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.

**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 isopropyl myristate: water partitioning was also studied.

**Introduction**

**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:

  \[
  q(t) = (kH)C_c D / H - \frac{1}{6} \frac{2}{h} \sum_{n=1}^{\infty} \left(-\frac{1}{H}ight)^n \exp \left(-\frac{1}{n^2} \frac{D}{H^2} \right)
  \]

  \(Q\): amount of paraben permeated

  \(K_a\): partitioning parameter

  \(C_c\): donor concentration

  \(D/H^2\): diffusive parameter

**Results & Discussion**

**Permeation & Partitioning**

**Solubility**

- **The presence of NA:**
  - Increased the solubility of all but ethyl paraben.

  **Complex stability constant**

  \[
  [S] = S_0 + K_{1 \rightarrow 2} [L]_0 + K_{2 \rightarrow 3} [L]_0^2
  \]

  \(S_0\): equilibrium solubility of the paraben in absence of nicotinamide

  \(S_0\): concentration of free nicotinamide

  \(S_0\): concentration of the 1:1 complex

  \(S_0\): concentration of the 2:3 complex

  \(S_0\): equilibrium solubility of the paraben in presence of nicotinamide

  \(L_0\): concentration of nicotinamide

**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 increases 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.