Poster # T 2122

NICOTINAMIDE REDUCES PARABENS TRANSDERMAL ABSORPTION

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AIM OF THE WORK

The aim of this work was to study the effect of nicotinamide (vitamin B_3) on the transdermal absorption of methyl (MP), ethyl (EP), propyl (PP) and butyl (BP) parahydroxybenzoates. An additional goal was to investigate the solubility of parabens in the presence of different concentrations of nicotinamide (3.5; 10; 20% w/v).

	Molecular Weigh t	Log P
Methylparaben (MP)	152.15	1.9 3
Ethylparaben (EP)	166.18	2.2 7
Propylparaben (PP)	180.20	2.8 1
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:

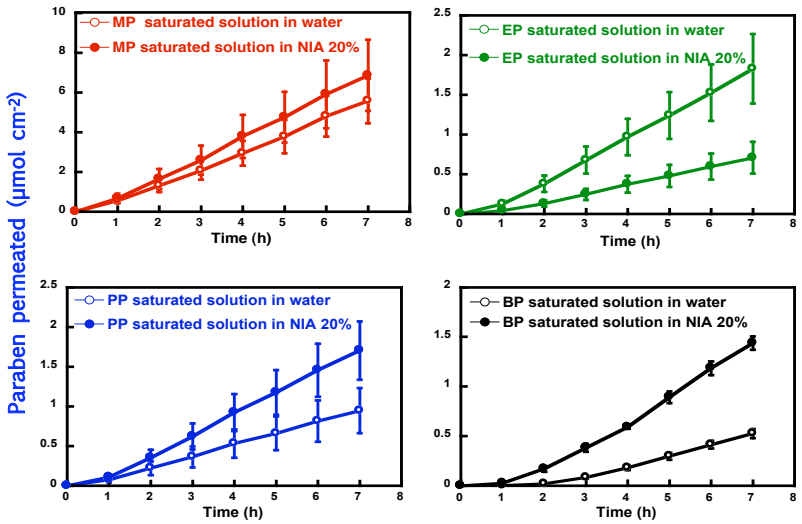
- Franz-type diffusion cells (0.6 cm²); Barrier: rabbit ear skin
- Donor compartment:
- MP, EP, PP, BP saturated sol. in water;
- MP, EP, PP, BP saturated sol. in water containing NIA 20% (w/v)
- EP solutions (0.08% w/v) in water containing NIA 0, 0.75, 3.5, 10, 20% (w/v)
- Data analysis (1):

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

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

RESULTS

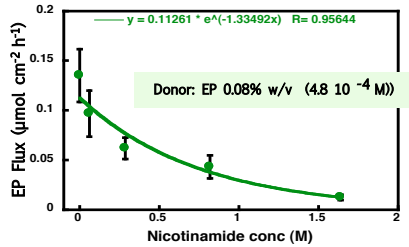
TRANSDERMAL PERMEATION



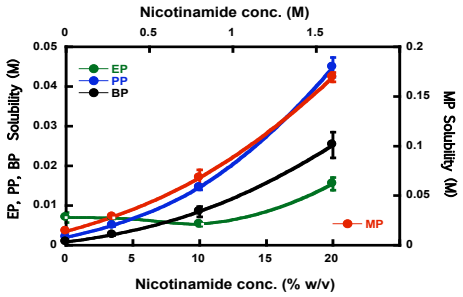
Permeation Parameters

	Water			Water+ Nicotinamide 20%		
	KH x10² (cm)	D/H² (h⁻¹)	P x10² (cmh⁻¹)	KH x10² (cm)	D/H² (h⁻¹)	P x10² (cmh⁻¹)
MP	18.6 ± 1.8	0.32 ± 0.0 4	6.1 ± 1.2	2.0* ± 0.46	0.32 ± 0.0 6	0.62 ± 0.1 6
EP	16.1 ± 2.9	0.25 ± 0.0 3	4.1 ± 0.9	3.8* ± 0.9 4	0.20 ± 0.0 2	0.77 ± 0.2 1
PP	16.0 ± 2.9	0.32 ± 0.0 3	5.1 ± 0.8	2.7* ± 0.2 9	0.24± 0.05	0.61 ± 0.1 1
B P	146.4# ± 2 0	0.09 ± 0.0 1	12.1 ± 0.1	11.9*# ± 0 .97	0.10 ± 0.0 1	1.10 ± 0.0 4

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



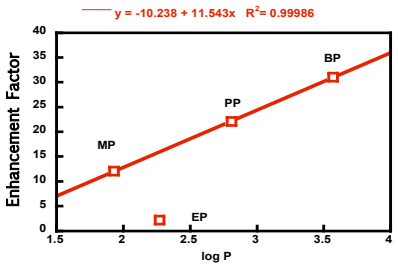
SOLUBILITY



	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:

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



CONCLUSION

1. Nicotinamide significantly increases the solubility of MP, PP, BP. It has very low effect on EP solubility.
2. Nicotinamide reduces by one order of magnitude the Permeability Coefficient, due to a significant reduction of the Partition parameter (KH). We speculate that nicotinamide reduces the partitioning between the stratum corneum and the vehicle by either:
   - modifying the polarity of the vehicle or
   - forming a complex more hydrophilic than the paraben alone (2)
3. Exponential reduction of the transdermal flux of EP (conc 0.08%) as a function of nicotinamide concentration

REFERENCES

(1) Moser K., Kriwet K., Froehlich C., Kalia Y.N., Guy R.H., Pharm. Res. 2001 (18) 1006-1011
(2) R. E. Coffmanand D. O. Kildsig. Hydrotropic solubilization–mechanistic studies. *Pharm Res* 13: 1460-3 (1996).