefit of serial hand washings both with and without soap to clear off ^{99m}Tc from the skin (Nishiyama et al., 1980a,b). The skin distribution of each radionuclide is illustrated on Fig. 2 in black after 6 h exposure time. The effect of skin cleansing by the diluted detergent solution is illustrated in grey in the same figure. The most striking result is the accumulation of ^{51}Cr in the skin layers (13% of applied dose in viable skin (Q_{abs}) the major part of which being located in the dermis (10%)). This accumulation has been previously demonstrated *in vitro* on cultured keratinocytes. The authors demonstrated the high intracellular uptake of this radionuclide (Ermolli et al., 2001). The effect of the decontamination procedure is significant for this radionuclide with a clearance of 50% of the accumulated amount in the dermis and of 80% in SC. Consequently Q_{abs} which corresponds to the absorbable dose is divided by a factor 2 after cleansing the skin and this result is fast significant. This result could be explained by its longest lag time and a consequence of its skin accumulation. As it crosses the skin within 6 h a cleansing after 6 h is almost effective. The extraction percentage from the dermis is questionable considering the barrier properties of the *stratum corneum*. For the other radiopharmaceuticals the effect of cleansing is weak with no valuable effect on Q_{abs} mainly because of their shorter lag times. For instance, the total amount of ^{67}Ga accumulated in the SC decreases from 75% after cleansing but this quantity represents only 10% of Q_{abs}. In the case of ^{125}I it represents only 0.26% of Q_{abs} because this radionuclide does not accumulate in SC. The effect of the detergent solution is poor particularly when the radionuclides permeate deeply in the skin and another strategy could be to apply decontamination within the lag time period. For ^{99m}Tc Fig. 3 shows that a decontamination strategy should be used as soon as possible within the first hour (Q_{abs} < 10%). We did not apply decontamination for ^{99m}Tc because after 6 h, 33% of the applied dose has already reached the receptor compartment. For this radionuclide, specific chelating agents (Nishiyama et al., 1980a,b) such as diethylenetriamine penta-acetic acid (DTPA), MAA (macroaggregated albumin) or disodium etidronate (EHDP) were successfully performed immediately after contamination. The use of a detergent solution additionally to the chelating agents was significantly useful to avoid the transfer rate of the radiopharmaceutical to the opposite hand or paper towel. However the role of chelating agents is unclear because other groups have demonstrated the more significant role of various formulations or devices (soap solutions, dressings or hydrogels) to absorb radionuclides (Magill and Galy, 2005; Moore and Mettler, 1980; Houpert et al., 2001, 2004; Tymen et al., 2000; Xu et al., 2008; Yang et al., 2005; Kassai et al., 2001; Khotimchenko et al., 2001; Frasca et al., 2009). In the future the use of active agents formulated in innovative carriers will be considered.

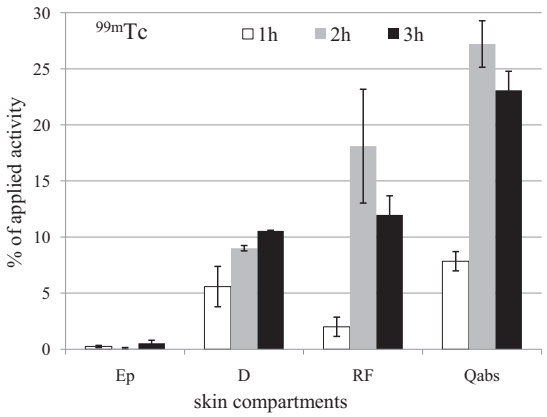

Fig. 3. Distribution of ^{99m}Tc into skin layers as percentage of applied activity over 3 h ($n = 3$): (□) 1 h; (▨) 2 h; (■) 3 h.

References

Anderson, C.J., Welch, M., 1999. Radiometal-labeled agents (non-Technetium) for diagnostic imaging. Chem. Rev. 99, 2219–2234.
Bauerova, K., Kassai, Z., Koprda, V., Harangozo, M., 2001. Contribution to the penetration of radionuclides across the skin. Concentration dependence of strontium through the skin in vitro. J. Appl. Toxicol. 21, 241–243.
Buchegger, F., Perillo-Adamer, F., Dupertuis, Y.M., Bishof Delaloye, A., 2006. Auger radiation targeted into DNA: a therapy perspective. Eur. J. Nucl. Med. Mol. Imaging 33, 1352–1363.
Cacace, M.G., Landau, E.M., Ramsden, J.J., 1997. The Hofmeister series: salt and solvent effects on interfacial phenomena. Q. Rev. Biophys. 30, 241–277.
Clarke, S.E.M., 2006. Diagnostic nuclear medicine investigations in the management of thyroid cancer. In: Mazzaferri, E.L., Harmer, C., Mallick, U.K., Kendall-Taylor, P. (Eds.), Practical Management of Thyroid Cancer. Springer, London, pp. 341–357.
Davis, S.S., Hardy, J.G., Newman, S.P., Wilding, I.R., 1992. Gamma scintigraphy in the evaluation of pharmaceutical dosage forms. Eur. J. Nucl. Med. 19, 971–986.
Ermolli, M., Menné, C., Pozzi, G., Serra, M.-A., Clerici, L.A., 2001. Nickel, cobalt and chromium-induced cytotoxixity and intracellular accumulation in human hacat keratinocytes. Toxicology 159, 23–31.
Förster, M., Bolzinger, M.A., Fessi, H., Briançon, S., 2009. Topical delivery of cosmetics and drugs. Molecular aspects of percutaneous absorption and delivery. Eur. J. Dermatol. 19, 309–323.
Frasca, S., Couvreur, P., Seiller, M., Pareau, D., Lacour, B., Stambouli, M., Grossiord, J.-L., 2009. Paraquat detoxication with multiple emulsions. Int. J. Pharm. 380, 142–146.
Gardin, I., Faraggi, M., Le Guludec, D., Bok, B., 1999. Cell irradiation caused by diagnostic nuclear medicine procedures: dose heterogeneity and biological consequences. Eur. J. Nucl. Med. 26, 1617–1626.
Hadgraft, J., Lane, M.E., 2005. Skin permeation: the years of enlightenment. Int. J. Pharm. 305, 2–12.
Hadgraft, J., Valenta, C., 2000. pH, pKa and dermal delivery. Int. J. Pharm., 243–247.

Hostynek, J.J., 2003. Factors determining percutaneous metal absorption. Food Chem. Toxicol. 41, 327–345.
Houpert, P., Chazel, V., Paquet, F., 2004. A local approach to reduce industrial uranium wound contamination in rats. Can. J. Physiol. Pharmacol. 82, 73–78.
Houpert, P., Chazel, V., Paquet, F., Bailly, T., Burgada, R., Henge-Napoli, M.H., 2001. Reduction of uranium transfer by local chelation in simulated wounds in rats. Hum. Exp. Toxicol. 20, 237–241.
Ilyin, L.A., Ivannikov, A.T., Parfenov Yu, D., Stolyarov, V.P., 1975. Strontium absorption through damaged and undamaged human skin. Health Phys. 29, 75–80.
Jurisson, S.S., Lydon, J.D., 1999. Potential technetium small molecule radiopharmaceuticals. Chem. Rev. 99, 2205–2218.
Kassai, Z., Bauerova, K., Koprda, V., Sandula, J., Harangozo, M., 2001. Penetration of radionuclides across the skin: Glucans as possible inhibitors of metals permeation. Radioanal. J. Nucl. Chem. 250, 189–191.
Kassai, Koprda, Z., Bauerova, V., Harangozo, K., Bendova, M., Bujnova, P., Kassai, A., 2003. Penetration of radionuclides across the skin: rat age dependent promethium permeation through skin in vitro. J. Radioanal. Nucl. Chem. 258, 669–672.
Kassai, Z., Koprda, V., Harangozo, M., 1999. Penetration of radionuclides across the skin: concentration dependence of 60Co permeation. J. Radioanal. Nucl. Chem. 242, 561–563.
Khotimchenko, Y.S., Kovalev, V.V., Savchenko, O.V., Ziganshina, O.A., 2001. Physical–chemical properties, physiological activity, and usage of alginates, the polysaccharides of brown algae. Russ. J. Mar. Biol. 27, S53–S64.
Kimbrough, D.E., Cohen, Y., Winer, A.-M., Creelman, L., Mabuni, C., 1999. A critical assessment of chromium in the environment. Crit. Rev. Environ. Sci. Technol. 29, 1–46.
Ko, Y., Kim, S.S., Han, S.K., 1995. Transdermal permeation-enhancing activities of some inorganic anions. Arch. Pharmacal. Res. 18, 231–236.
Koprda, V., Harangozo, M., Bohacik, L., 1998. Permeation of Cs+ ions across skin barriers. J. Radioanal. Nucl. Chem. 229, 91–93.
Koprda, V., Harangozo, M., Kassai, Z., 2000. Transfer of radionuclides across skin barriers of animal skin models in vitro. J. Radioanal. Nucl. Chem. 246, 505–509.
Kunz, W., Nostro, P.L., Ninham, B., 2004. The present state of affairs with Hofmeister effects. Curr. Opin. Colloid Interface Sci. 9, 1–18.
Liu, S., 2004. The role of coordination chemistry in the development of target-specific radiopharmaceuticals. Chem. Soc. Rev. 33, 445–461.
Liu, S., 2008. Bifunctional coupling agents for radiolabeling of biomolecules and target-specific delivery of metallic radionuclides. Adv. Drug Deliv. Rev. 60, 1347–1370.
Magill, J., Galy, J., 2005. Radioisotopes in medicine. In: Magill, J., Galy, J. (Eds.), Radioactivity, Radionuclides, Radiation. Springer, Berlin/Heidelberg, pp. 117–123.
Marcus, Y., 2009. Effect of ions on the structure of water: structure making and breaking. Chem. Rev. 109, 1346–1370.
Mitragotri, S., 2003. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. J. Control. Release 86, 69–92.
Moore, P.H., Mettler, F.A., 1980. Skin decontamination of commonly used medical radionuclide. J. Nucl. Med. 21, 475–476.
Nishiyama, H., Lukes, S.J., Feller, P.A., Richard, M.S., Van Tuinen, J., Williams, C.C., Saenger, E.L., 1980a. Survey of ^{99m}TC contamination of laboratory personnel: its degree and routes. Radiology 135, 467–471.
Nishiyama, H., Van Tuinen, R.J., Lukes, S.J., Feller, P.A., 1980b. Survey of ^{99m}Tc contamination of laboratory personnel: hand decontamination. Radiology 137, 549–551.
Osanov, D.P., Ershov, E.B., Klickov, O.V., Rackova, V.A., 1971. Kinetics of dose distribution in structural layers of skin contaminated with radioactive materials. Health Phys. 20, 559–566.
Petitot, F., Frelon, S., Moreels, A.M., Claraz, M., Delissen, O., Tourlonias, E., Dhieux, B., Maubert, C., Paquet, F., 2007. Incorporation and distribution of uranium in rats after a contamination on intact or wounded skin. Health Phys. 92, 464–474.
Petitot, F., Gautier, C., Moreels, A.M., Frelon, S., Paquet, F., 2006. Percutaneous penetration of uranium in rats after a contamination on intact or wounded skin. In: Workshop on Internal Dosimetry. Oxford Univ. Press, Montpellier, France, pp. 125–130.
Potard, G., Laugel, C., Schaefer, H., Marty, J.P., 2000. The stripping technique: in vitro absorption and penetration of five UV filters on excised fresh human skin. Skin Pharmacol. Appl. Skin Physiol. 13, 336–344.
Potts, R.O., Guy, R.H., 1992. Predicting skin permeability. Pharm. Res. 9, 663–669.
Pugh, W.J., Degim, I.T., Hadgraft, J., 2000. Epidermal permeability-penetrant structure relationships: 4 QSAR of permeant diffusion across human stratum corneum in terms of molecular weight, H-bonding and electronic charge. Int. J. Pharm. 197, 203–211.
Reichert, D.E., Lewis, J.S., Anderson, C.J., 1999. Metal complexes as diagnostic tools. Coord. Chem. Rev. 184, 3–66.
Reinhardt, M.J., Moser, E., 1996. An update on diagnostic methods in: the investigation of diseases of the thyroid. Eur. J. Nucl. Med. 23, 587–594.
Rougier, A., Dupuis, D., Lotte, C., Roguet, R., Schaefer, H., 1983. In vivo correlation between stratum corneum reservoir function and percutaneous absorption. J. Invest. Dermatol. 81, 275–278.
Samitz, M.H., Katz, S.-A., 1969. Chromium–protein interactions. Acta Derm.-Venereol. 49, 142–146.
Schibli, R., Schubiger, P.A., 2002. Current use and futur potential of organometallic radiopharmaceuticals. Eur. J. Nucl. Med. 29, 1529–1542.
Tymen, H., Gerasimo, P., Hoffschir, D., 2000. Contamination and decontamination of rat and human skin with plutonium and uranium, studied with a Franz's chamber. Int. J. Radiat. Biol. 76, 1417–1424.
Verbruggen, A.M., 1990. Radiopharmaceuticals: state of the art. Eur. J. Nucl. Med. 17, 346–364.
Wahlberg, J.E., 1965a. Percutaneous absorption of sodium chromate (^{51}Cr), cobaltous (^{58}Co), and mercuric(^{203}Hg) chlorides through excised human and guinea pig skin. Acta Derm.-Venereol. 45, 415–426.
Wahlberg, J.E., 1965b. "Disappearance measurements", a method for studying percutaneous absorption of isotope-labelled compounds emitting gamma-rays. Acta Derm.-Venereol. 45, 397–414.
Xu, K., Ge, W., Liang, G., Wang, L., Yang, Z., Wang, Q., Hsing, I.-M., Xu, B., 2008. Bisphosphonate-containing supramolecular hydrogels for topical decorporation of uranium-contaminated wounds in mice. Int. J. Radiat. Biol. 84, 353–362.
Yang, Z., Xu, K., Wang, L., Gu, H., Wei, H., Zhang, M., Xu, B., 2005. Self-assembly of small molecules affords multifunctional supramolecular hydrogels for topically treating simulated uranium wounds. Chem. Commun., 4414–4416.