Thiocolchicoside is a muscle-relaxant agent used for the treatment of orthopedic, traumatic and rheumatologic disorders (1). It is currently administered by the oral, injective and topical routes. The physico-chemical properties of thiocolchicoside are not favorable for its permeation across the skin. Thiocolchicoside has a relatively high molecular weight (563), relatively high water solubility (16.1 mg/ml) and low octanol/water partition coefficient (log P= -0.34).

### Introduction

To study the permeation of thiocolchicoside across the skin in vitro.

### Objectives

To study the effect of permeation enhancers:
- lauric acid
- iontophoresis

### Experimental Methods

**Permeation experiments:**
- Franz type diffusion cells (area 0.6 cm²).
- Barrier: rabbit ear skin and human skin.
- Donor solution (0.5 ml): thiocolchicoside saturated solution in:
  - (a) water (16.1 mg/ml);
  - (b) ethanol:water (60:40 v/v) with 0, 2 or 4% of lauric acid (12 mg/ml).
  - (c) ethanol with 4% of lauric acid (0.5 mg/ml).
- Receptor solution: saline

**Thiocolchicoside HPLC analysis:**
- C8 column (Nova-Pak®, Waters, Milford, USA).
- UV detection @ 370 nm.
- Mobile phase acetonitrile: water (15:85) @ 1 ml/min.

**Partitioning (KH) and diffusion (D/H) parameters were calculated according to the following equation (2):**

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

### Results & Discussion

**Effect of Lauric Acid**

- Rabbit Ear Skin
- Human Skin

**Effect of Iontophoresis**

- Rabbit Ear Skin
- Human Skin

### Permeation parameters of thiocolchicoside across the skin

<table>
<thead>
<tr>
<th>Skin</th>
<th>Solvent</th>
<th>Lauric Acid (w/v)</th>
<th>KH x 10⁴ (cm²)</th>
<th>D/H² x 10⁴ (h⁻¹)</th>
<th>P x 10⁴ (cm/h)</th>
<th>Jss (µg cm⁻² h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit</td>
<td>Water</td>
<td>0</td>
<td>0.2201</td>
<td>5.914</td>
<td>5.81±1</td>
<td>0.229±1</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Ethanol</td>
<td>0</td>
<td>317±50</td>
<td>1018±322</td>
<td>122±39</td>
<td>0.229±1</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Ethanol</td>
<td>2%</td>
<td>433±2128</td>
<td>4.22±1.6</td>
<td>1494±527</td>
<td>179±29</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Ethanol</td>
<td>4%</td>
<td>164±56</td>
<td>937±514</td>
<td>113±262</td>
<td>0.45±2</td>
</tr>
<tr>
<td>Human epidermis</td>
<td>Ethanol</td>
<td>0</td>
<td>433±2128</td>
<td>4.22±1.6</td>
<td>1494±527</td>
<td>179±29</td>
</tr>
<tr>
<td>Human full thickness</td>
<td>Ethanol</td>
<td>0</td>
<td>144±56</td>
<td>937±514</td>
<td>113±262</td>
<td>0.45±2</td>
</tr>
</tbody>
</table>

\[ P = KH * D/H^2 \quad Jss = P * C_{veh} \]

### Conclusions

- The permeation of thiocolchicoside across the skin can be enhanced using chemical or physical penetration enhancers.
- Lauric acid dissolved in water:ethanol increases the stratum corneum/vehicle partition coefficient.
- The use of lauric acid dissolved in ethanol not only decreased thiocolchicoside solubility but also depressed the partitioning parameter.
- When iontophoresis was used as enhancing technique, the flux of thiocolchicoside increased compared to the passive control.
- With human epidermis, the permeation parameters were generally lower, albeit not significantly different from those of rabbit ear skin.
- The data obtained with full thickness human skin indicate that, despite the hydrophilic nature of thiocolchicoside, the resistance to drug diffusion is not located only in the stratum corneum, but that the underlying dermal tissues can also contribute.

### References

3. The work was supported by a grant from the University of Parma.
4. Sanofi-Synthelabo is acknowledged