DERMATOPHARMACOKINETICS OF BETAMETHASONE 17-VALERATE: INFLUENCE OF DRUG THERMODYNAMIC ACTIVITY

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INTRODUCTION

The dermatopharmacokinetic approach (DPK), using tape-stripping, is a promising technique for bioequivalence testing of topically applied drugs.

⇨ Objective:

- To investigate whether two formulations containing the same drug at equal thermodynamic activity results in similar delivery into the SC.

EXPERIMENTAL METHODS

- **Materials**

Betamethasone 17-valerate (BMV, Crystal Pharma, Spain) was dissolved in

(i) a reference vehicle consisting of medium chain triglycerides (MCT, Synopharm, Germany) containing 15% (w/w) polypropylene and

(ii) the microemulsion Micro 100® (ME, Sebapharma, Germany) incorporating 10% (w/w) Aerosil 200®.

BMV concentration was adjusted to 10% and 80% of saturation (constant thermodynamic activities),

⇨ 0.21 and 1.7 mg/ml in MCT, 1.22 and 9.3 mg/ml in ME, respectively.

- **Tape Stripping procedure**

600 µl of formulation were applied in a Hill Top Chamber® to a 3.14 cm^2 area on the forearm.

After an exposure time period of 2 h, the SC was progressively removed by repeated adhesive tape-stripping (Scotch Book Tape, 3M, MN, USA) [1].

Each tape was weighed before and after stripping.

The quantity of BMV in each tape strip was determined by quantitative extraction and HPLC analysis.

- **Analysis of the SC distribution profile**

SC concentration (C_x) vs. normalized position (x/L) profiles of BMV were fitted to Fick´s second law of diffusion (Eq. 1):

$$C_x = KC_{veh}\left(1-\frac{x}{L}-\frac{2}{\pi}\sum_{n=1}^{7}\frac{1}{n}\sin(n\pi\frac{x}{L})\exp(-\frac{D}{L^2}n^2\pi^2t)\right) \quad \text{Eq. 1}$$

t	exposure time period
C_{veh}	BMV concentration in vehicle
K	SC-vehicle partition coefficient
D/L^2	diffusivity parameter across the SC

AUC was calculated from the integral of C_x.

RESULTS AND DISCUSSION

BMV delivery into the SC was significantly higher ($p<0.05$) from ME than from MCT at equal thermodynamic activities (Figure 1a, 1b).

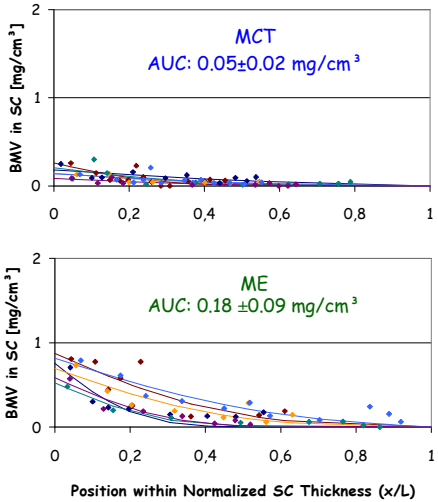

Figure 1a: SC distribution profiles of BMV delivered from MCT and ME at 10% of saturation (n=6)

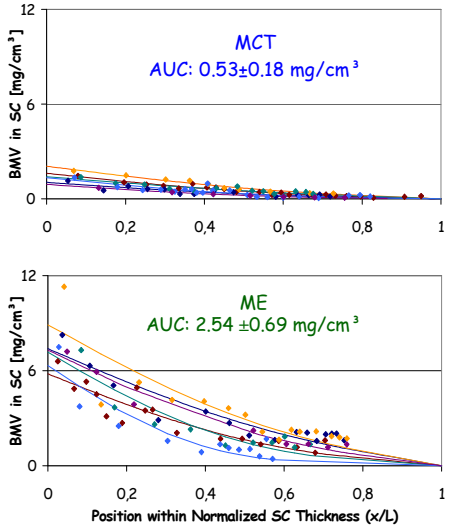

Figure 1b: SC distribution profiles of BMV delivered from MCT and ME at 80% of saturation (n=6)

Plotting the AUC versus the absolute BMV concentration applied resulted in a linear relationship (Figure 2).

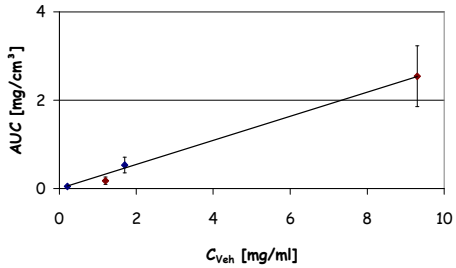

Figure 2: AUC vs. absolute BMV concentration applied (C_{veh}) in the vehicles MCT (◆) and ME (◆). R^2=0.99

Fitting the distribution profiles to Eq. 1 indicated that K and D/L^2 were similar for the two vehicles and two drug activities (Table 1).

⇨ apparent solubility of BMV in the SC ($C_{s,SC}$) may be significantly affected by the vehicle

⇨ this is inconsistent with the linear correlation between the AUC and C_{veh}, which is independent of the vehicle

⇨ an indication that excess formulation may be trapped in the furrows of the SC

Table 1: K, D/L^2 and $C_{s,SC}$ of BMV applied in MCT and ME at 10% and 80% of saturation (mean±SD; n=6)

	K	D/L^2 [h^{-1}]	$C_{s,SC}$ [mg/ml]
	10% Cs		
MCT	0.80±0.29	0.036±0.020	1.72±0.62
ME	0.59±0.11	0.025±0.017	6.92±1.32[a]
	80% Cs		
MCT	0.83±0.24	0.059±0.013	1.73±0.51
ME	0.76±0.11	0.053±0.019	8.93±1.33[a]

[a]Significantly different ($p<0.05$) from the reference vehicle

CONCLUSIONS

The SC distribution profiles of BMV are reproducible and distinguish clearly between the two formulations.

The impression that the ME enhances drug delivery into the SC may be caused by excess formulation trapped in the skin furrows which is not removed efficiently by the skin cleaning procedure.

ACKNOWLEDGEMENTS

We thank Sebapharma GmbH for providing Micro 100® and we are grateful to our volunteer-colleagues in Bath.

REFERENCES

[1] Kalia Y.N. et al., Skin Pharmacol. Appl. Skin Physiol. 2001; 14(suppl 1):82-86