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FACULTY OF PHARMACEUTICAL SCIENCES

TRANSDERMAL PENETRATION ENHANCING EFFECT OF THE *N*-ALKYLAMIDE SPILANTHOL

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INTRODUCTION

The dermal penetration of compounds may be influenced by other compounds when mixtures are presented to the skin. Plant extracts, often used in cosmeceuticals, are complex mixtures of bio-actives but contain undesirable impurities as well. A major question is if plant bio-actives (like spilanthol, Figure 1) can significantly alter the dermal penetration of other compounds which can be other actives (like testosterone) or impurities (like mycotoxins). If so, the qualification assessment of the product quality needs to include this influence within the Quality-by-Design strategy.

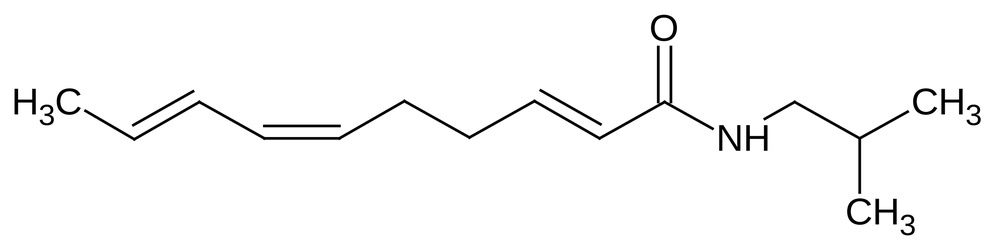

Figure 1: Structure of spilanthol

EXPERIMENTAL

The concentration-dependent penetration promoting effect of spilanthol was investigated on the three CART transdermal model compounds (caffeine, ibuprofen and testosterone (80% of S_{max})) in 50/50 EtOH/H_2O (V/V) [1]. Spilanthol was added in different concentrations: 0, 0.05, 0.1, 0.5 and 1% (m/V). *In vitro* human skin penetration studies using static Franz diffusion cells, thermostated at 32°C and dermatomed (~ 400 µm) abdominal human skin, were performed. Enhancing ratios (ER) were defined as the ratio of K_p values.

RESULTS and DISCUSSION

1. FLUX CURVES

The enhancing effect of spilanthol (S) on caffeine (C) and testosterone (T) was illustrated in Figure 2 and 3. From these curves, the steady-state flux (J_{ss}) and primary transdermal parameters K_p (permeability), D_m (diffusion) and K_m (partition) were calculated.

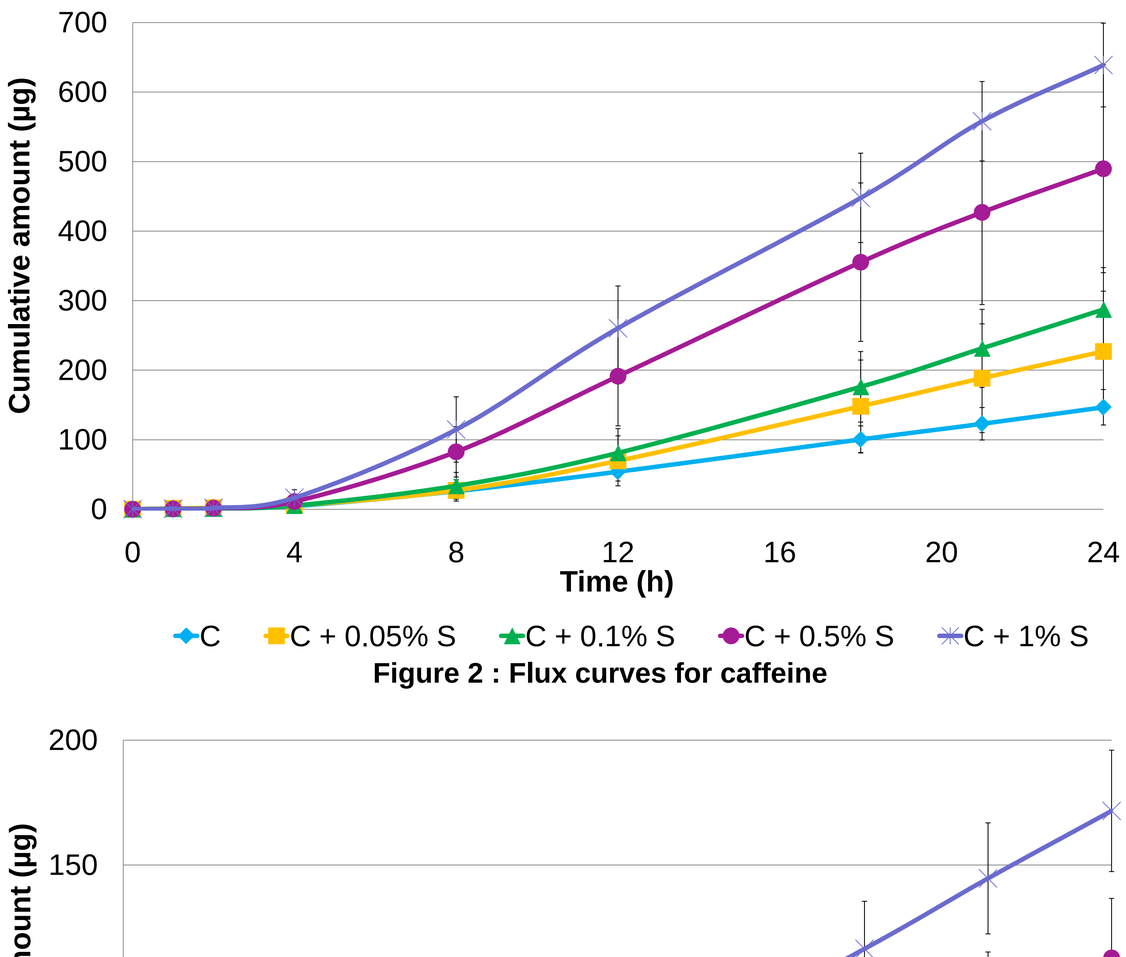

Figure 2 : Flux curves for caffeine

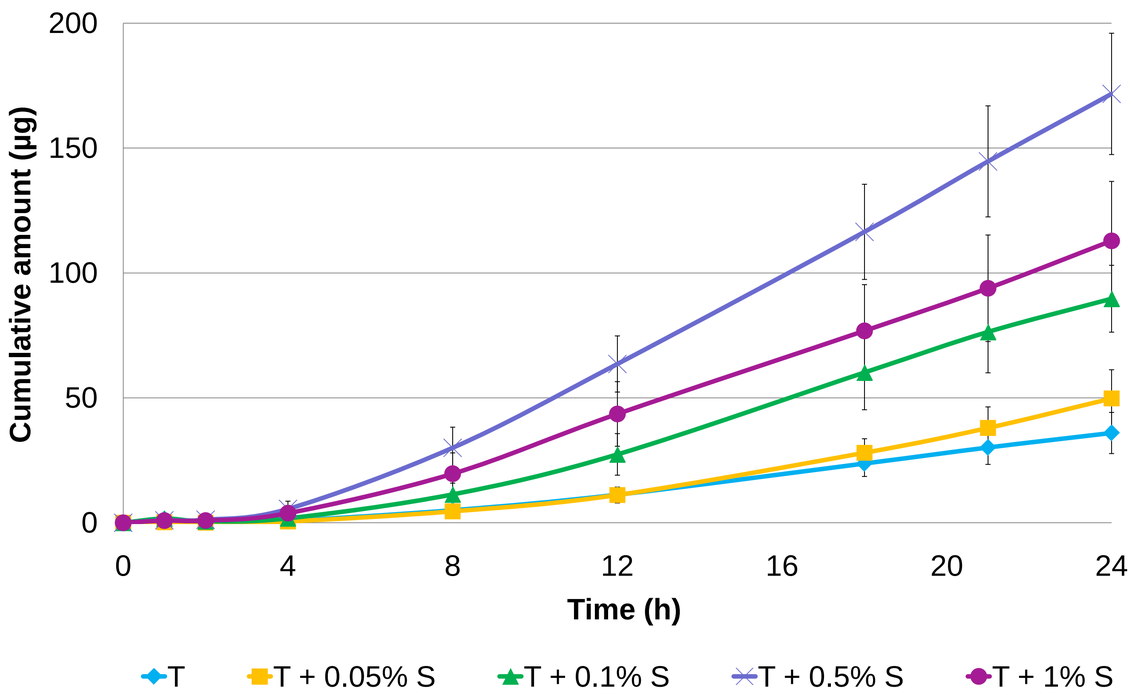

Figure 3 : Flux curves for testosterone

2. PRIMARY TRANSDERMAL PARAMETERS

Table 1 lists the K_p and mechanistic transdermal coefficients (D_m and K_m).

Table 1: Primary transdermal parameters (mean ± SEM, n=3-4).

% Spilanthol (m/V)	CAFFEINE			TESTOSTERONE		
	K_p ($\cdot 10^{-4}$) (cm/h)	D_m ($\cdot 10^{-5}$) (cm/h)	K_m	K_p ($\cdot 10^{-4}$) (cm/h)	D_m ($\cdot 10^{-5}$) (cm/h)	K_m
0	2.23 ± 0.34	6.15 ± 0.98	0.15 ± 0.02	3.97 ± 0.83	4.88 ± 0.61	0.34 ± 0.06
0.05	3.74 ± 1.37	4.47 ± 0.51	0.34 ± 0.10	5.66 ± 1.23	4.04 ± 0.72	0.61 ± 0.16
0.1	4.63 ± 0.76	4.53 ± 0.87	0.43 ± 0.03	10.19 ± 1.38	4.77 ± 0.75	0.89 ± 0.04
0.5	7.52 ± 2.18	7.62 ± 2.01	0.53 ± 0.18	17.69 ± 1.93	6.19 ± 0.63	1.21 ± 0.10
1	9.77 ± 0.46	8.39 ± 3.33	0.67 ± 0.16	11.45 ± 2.20	6.45 ± 1.28	0.76 ± 0.14

The enhancing effect of spilanthol is mainly driven by an altered partitioning effect of the model compound out of the donor solution into the skin.

3. PENETRATION ENHANCING EFFECT

Calculating the ER for the three model compounds demonstrated no relevant penetration-enhancing effect of ibuprofen in the presence of spilanthol (ER <2). However, for caffeine and testosterone, a concentration dependent enhancing effect is illustrated (Figure 4).

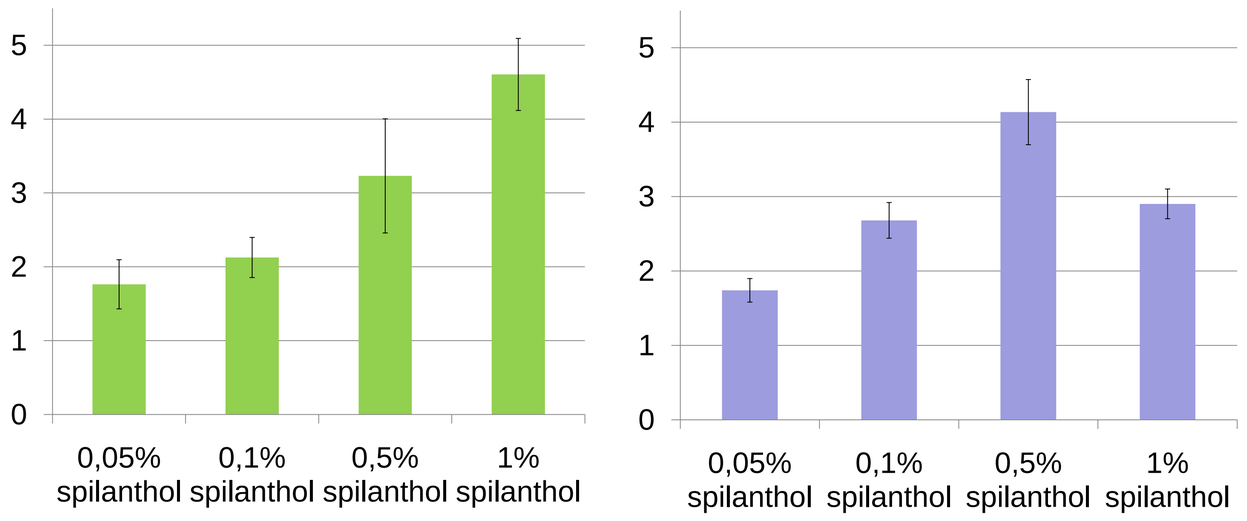

Figure 4 : ER for caffeine (left) and testosterone (right)

CONCLUSIONS

Spilanthol as model plant constituent used in cosmeceuticals, has the potential to increase the transdermal penetration of other components. An enhancing effect up to a factor higher than 4 has been found. Therefore, as part of the functional quality evaluation, it is recommended to include this mutual influence in topical product development [2].

REFERENCES

[1] B. Baert, E. Deconinck, M. Van Gele, et al. Transdermal penetration behaviour of drugs: CART-clustering, QSPR and selection of model compounds, 2007, Bioorganic & medicinal chemistry, 15(22): 6943-6955.

[2] B. De Spiegeleer, J. Boonen, L. Veryser, et al. Skin penetration enhancing properties of the plant *N*-alkylamide spilanthol, 2012, manuscript in preparation.