# Code

# DSC Measurements on full Thickness Mice Skin, a Way to Evaluate the Mechanism of Permeation Enhancement of highly Lipophilic Drugs

**R. Schiller [a], H.W. Motzkus [a], A. Funke [b], C. Günther [c], R. Lipp [b]**

[a] Pharmaceutical-Development, Thermal Analysis, Schering-AG Berlin, Müllerstraße 170-178, 13342 Berlin, Germany

[b] Pharmaceutical-Development, Oral Dosage Forms, Schering-AG Berlin, Müllerstraße 170-178, 13342 Berlin, Germany

[c] Preclinical Development, Schering-AG, Müllerstrasse 170-178, 13342 Berlin, Germany

Transdermal application is a promising way of drug administration, providing several benefits. Though the outermost layer of skin, the stratum corneum forms an excellent barrier against permeation of drugs, because of it´s rigid lipid lamellar structure. The most easiliy permeating drugs are small molecules of moderate lipophilicity. The aim of this study was to improve the skin permeability for highly lipophilic drugs. As model compound, two new antiestrogens were chosen. For that purpose, the effects of several permeation enhancers [propylene glycol (PG), dimethyl isosorbide (DMI), dimethylsulfoxide (DMSO), and lauric acid (LA)] and various combinations thereof on the diffusion of these drugs through excised skin of hairless mice were to be determined .

Thermoanalytic (DSC) measurements of skin lipid phase transition temperatures in combination with drug absorption studies in a modified flow through Franz diffusion cell were performed, using full thickness mice skin to investigate the effect of skin lipid softening and the correlation with transdermal delivery of the drug substance.

Sections of full thickness mice skin were placed on PBS soaked paper sheets. Various permeation enhancers were applied onto the stratum corneum side. Sections of approx. 10-20mg were placed in 40µl aluminium crucibles with perforated lid. Untreated samples as well as pure permeation enhancer formulation served as control. All samples were analyzed over a heating range from –20°C up to 150°C with 10K/min under nitrogen, using a METTLER-TOLEDO DSC 821e with IntraCooler.

Transdermal flux of highly lipophilic drugs was extraordinarily enhanced by the unique permeation enhancer combination propylene glycol and lauric acid (9+1). This dual enhancer formulation also resulted in a marked increase in the dermal fluxes of the enhancer. Therefore it was concluded that the permeation enhancement of LA must be due to effects onto the skin. Untreated skin shows three endothermic peaks at 33°C, 56°C and 62°C, the latter two being attributed to phase transitions of the stratum corneum lipids. Skin treatment with pure solvents, PG and DMI, respectively, slightly altered the transition temperatures. However, formulations containing LA markedly decreased these temperatures, indicating a lipid fluidising action of LA. In those cases, an additional endothermic peak was observed at 39-41°C, which correlates with the melting of LA. It is very likely, that LA crystalizes in the lipid phase of the stratum corneum during the DSC experiment (-20°C to 150°C).

**Conclusion**

DSC measurements can be performed on full skin without separation of the stratum corneum. A fluidising effect on the lipids in the skin and a deposition of fluid enhancer LA can be directly investigated. The shift of lipid phase transitions to lower temperatures correlates with the fluidising effect of the formulation and the transdermal delivery of the drug substance**.**

**References**

1 B.W. Barry. Lipid protein partitioning theory of skin penetration enhancement. J. Control. Release **15**:237-248 (1991)

2 T.M. Suhonen. Chemical enhancement of percutaneous absorption in relation to stratum corneum structural alterations. J. Control. Release **59**:149-161 (1999)

3 K.I. Cumming and A.J. Winfield. In vitro evaluation of a series of sodium carboxylates as dermal penetration enhancers. Int. J. Pharm. **108**:141-148 (1994)

5 C.S. Leopold and B.C. Lippold. An attempt to clarify the mechanism of the penetration enhancing effects of lipophilic vehicles with DSC. J. Pharm. Pharmacol. **47**:276-281 (1995)

**(Full Reference list available on Pharm. Research Vol. 19, No. 5, May 2002)**