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Research paper

Association of nicotinamide with parabens: Effect on solubility, partition and transdermal permeation

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Abstract

Nicotinamide is a hydrophilic molecule, freely soluble in water, used as cosmetic active ingredient for its moisturizing and depigmenting properties. Moreover it has the ability to augment the solubility of poorly water-soluble molecules acting as a hydrotrope. The aim of this work was to study the effect of nicotinamide on the transdermal permeation of methyl, ethyl, propyl and butyl paraben. Parabens flux was measured *in vitro* in the presence and absence of different amounts of nicotinamide. From solubility studies it was found that nicotinamide forms one or more complexes with methyl, propyl and butyl paraben in water, even though with low stability constants. The interaction of ethyl paraben seems to be less easy to explain. The association of nicotinamide with parabens causes a significant reduction of the permeability coefficients of these preservatives through rabbit ear skin, caused by a reduction of the stratum corneum/vehicle partition coefficient. The effects of nicotinamide on parabens solubility, permeation and partitioning are potentially very interesting because nicotinamide can facilitate paraben dissolution in aqueous media (solutions, gels), reduce parabens partitioning in the oily phase thus guaranteeing an effective concentration in the water phase in emulsion and reduce transdermal penetration, thus reducing the toxicological risk.

Keywords: Parabens; Nicotinamide; Topical formulations; Permeability coefficient; Partition coefficient

1. Introduction

Semisolid topical formulations applied on skin may contain several additives, such as surfactants, solubilizers, stabilizers, rheological agents and preservatives.

While generally high absorption of the active ingredient is desirable, absence of transdermal penetration is required for the excipients, because their absorption can be potentially harmful. Several additives for pharmaceutical and cosmetic skin formulations are considered safe because of their very low skin permeability, caused to their high molecular weight and/or hydrophilicity. Other ingredients are, on the contrary, absorbed to a high extent by the skin. This is for instance the case of parabens (esters of *p*-hydroxybenzoic acid), antimicrobial agents widely used in cosmetic and pharmaceutical formulations. These molecules of low molecular weight and relatively high lipophilicity (Table 1) proved to be able to easily penetrate the skin [1–3] and, due to the limited extent of skin metabolism, to reach unmodified the underlying tissues and the systemic circulation [4].

Recent reports indicate that parabens might affect health due to their estrogenic activity [5] and it was even hypothesized a link between the use of underarm cosmetics containing parabens and an increased incidence of breast cancer [6–8]. Very recently, an anti-androgenic effect of methyl and propyl paraben has also been observed in *in vitro* experiments [9]. Even though there is no complete agreement on the potential toxicity of parabens as endocrine disruptors [10], the ubiquitous presence of these antimicrobial agents in preserved pharmaceutical and cosmetic

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Table 1
Physico-chemical characteristics and stability constants of nicotinamide and parabens

	Molecular weight	log $K_{oct/w}$ [a]	Water solubility (mg ml^{-1})	$K_{1:1}$ [b]	$K_{1:2}$ [c]
Methyl paraben (MP)	152.15	1.93 [23]	2.13 ± 0.12	2.62	0.96
Ethyl paraben (EP)	166.18	2.27 [23]	1.16 ± 0.21	nd	nd
Propyl paraben (PP)	180.20	2.81 [23]	0.37 ± 0.03	2.85	2.00
Butyl paraben (BP)	194.23	3.57 [23]	0.158 ± 0.014	3.50	2.72
Nicotinamide (NA)	122.13	−0.40 [22]	>750	na	na

nd, not determinable.
na, non-applicable.
[a] Octanol/water partition coefficient.
[b] Stability constant of the 1:1 complex calculated according to Eq. (7).
[c] Stability constant of the 1:2 complex calculated according to Eq. (8).

formulations, and the consequent high opportunity of exposure, gives particular relevance to this subject. In 2005 FDA re-opened the safety assessment for parabens, to request exposure estimates and risk assessment for cosmetic use. The conclusion of the FDA is that, at present, there is no reason for consumers to be concerned about the use of cosmetics containing parabens. However, the agency will continue to evaluate new data in this area [8].

To reduce the penetration of chemicals through the skin different approaches can be considered: (1) application of an external barrier on the skin surface (i.e. Skin Protectant Drug Products [11]); (2) strengthening of the stratum corneum barrier through the application of ceramides or their analogues [12,13]; (3) use of permeation retardants, acting by imparting order to the skin lipids [14] thus making the stratum corneum more impermeable. These approaches are useful for preventing absorption of agents such as the mosquito repellents, pesticides, and sunscreens. However, sometimes, there is the need to reduce the permeation of a specific component of the formulation without interfering with the penetration of the active drug.

Few attempts have been performed to reduce the skin absorption of parabens: some authors studied cyclodextrins [15–17] while other authors found that the addition of poly(2-methacryloyloxyethyl phosphorylcholine-co-butylmethacrylate) reduced the transdermal absorption of parabens from semisolid formulations [18], but their antimicrobial activity was decreased. Previous studies performed in our laboratory showed that the presence of nicotinamide (vitamin B_3) in cosmetic formulations was able to reduce the skin accumulation of ethyl paraben *in vitro* [19]. In particular, hydrophilic gels containing ethyl paraben (0.1% w/w) and two different concentrations of nicotinamide (3.5% or 10% w/w) were applied to human skin *in vitro* for 20 min. The results indicated that the presence of nicotinamide significantly reduced paraben accumulation in the skin to an extent proportional to its concentration [19]. Nicotinamide is a hydrophilic molecule, freely soluble in water, used as a cosmetic active ingredient for its moisturizing and depigmenting properties. Nicotinamide has low toxicity and has been listed by the FDA among GRAS substances (Generally Regarded As Safe; 184.1535).

The aim of this work was to study the effect of nicotinamide (vitamin B_3) on the transdermal permeation of four parabens (methyl, ethyl, propyl and butyl *p*-hydroxybenzoate). The flux of the four parabens was measured *in vitro* in the presence and absence of different amounts of nicotinamide. The skin model used for permeation experiments was rabbit ear skin, which has been shown to be a reasonable model for human skin, due to the comparable permeability towards different molecules (lidocaine, triptorelin, tiocholchicoside) [20–22]. To better understand the permeation data, the effect of nicotinamide on parabens water solubility and isopropylmyristate/water partition coefficient was also studied.

2. Materials and methods

2.1. Materials

Methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), butyl paraben (PP) and nicotinamide (NA) (Fig. 1) were purchased from Sigma (St. Louis, USA). For HPLC analysis, acetonitrile (HPLC grade) and distilled water were used. All other chemicals used were of analytical grade.

Rabbit skin was excised post-sacrifice from the inner part of rabbit ears (6 months old) obtained from a local slaughter's house. The skin was frozen for not more than 30 days. Before the experiment, the skin was thawed at room temperature for 30 min.

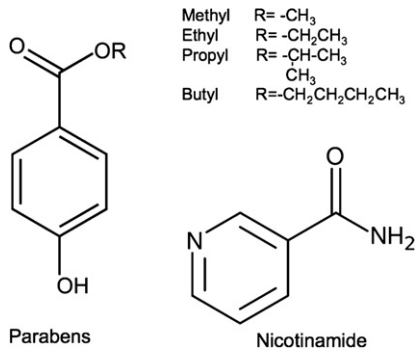

Fig. 1. Molecular structure of nicotinamide and parabens.

2.2. HPLC analysis

Parabens HPLC analyses were performed using a Perkin-Elmer instrument (Norwalk, CT, USA) and a μBondapak C18 column (Waters, Milford, MA, USA). The UV detector was set at 254 nm. The mobile phase was a mixture of water and acetonitrile (60:40 v/v) pumped at 1.2 ml min^{-1}. When nicotinamide-containing solutions were analysed, it was necessary to increase the percentage of aqueous phase (up to 80%) to separate methyl and ethyl paraben from nicotinamide peak. The two methods were compliant to the system suitability tests according to USP 30.

2.3. Solubility

The solubility of each paraben was determined by adding an excess amount of paraben to 1.0 ml of water or to 1.0 ml of a solution of nicotinamide at different concentrations: 3.5%, 10% and 20% (w/v) (molar concentration: 0.287, 0.819 and 1.638, respectively). The dispersions were magnetically stirred for 48 h at 25 °C, then filtered through regenerated cellulose filters (pore size 0.45 μm), diluted and analysed by HPLC. Each experiment was replicated at least six times.

Parabens solubility values (M) were then plotted as a function of nicotinamide concentration (M) to build the phase solubility diagram [23]. Moreover, for each nicotinamide concentration the Solubility Ratio (SR) was calculated as the ratio between the solubility in the presence and in the absence of nicotinamide [18].

2.4. Thermal analysis

Differential scanning calorimetry was performed on the dried solid phases recovered from the solubility experiments, using an indium calibrated Mettler DSC 821e (Mettler Toledo, USA) driven by a STARe software (Mettler Toledo, USA). DSC traces were recorded on accurately weighed quantities (5–7 mg) of powder samples placed in an aluminium pan sealed and twice pierced. Scans were performed between 25 and 150 °C at 1 K min^{-1} under a flux of dry nitrogen (100 ml min^{-1}). Each powder sample was analysed at least in triplicate.

2.5. Partition coefficient

Partition coefficients of parabens between isopropylmyristate (IPM) and distilled water (W) or between IPM and an aqueous solution of nicotinamide 3.5% or 20% (w/v) (N) were determined using the shake flask method, following the guidelines of the European Chemical Bureau [24]. Briefly, before the partition coefficient determination, the two phases of the solvent system were mutually saturated by shaking overnight at the same temperature (20 ± 2 °C) and in the same ratio (1:3) (IPM:W) as in the partitioning experiments. Each paraben was individually dissolved in saturated IPM, at a concentration of 7 mg ml^{-1}. 0.3 ml of this solution was transferred to 2.0 ml vials and added of 1.0 ml of IPM-saturated W or N phase. The vials were shaken overnight, then the two phases were separated. Parabens were quantified in both phases: 10 μl of the IPM phase was sampled, added of 1.6 ml of acetonitrile and analysed by HPLC. One hundred and fifty microliters of the N or W phases was carefully sampled, minimizing the risk of including traces of IPM, added of 150 μl of acetonitrile and analysed by HPLC. The partition coefficient in the absence, $K_{IPM/W}$, or in the presence, $K_{IPM/N}$, of nicotinamide was calculated as:

$$K_{IPM/W} = \frac{[IPM]}{[W]} \frac{V_W}{V_{IPM}} \quad K_{IPM/N} = \frac{[IPM]}{[N]} \frac{V_N}{V_{IPM}} \tag{1}$$

where [IPM] is the concentration of paraben in the organic phase; [N] and [W] are the concentrations of the paraben in the aqueous phase, with (N) or without (W) nicotinamide, respectively; V_{IPM} is the volume of the organic phase (0.3 ml); V_W and V_N are the volumes of the aqueous phase (1.0 ml).

Each experiment was repeated at least four times.

2.6. Transdermal permeation experiments

Permeation experiments were conducted in Franz-type diffusion cells (Disa, Milan, Italy), with an exposed surface area of 0.6 cm^2. Rabbit ear skin, previously validated as a reasonable model for human skin [20–22], was used as barrier. The receptor phase was 0.9% NaCl solution thermostatted at 37 °C and magnetically stirred to prevent any boundary layer effect. At predetermined time intervals the receptor solution was sampled and analysed by HPLC for the determination of the amount of paraben permeated.

The donor solutions tested were the following:

- ethyl paraben solutions (0.08% w/v) in water containing nicotinamide 0%, 0.74%, 3.5%, 10% and 20% (w/v);
- methyl, ethyl, propyl and butyl paraben saturated solutions in water;
- methyl, ethyl, propyl and butyl paraben saturated solutions in water containing nicotinamide 20% (w/v).

Each experiment was replicated at least five times.

The permeation profiles obtained were fitted to the equation proposed by Moser et al. [25]:

$$Q = (KH)C_{veh}\left[\frac{D}{H^2}t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{1}\frac{(-1)^n}{n^2}\exp\left(\frac{-Dn^2\pi^2 t}{H^2}\right)\right] \tag{2}$$

where Q is the cumulative amount of paraben permeated per unit area at time t, C_{veh} is the concentration of the paraben in the donor vehicle, K is the stratum corneum/vehicle partition coefficient, D is the diffusion coefficient and H is the diffusion path-length. The fitting was per-

formed using KaleidaGraph 3.6.2 (Synergy Software, Essex Junction, VT, USA) running on a Macintosh Power Book G4 (Apple Computers, Cupertino, CA, USA). The average error associated with each fitted value was in the range 3–15%.

The permeability coefficient P was calculated as:

$$P = KH\frac{D}{H^2} \tag{3}$$

2.7. Statistical analysis

The results were expressed as means ± standard error of the mean (sem), and statistical differences were determined by Student's t-test.

3. Results and discussion

Previous studies indicated that the presence of nicotinamide in cosmetic formulations containing ethyl paraben as preservative is able to reduce the skin accumulation of the preservative *in vitro* [19].

To better investigate nicotinamide potential in reducing EP absorption, the transdermal permeation of ethyl paraben from aqueous solutions containing different percentages of nicotinamide, namely 0%, 0.74%, 3.5%, 10% and 20% (w/v), was investigated. The concentration of ethyl paraben was 0.08% (w/v). The experiments were performed for 8 h: the amount of EP permeated was plotted as a function of time and the flux was calculated as the slope of the regression line of the linear portion of the curve, in the 2–8 h interval. The results obtained are illustrated in Fig. 2 where the fluxes are reported as a function of nicotinamide concentration in the vehicle. Evidently, nicotinamide significantly decreased, although in a non-linear way, the transdermal flux of ethyl paraben. This decrease in EP flux might reflect a decrease of EP thermodynamic activity, produced by an augmented solubility. In fact, it is well known that nicotinamide, when present at high concentration, is able to increase the solubility in water of other molecules, behaving as a hydrotropic agent [26,27].

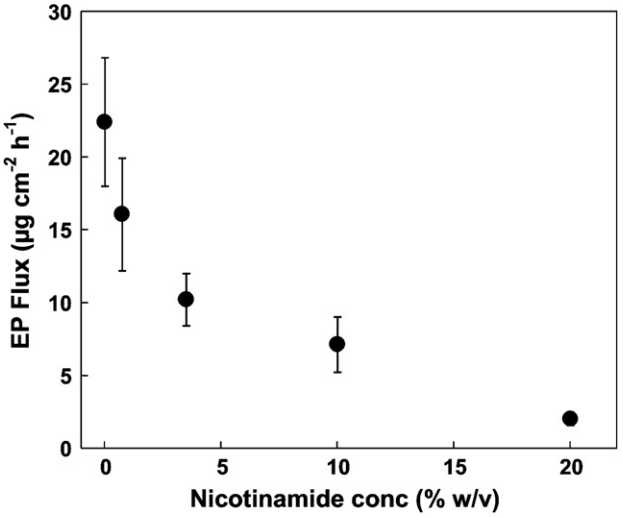

Fig. 2. Ethyl paraben transdermal fluxes obtained *in vitro* through rabbit ear skin as a function of nicotinamide concentration in the donor solution (paraben concentration 0.08% w/v) (average ± sem; $n \geqslant 5$).

To confirm this hypothesis, the effect of nicotinamide on the solubility of ethyl paraben was studied. Furthermore, in order to obtain more general information, methyl, propyl and butyl paraben solubility diagrams in the presence of nicotinamide 3.5%, 10% and 20% (w/v) (molar concentration: 0.287, 0.819 and 1.638, respectively) were built as well. The results obtained are reported in Fig. 3. The water solubilities of the parabens (see also Table 1) are comparable with those found in the literature [28]. When nicotinamide was added, MP, PP and BP solubilities were significantly enhanced originating an Ap type diagram [23]. A similar profile is reported in the literature for nifedipine [27], riboflavin [29], estrone, griseofulvin and ketoprofen [26] in the presence of nicotinamide. EP solubility diagram, instead, was characterized by an initial slight decrease of EP apparent solubility followed by a moderate increase: at 20% (w/v) nicotinamide, EP concentration doubled compared to the value obtained in water.

The mechanism by which nicotinamide is able to solubilize other molecules is still a matter of debate [26,27,29]. Proposed mechanisms are micellization, changes in the polarity of the solvent or complexation [29]. Assuming that parabens solubility increase is due to molecular interactions between the paraben and nicotinamide to form one or more complexes, it is possible to calculate the apparent stability constants on the basis of a given stoichiometry [23]. Due to the positive curvature of the diagram, one can hypothesize the contemporary presence of 1:1 and 1:2 complexes between paraben and nicotinamide, characterized by $K_{1:1}$ and $K_{1:2}$ complexation constants, respectively [23]:

$$K_{1:1} = \frac{[\mathrm{SL}]}{S_0[\mathrm{L}]} \tag{4}$$

$$K_{1:2} = \frac{[\mathrm{SL_2}]}{[\mathrm{SL}][\mathrm{L}]} \tag{5}$$

where S_0 is the equilibrium solubility of the paraben in the absence on nicotinamide; [L] is the concentration of free nicotinamide; [SL] is the concentration of the 1:1 complex; [SL_2] is the concentration of the 1:2 complex.

If the extent of complexation is fairly small, the concentration of free nicotinamide [L] can be approximated to the total concentration of nicotinamide [L_t] and then the complexation constants can be determined as [23]:

$$[S_t] = S_0 + K_{1:1}S_0[\mathrm{L}_t] + K_{1:1}K_{1:2}S_0[\mathrm{L}_t]^2 \tag{6}$$

where [S_t] is the equilibrium solubility of the paraben in the presence of nicotinamide.

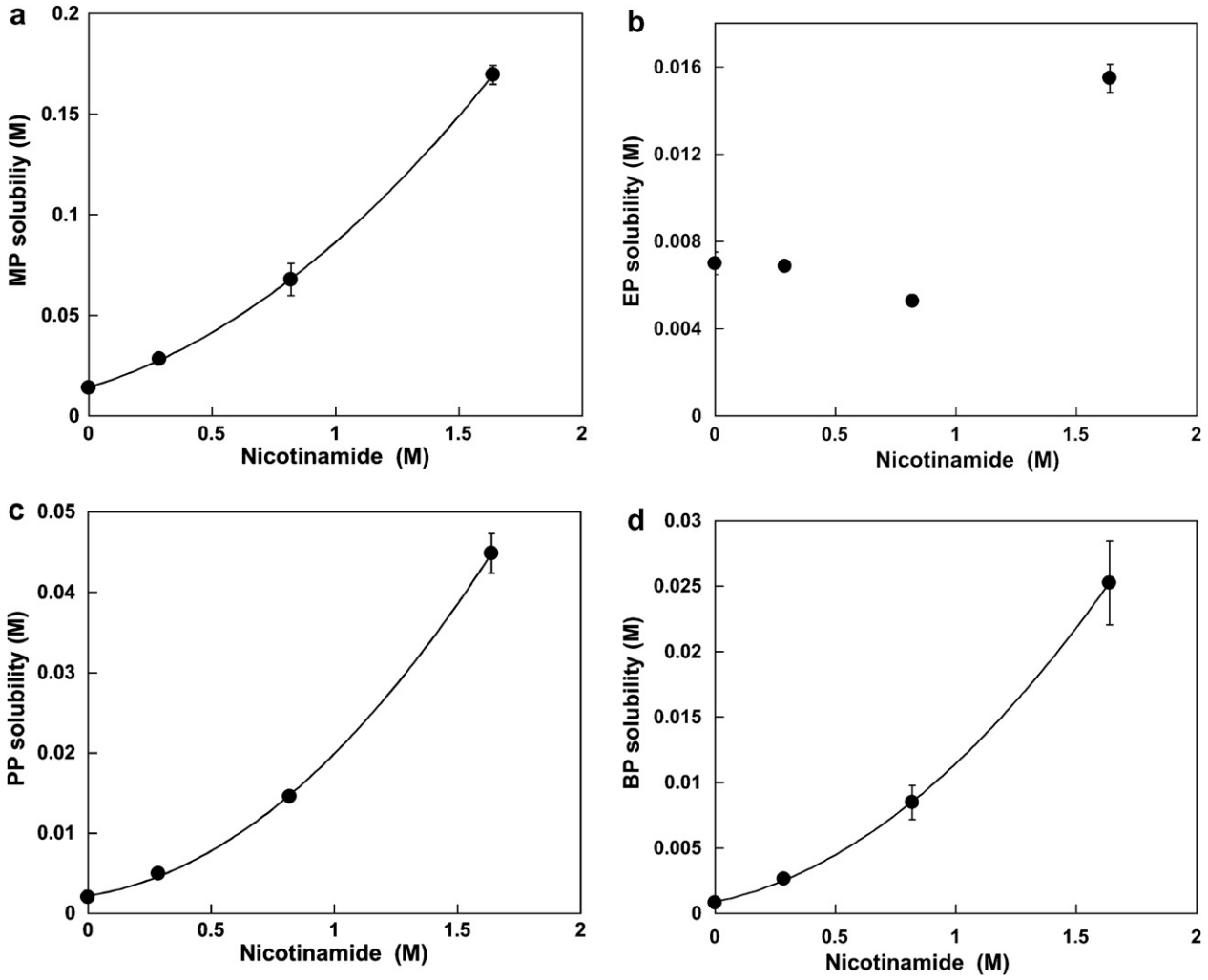

Fig. 3. Solubility diagrams of methyl (a), ethyl (b), propyl (c) and butyl (d) paraben in the presence of nicotinamide. The lines represent the parabolic fitting of the experimental data points (average ± sem; $n \geqslant 5$). The fitting equations were: MP $y = 0.0144 + 0.0368x + 0.035x^2$ ($R^2 = 0.9999$); PP: $y = 0.0022 + 0.0045 + 0.0130x^2$ ($R^2 = 0.9998$); BP: $y = 0.0009 + 0.0038x + 0.0067x^2$ ($R^2 = 0.9999$).

The experimental data can be fitted to a parabolic curve [30] ($y = c + bx + ax^2$, where $c = S_0$ and $x = [L_t]$), from which the complexation constants can be calculated as:

$$K_{1:1} = \frac{b}{S_0} \tag{7}$$

$$K_{1:2} = \frac{a}{b} \tag{8}$$

The results obtained are reported in Table 1 for MP, PP and BP. Due to the peculiar shape of the EP solubility diagram it was not possible to perform this calculation.

The complexation constants calculated are quite low and comparable to those found in the literature between nicotinamide and molecules with lipophilicity similar to that of parabens [26]. Moreover, the constants found were in the order BP > PP > MP, i.e. they followed the rank of decreasing lipophilicity, in agreement with the literature hypothesis of a stacking complexation to reduce the exposure of the hydrophobic region of both molecules

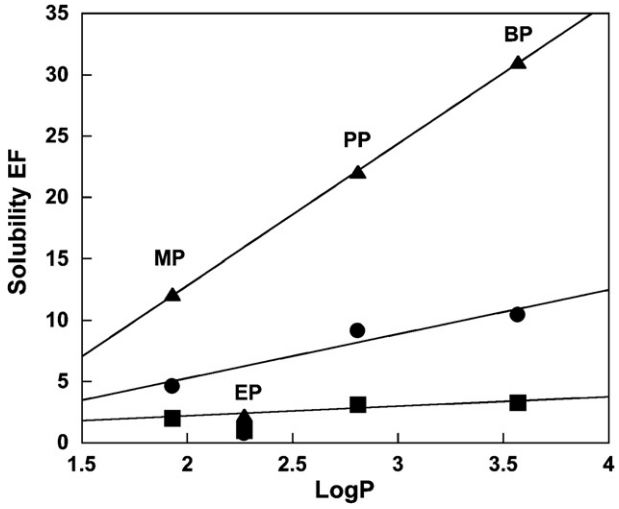

Fig. 4. Solubility Ratio of parabens at 25 °C in an aqueous solution of nicotinamide 3.5% (■), 10% (●) and 20% (▲) as a function of their molecular weight.

(nicotinamide and substrate) to water. Less polar molecules proved to have a stronger driving force to complex formation [27]. This behaviour can be more easily appreciated by calculating the Solubility Ratio (SR), i.e. the ratio of solubility with and without NA. When this SR was plotted against paraben log*P* (Fig. 4), a linear correlation was evident and the slope of the line increased with NA concentration. It is evident that EP had a completely different behaviour: its SR is only slightly influenced by NA and, more interestingly, it deviates from the linearity observed with the other parabens.

To explain this anomaly, the solid phase recovered from each solubility test was analysed by DSC: in the case of MP, PP and BP a single peak corresponding to the pure paraben melting temperature was obtained. In the case of EP, on the contrary, two different peaks were present at temperatures different from both EP and nicotinamide melting temperature, suggesting a possible interaction between the two molecules in the solid phase. This interaction has been discussed in detail in a further paper [31]. Whatever the nature of this interaction, the decrease of EP flux in the presence of nicotinamide previously observed (Fig. 2) cannot be simply justified by an increase of its solubility in the donor compartment.

In order to systematically evaluate the effect of nicotinamide on parabens transdermal permeation, *in vitro* experiments were performed starting from solutions having the same thermodynamic activity, i.e. parabens saturated solutions in either neat water or in a 20% (w/v) nicotinamide solution. The results obtained are reported in Fig. 5.

The profiles of the four antimicrobial agents from the neat water solution were characterized by a very short time lag after which they become linear. The fluxes of MP, EP, PP and BP were 110, 48, 33 and 22 $\mu g\,cm^{-2}\,h^{-1}$ in water and 161, 19, 46 and 52 $\mu g\,cm^{-2}\,h^{-1}$ in the presence of nicotinamide, respectively. The flux values in water are consistent with the data found in the literature and obtained *in vitro* through human epidermis for methyl and butyl parabens [1,2,32], confirming that rabbit skin is a reasonable model for human skin. The fluxes obtained in the presence of nicotinamide are higher than those obtained from water in the case of MP, PP and BP while, once again, EP behaviour, being characterized by a lower transdermal flux in the presence of nicotinamide, was different. To inter-

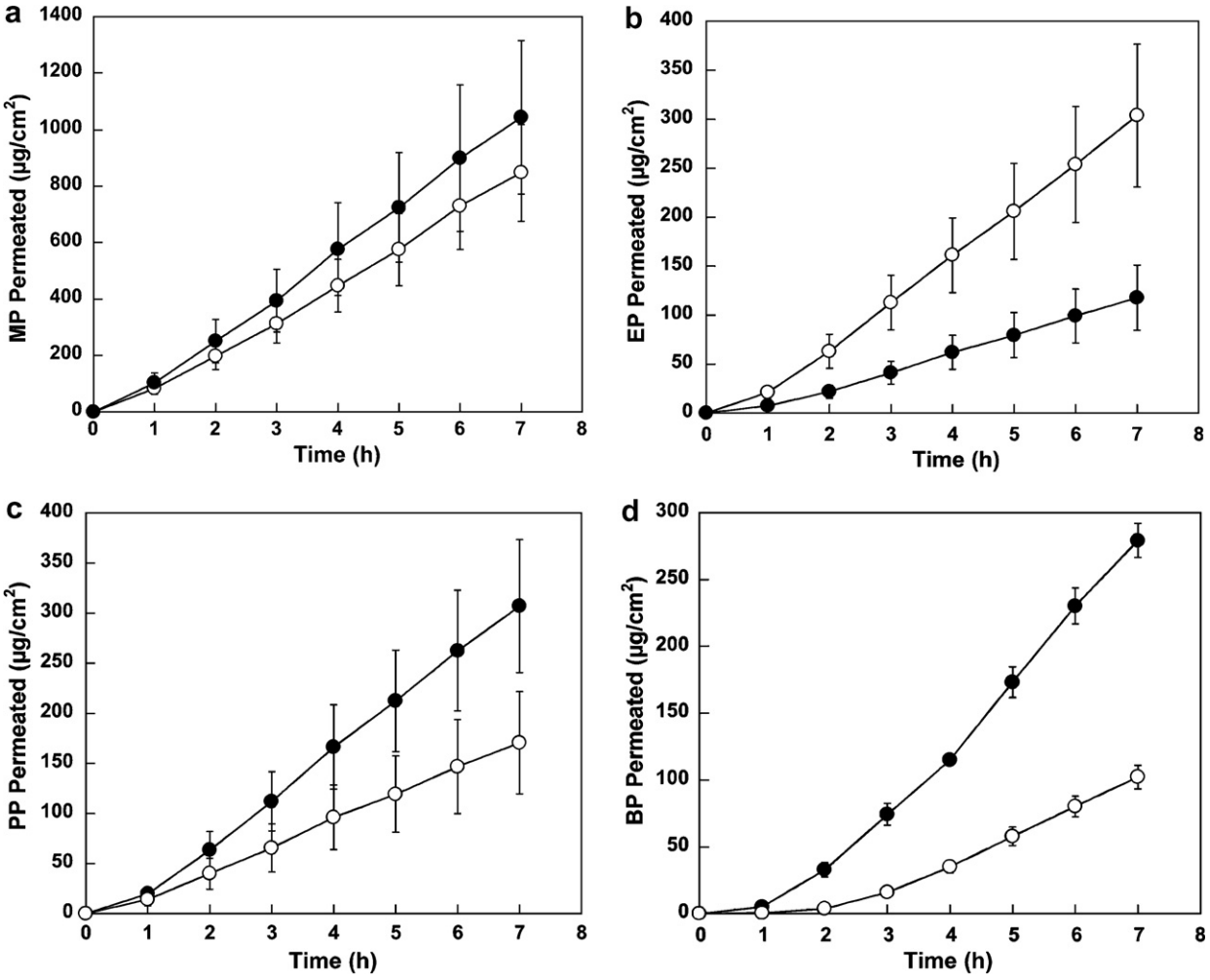

Fig. 5. Permeation profiles of methyl (a), ethyl (b) and propyl (c) and butyl (d) paraben through rabbit ear skin from saturated solutions in either neat water (○) or nicotinamide 20% w/v solution (●) (average ± sem; $n \geqslant 6$).

Table 2
Permeation parameters of parabens (obtained from Eq. (2)) in the presence and absence of nicotinamide 20% (w/v)

	Water (W)			Water + nicotinamide 20% (NA)			KH_{NA}:KH_W	S_{NA}:S_W[c]
	KH (cm)	D/H^2 (cm^{-1})	P (cm h^{-1})	KH (cm)	D/H^2 (cm^{-1})	P (cm h^{-1})		
MP	0.186	0.317	0.061	0.020[a]	0.325	0.006[a]	0.11	12.1
	(0.018)	(0.036)	(0.012)	(0.005)	(0.064)	(0.002)		
EP	0.161	0.250	0.041	0.038[a]	0.198	0.008[a]	0.23	2.1
	(0.029)	(0.034)	(0.009)	(0.009)	(0.017)	(0.002)		
PP	0.160	0.320	0.051	0.027[a]	0.238	0.006[a]	0.17	22.1
	(0.029)	(0.027)	(0.008)	(0.003)	(0.052)	(0.001)		
BP	1.464[b]	0.087[b]	0.121	0.119[a,b]	0.095	0.011[a]	0.08	31.0
	(0.202)	(0.010)	(0.010)	(0.010)	(0.007)	(0.001)		

Mean values (sem).
[a] Statistically different from the value in water for the same paraben ($p < 0.01$).
[b] Statistically different from the value of the other parabens ($p < 0.01$).
[c] S solubility of parabens in water (S_W) or in nicotinamide 20% (S_{NA}).

pret these results, the experimental data were fitted to a solution of Fick's law, which does not assume the achievement of steady-state [25] (Eq. (2)). With this equation it was possible to calculate the permeation parameters KH and D/H^2, that are reported in Table 2. The parameter KH gives indications as to the partitioning characteristics of the molecule, while D/H^2 represents the diffusive parameter across the skin. The calculated permeability coefficient was not different among MP, EP and PP while, surprisingly, BP showed a permeability coefficient statistically higher ($p < 0.01$) due to a considerably higher partitioning parameter. The diffusive parameter of BP was significantly lower ($p < 0.001$) than those of MP, EP and PP.

When the saturated solutions of parabens in nicotinamide 20% (w/v) were applied to the skin, the permeability coefficient was significantly reduced ($p < 0.01$) for all parabens. It was possible to attribute this 10-fold reduction to the decrease of the partition parameter (KH), while the diffusion parameter (D/H^2) did not change. The immediate conclusion was that nicotinamide at the concentration of 20% modified the partitioning between the stratum corneum and the vehicle. Despite the lower permeability coefficient, however, the fluxes of all parabens, except EP, were higher with nicotinamide, because the presence of the hydrotropic agent increased to a significant extent drug donor concentration. Since the flux of a molecule across a barrier depends on donor concentration and on diffusion and partition coefficient, the higher donor concentration counterbalanced the lower partition coefficient, leading to an increased flux. EP solubility, on the contrary, was not increased sufficiently enough to compensate for the reduced partitioning in the presence of nicotinamide.

In order to confirm the effect of nicotinamide on the partition parameter of parabens between skin and water, the partition coefficient of the parabens was measured between isopropylmyristate (IPM) and water or isopropylmyristate and a solution of nicotinamide (3.5% or 20% w/w) in water, using the shake flask method. IPM was chosen as lipophilic phase because its lipophilicity is considered similar to that of stratum corneum [33]. The results obtained are represented in Fig. 6. Nicotinamide, at both concentrations tested, reduced in a significant way IPM/water partition coefficient of all parabens studied. The highest reduction was observed for methyl paraben whose $\log P_{(IPM/W)}$ decreased from 2.02 to 0.73. From the data obtained we can affirm that the presence of nicotinamide in the donor compartment was able to reduce parabens permeability coefficient by reducing their partitioning into the stratum corneum. Despite what happened with solubility, EP behaviour was in line with that of the other parabens.

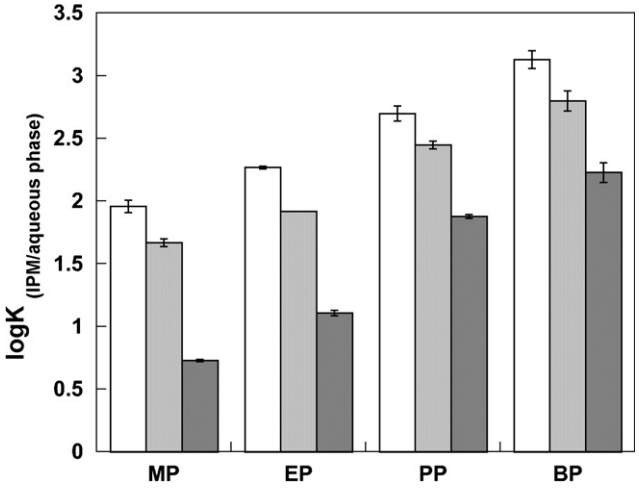

Fig. 6. IPM/water (□) and IPM/nicotinamide 3.5% (▒) or 20% (■) partition coefficient of methyl, ethyl, propyl and butyl paraben.

Finally, it should be underlined that the effect of nicotinamide on partitioning can have an impact on efficacy, because the antimicrobial activity of parabens is closely related to their ability to penetrate the lipophilic cell membranes of the microorganisms [34]. Preliminary experiments on selected microorganisms (*Bacillus subtilis, Escherichia coli* and *Candida albicans*) suggest that the presence of nicotinamide does not modify the activity of parabens, and this will be the subject of further studies.

4. Conclusions

Nicotinamide is a hydrotropic molecule able to increase the solubility of methyl, ethyl, propyl and butyl *p*-hydroxybenzoate in water. Nicotinamide forms one or more complexes with methyl, propyl and butyl paraben in water, even though with low stability constants. Ethyl paraben interacts with nicotinamide, although the data obtained to date do not allow drawing a definite conclusion, and this is worth further studies.

The association of nicotinamide with parabens causes a significant reduction of the permeability coefficients of these preservatives through rabbit skin, caused by a reduction of the stratum corneum/vehicle partition coefficient. The effect of nicotinamide on paraben partitioning was confirmed directly, by determining the isopropyl myristate/water partition coefficient, which was reduced in a concentration dependent manner by nicotinamide.

The effects of nicotinamide on parabens solubility, permeation and partitioning are potentially very interesting because nicotinamide can (i) facilitate paraben dissolution in aqueous media (solutions, gels), (ii) reduce parabens partitioning in the oily phase thus guaranteeing an effective concentration in the water phase in emulsion and (iii) reduce transdermal penetration, thus reducing the toxicological risk. However, the possible influence of nicotinamide on the antimicrobial activity of parabens remains to be examined in detail.

Moreover, the results obtained in the present work should be confirmed by using more complex formulations, such as emulsion and also by investigating lower concentrations of nicotinamide, namely concentrations closer to real use.

This work opens other research opportunities, such as the analysis of the interaction of ethyl paraben with nicotinamide and the effect of nicotinamide on paraben antimicrobial activity, both of which are underway and will be the object of future publications.

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