EFFECT OF NICOTINAMIDE ON PARABENS SOLUBILITY AND TRANSDERMAL PERMEATION

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AIM OF THE WORK

To study the ability of a hydrotropic agent - nicotinamide (vitamin B_3) (1)- to increase the solubility of parabens.

In view of the recent controversy on the safety of parabens (2), the transdermal flux of these preservatives, alone and in association with nicotinamide, was also studied in vitro.

	Molecular Weight	Log P
Methylparaben (MP)	152.15	1.93
Ethylparaben (EP)	166.18	2.27
Propylparaben (PP)	180.20	2.81
Butylparaben (BP)	194.23	3.57
Nicotinamide (NIA)	122.13	- 0.40

METHODOLOGY

Solubility determination:

- Solvent: water or water solutions of NIA (3.5%, 10%, 20% (w/v))
- Stirring for 48 hours in a thermostatic chamber (25°C; RH: 65%)
- Filtration, dilution, HPLC analysis

Permeation experiments:

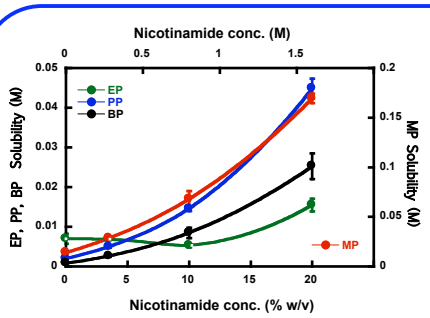
- Franz-type diffusion cells (0.6 cm²); Barrier: rabbit ear skin
- Donor compartment:
- MP, EP, PP, BP saturated sol. in water;
- MP, EP, PP, BP saturated sol. in water containing NIA 20% (w/v)
- EP solutions (0.08% w/v) in water + NIA 0, 0.75, 3.5, 10, 20% (w/v)
- Data analysis (3):

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

Q: amount of paraben permeated
K: partition coefficient
H : Stratum Corneum thickness
C_d: donor concentration
D: apparent diffusion coefficient

RESULTS

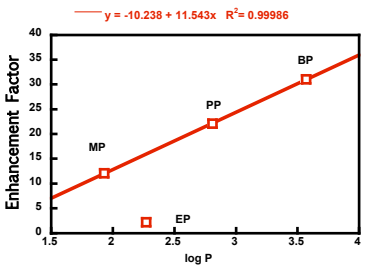
SOLUBILITY



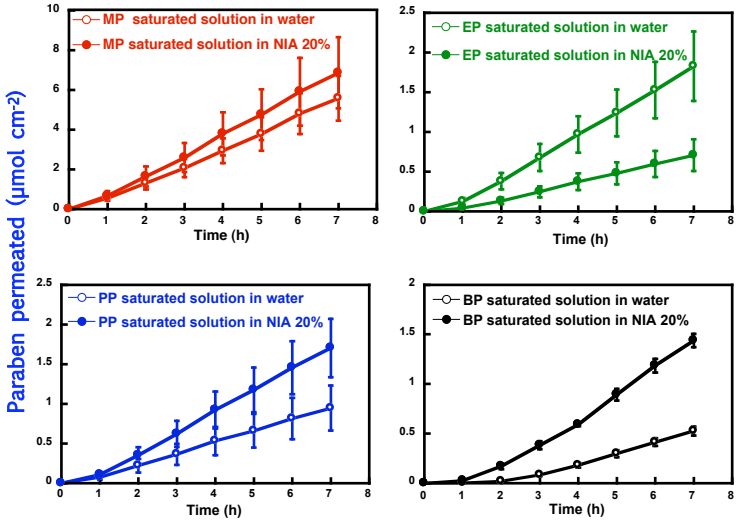
	Solubility x10² (M)
MP in H_2O	1.40 ± 0.08
MP in NIA 20%	16.96 ± 0.47
EP in H_2O	0.70 ± 0.12
EP in NIA 20%	1.49 ± 0.15
PP in H_2O	0.21± 0.02
PP in NIA 20%	4.48± 0.24
BP in H_2O	0.081± 0.007
BP in NIA 20%	2.53 ± 0.32

Enhancement Factor:

$$\frac{\text{Solubility in presence of NIA 20\%}}{\text{Solubility in water}}$$



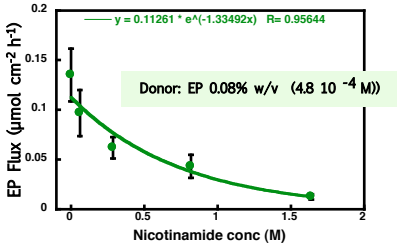
TRANSDERMAL PERMEATION



Permeation Parameters

	Water			Water+ Nicotinamide 20%		
	KH x10² (cm)	D/H² (cm⁻¹)	P x10² (cmh⁻¹)	KH x10² (cm)	D/H² (cm⁻¹)	P x10² (cmh⁻¹)
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	0.20 ± 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
B P	146.4# ± 20	0.09 ± 0.01	12.1 ± 0.1	11.9*# ± 0.97	0.10 ± 0.01	1.10 ± 0.04

* Statistically different from the KH value in water for the same paraben
\# Statistically different from the other parabens



CONCLUSIONS

Nicotinamide significantly increases the solubility of MP, PP, BP. It has very low effect on EP solubility.

Nicotinamide reduces by one order of magnitude the Permeability Coefficient, due to a significant reduction of the Partition parameter (KH).

Exponential reduction of the transdermal flux of EP (conc 0.08%) as a function of nicotinamide concentration

REFERENCES

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