AN IN VITRO TEST METHOD FOR EVALUATING THE EFFECT OF HEAT ON TDDS PERFORMANCE

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Purpose

A better understanding of the effects of heat on the performance of transdermal drug delivery systems (TDDS) and the establishment of an *in vivo-in vitro* correlation are needed for development of regulatory guidance to evaluate heat effects on TDDS and the approval of generic transdermal products. To identify *in vitro* test conditions for evaluating the effect of heat on drug delivery from transdermal drug delivery systems (TDDS), the effective thermal resistance of the skin and the TDDS was characterized, and *in vitro* parameters were identified that correlate with in vivo observations.

Methods

In a human clinical study, micro-thermocouples (Ultrafine IT-Series Flexible Microprobe) were used with single (1-Layer) and multilayer (5-Layer) drug-depleted nicotine TDDS to record the temperature at the skin and at the TDDS, both, at room temperature and following heat application. In addition, *in vitro* experiments with human cadaver skin in thermostatically controlled Franz diffusion cells were performed similarly, using nicotine TDDS. Skin and TDDS temperatures were regulated with a PID-controlled heat lamp (HL-1, Physitemp Instruments).

Conclusion

There are no significant differences among the skin temperatures on the forearm, upper arm, and abdomen under the TDDS without heat application. Approximately 42 °C at the skin surface is the relevant limit for applied heat *in vitro*. Higher temperatures are not well tolerated *in vivo*, and thermoregulation in vivo appears to counteract further warming of the skin. The effective thermal resistance of the skin was 4-12 times larger than that of a single nicotine adhesive patch under heat application *in vivo*. *NOTE: The views presented in this poster by the authors do not necessarily reflect those of the Food and Drug Administration (FDA).*

Results

(Table 1) Under baseline conditions (no heat application), variation of application site *in vivo (n = 6)* showed no significant difference in skin temperatures under applied TDDS of varying thicknesses (average values of 32.2-32.8 °C). TDDS with higher thermal resistance lead to larger difference between the skin and TDDS surface temperatures, but had minimal effect on the temperature at the skin surface under the TDDS without heat application. *(Figure 1) In vivo* (n = 6) Graded heat application (38-45 °C TDDS Temperature) to the forearm demonstrated that approximately 42-43 °C was the maximum tolerable skin surface temperature. *(Figure 2) In vivo* (n = 6), the average temperature differential between skin surface and TDDS surface following graded heat application was less for 1-Layer TDDS (0.08 – 1.04 °C) as compared with multilayer (5-Layer) TDDS (0.56 – 2.31 °C). *(Figure 3)* Higher TDDS thermal resistance leads to an increase in the temperature difference between skin and TDDS surfaces *in vivo* (e.g. 0.004 m^2K/W, ranging from less than 1 °C to approximately 3 °C as the temperature increases from 39 °C and 45 °C, respectively). An unstirred layer alters the relationship between the thermal resistance of skin *in vitro* compared to that *of in vivo.*

Table 1: Baseline Skin Temperatures

	Skin Surface Under TDDS	TDDS Surface	Difference Between Skin and TDDS
1-Layer TDDS			
Forearm	32.8 ± 1.2 °C	32.5 ± 1.1 °C	0.2 °C
Upper Arm	32.2 ± 0.7 °C	32.0 ± 0.7 °C	0.2 °C
Abdomen	32.3 ± 1.6 °C	32.2 ± 1.6 °C	0.04 °C
5-Layer TDDS			
Forearm	32.4 ± 0.6 °C	31.8 ± 0.6 °C	0.6 °C
Upper Arm	32.3 ± 1.0 °C	31.8 ± 1.0 °C	0.5 °C
Abdomen	32.8 ± 1.5 °C	32.3 ± 1.5 °C	0.6 °C

Figure 1: Tolerability of Skin Surface Temperatures

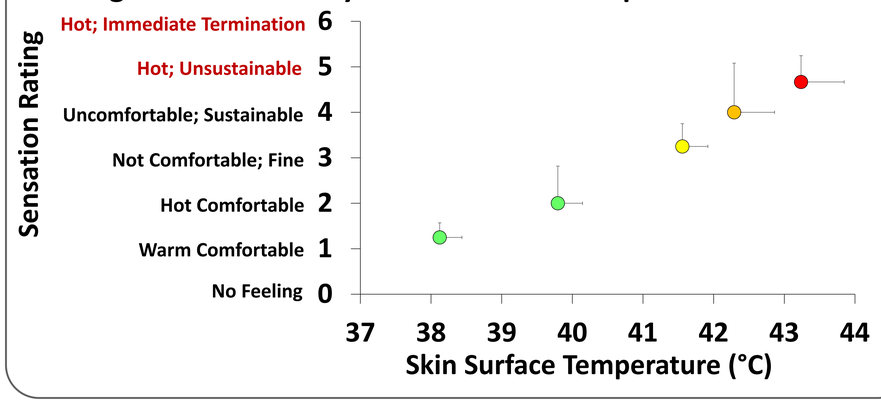

Figure 2: Temperature Differences between TDDS and Skin Surface

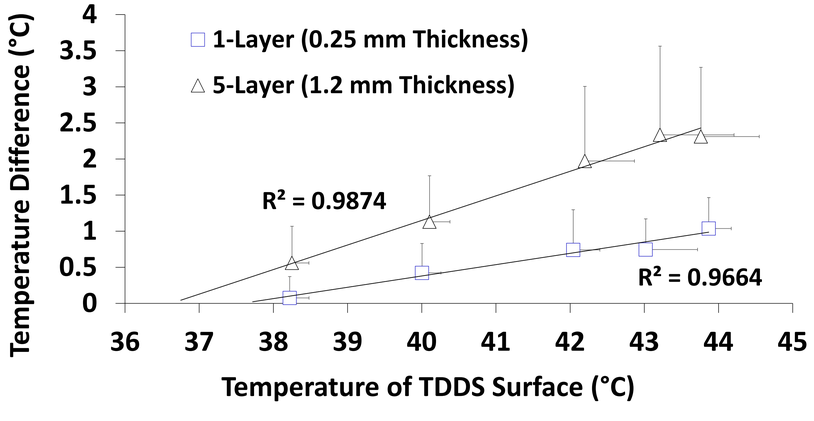

Figure 3: TDDS Thermal Resistance on Temperature Differentials