Permeation Parameters of Thiocolchicoside Across the Skin In Vitro

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Introduction

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 (logP=-0.34).

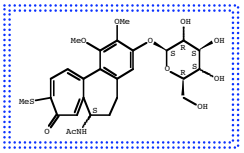
Aim of the work

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:

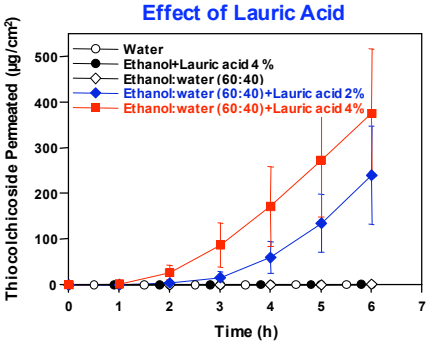
- Franz type diffusion cells (area 0.6 cm²).
- Barrier: rabbit ear skin and human skin.
- Donor solution (0.5 ml): thiocolchicoside saturated solution in:
  - (a) water (16.1 mg/ml);
  - (b) ethanol:water (60:40 v/v) with 0, 2 or 4% of lauric acid (12 mg/ml);
  - (c) ethanol with 4% of lauric acid (0.5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

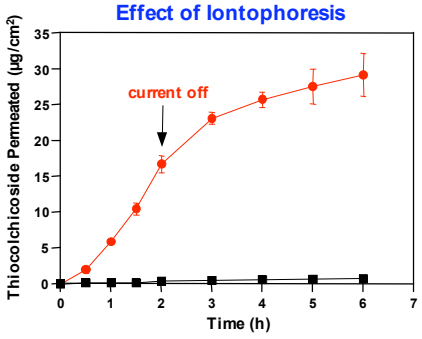
Thiocolchicoside HPLC analysis:

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

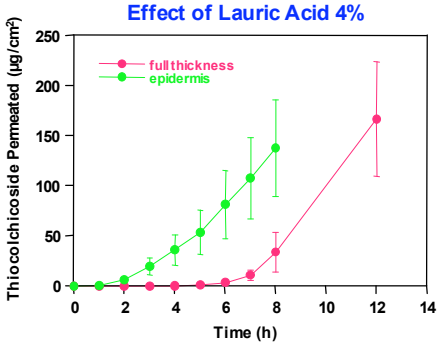
Results & Discussion

Rabbit Ear Skin





Human Skin



Partitioning (KH) and diffusion (D/H²) parameters were calculated according to the following equation (2):

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

Permeation parameters of thiocolchicoside across the skin

Skin	Solvent	Lauric Acid (%w/v)	KH x 10³ (cm)	D/H² x 10² (h⁻¹)	P x 10⁵ (cm h⁻¹)	J_{ss} (µg cm⁻² h⁻¹)
Rabbit	Water	0	0.2±0.1	5.9±1.4	0.9±0.4	0.1±0.1
Rabbit	Ethanol:water	0	2.1±1.6	5.9±3.1	4.4±3.3	0.5±0.4
Rabbit	Ethanol:water	2	317±69	3.0±0.5	1018±322	122±39
Rabbit	Ethanol:water	4	433±128	4.2±1.6	1494±327	179±39
Rabbit	Ethanol	4	20.1±9.4	4.9±1.5	70.6±30.4	0.4±0.2
Human epidermis	Ethanol:water	4	144±66	6.5±1.5	937±514	113±62
Human full thickness	Ethanol:water	4	305±100	1.4±0.2	355±113	43±14

$P = KH * D/H^2$ $\quad J_{ss} = P * C_{veh}$

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

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2. Moser K., Kriwet K., Froehlich C., Kalia N.Y., Guy R.H., 2001. Supersaturation: enhancement of skin penetration

Acknowledgements

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