



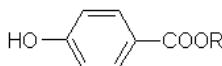
Association of nicotinamide with parabens: effect on solubility, partition and transdermal permeation

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Introduction

- Parabens proved to be able to easily penetrate the skin and due to the limited extent of skin metabolism, to reach unmodified the underlying tissues and the systemic circulation.
- Recent reports indicate that parabens might have harmful consequences on human health due to their estrogenic activity.



	R	Molecular Weight	Log P
Methylparaben (MP)	-CH ₃	152.15	1.93
Ethylparaben (EP)	-C ₂ H ₅	166.18	2.27
Propylparaben (PP)	-C ₃ H ₇	180.20	2.81
Butylparaben (BP)	-C ₄ H ₉	194.23	3.57
Nicotinamide (NA)	-	122.13	-0.40

Aim of the work

- The aim of this work was to study the association of nicotinamide (vitamin B₃) with parabens to reduce the transdermal permeation of the preservatives.
- The flux of the four parabens was measured in vitro across rabbit ear skin in the presence and in absence of different amounts of nicotinamide.
- The effect of nicotinamide on paraben water solubility and isopropylmyristate : water partitioning was also studied.

Experimental Methods

Solubility determination

- In water or in water with NA (3.5, 10 or 20% w/v).

Partition experiments

- Solution of parabens in water or in water with 20 % w/v NA equilibrated with Isopropyl myristate (IPM).

Permeation experiments:

- Franz type diffusion cells (area 0.6 cm²).
- Barrier: rabbit ear skin.
- Donor (1 ml): Saturated solution of parabens in water or in water with 20 % w/v NA.
- Receptor solution: saline (4 ml).
- Data analysis:

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

Q: amount of paraben permeated

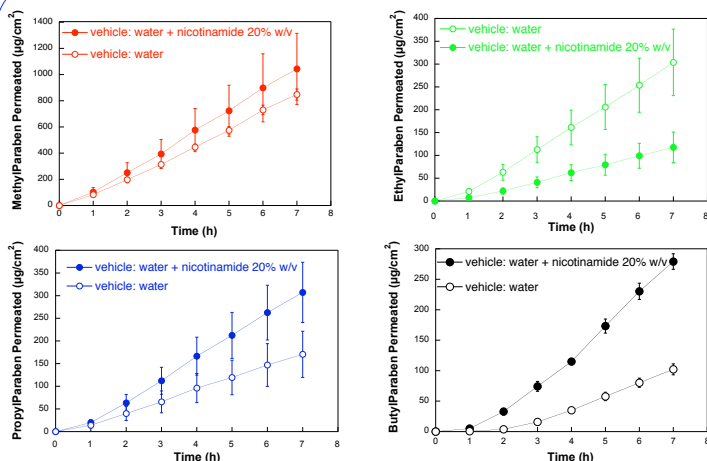
KH: partitioning parameter

C_d: donor concentration

D/H²: diffusive parameter

Results & Discussion

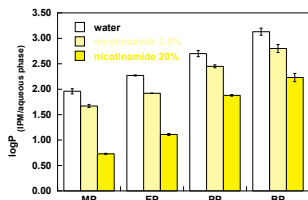
Permeation & Partitioning



Permeation Parameters

	Water			Water+ Nicotinamide 20%		
	KH × 10 ⁷ (cm)	DH ² (h ²)	P × 10 ⁷ (cmh ²)	KH × 10 ⁷ (cm)	DH ² (h ²)	P × 10 ⁷ (cmh ²)
MP	18.6 ± 1.8	0.32 ± 0.04	6.1 ± 1.2	2.0 ± 0.46	0.32 ± 0.06	0.62 ± 0.16
EP	16.1 ± 2.9	0.25 ± 0.03	4.1 ± 0.9	3.8 ± 0.94	0.29 ± 0.02	0.77 ± 0.21
PP	16.0 ± 2.9	0.32 ± 0.03	5.1 ± 0.8	2.7 ± 0.29	0.24 ± 0.05	0.61 ± 0.11
BP	146.4 ± 2.0	0.09 ± 0.01	12.1 ± 0.1	11.9 ± 0.97	0.10 ± 0.01	1.10 ± 0.04

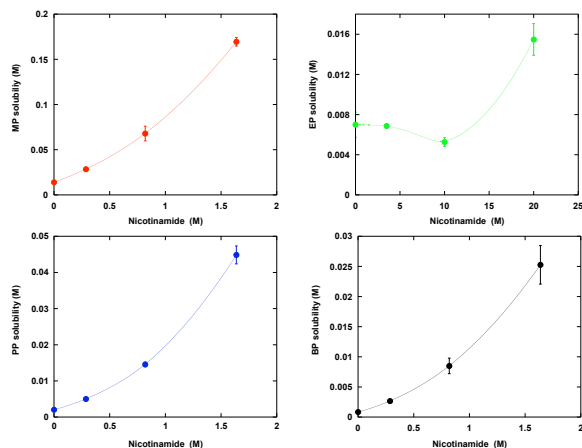
IPM/water Partition Coefficient



The presence of NA:

- Decreased the permeability coefficient of one order of magnitude due to a decrease in the partitioning parameter KH.
- Decreased IPM/water partition coefficient.

Solubility



The presence of NA:

- Increased the solubility of all but ethyl paraben.

Complex stability constant

$$[S_f] = S_0 + K_{1:1}S_0[L_f] + K_{1:1}K_{1:2}S_0[L_f]^2$$

S₀ = equilibrium solubility of the paraben in absence on nicotinamide

L = concentration of free nicotinamide

SL = concentration of the 1:1 complex

SL₂ = concentration of the 1:2 complex

S_f = equilibrium solubility of the paraben in presence of nicotinamide

L_f = concentration of nicotinamide

	K 1:1	K 1:2
Methylparaben	2.62	0.96
Ethylparaben	nd	nd
Propylparaben	2.85	2.00
Butylparaben	3.50	2.72

Conclusions

- Nicotinamide significantly increases the solubility of MP, PP, BP. It has limited effect on EP solubility.
- Nicotinamide reduces the IPM/water partition coefficient of all parabens.
- Nicotinamide reduces by one order of magnitude paraben permeability coefficient, due to a reduction of the partitioning parameter.
- The effects of nicotinamide can be due to:
 - Modification of the polarity of the vehicle.
 - Formation of a complex more hydrophilic than the paraben alone.
 - Formation of nicotinamide micelles able to include parabens.