SKIN TEMPERATURE UNDER TRANSDERMAL PATCH WITH HEAT APPLICATION

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Abstract

Purpose: Transdermal drug delivery provides a convenient route of drug administration. It has been suggested that drug absorption with transdermal patches can be significantly elevated by heat, which can lead to unanticipated toxicity and drug dosing complications. To identify in vitro test conditions for the evaluation of heat effect on transdermal systems, the objectives in the present study were to characterize the effective thermal resistance of skin and associated transdermal delivery systems and to determine optimal in vitro thermal parameters that correlate with in vivo observations.

Methods: In vivo experiments were performed to record the skin and patch temperatures with micro thermocouples at room temperature and under heat application on human volunteers using single and multilayer drug depleted nicotine adhesive patches. In vitro experiments were performed with human cadaver skin and nicotine patches in thermostatically controlled water jacketed Franz diffusion cells regulating the temperature in the receptor. Patch and skin temperatures were regulated with a PID-controlled heat lamp.

Results: Skin temperatures recorded on the forearm, upper arm, and abdomen under applied patches of varying thicknesses showed no significant differences (average values of 31.7-32.8 °C). These data suggest patch location did not significantly influence skin temperature. In vivo experiments utilizing graded heat application to the forearm (40-46 °C) demonstrated that the maximum tolerable skin surface temperature for humans was approximately 42-43 °C under the heat lamp. The difference between skin surface and patch surface temperatures in the In vivo graded heat experiments for single nicotine patch ranged from 0.2 to 1.3 °C when the temperature increased, while it was 0.5 to 2.3 °C for multilayer patch of five times the thickness under the same conditions.

Conclusion: The in vivo graded heat experiments suggest the utilization of approximately 42 °C as the upper limit of applied heat in Franz cell experiments for the evaluation of heat effect on transdermal delivery in vitro. 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.

Purpose

Most transdermal drug delivery systems (TDDS) are affected by temperature. Due to the potential effects of temperature on the clinical efficacy and toxicity of TDDS, a number of TDDS have warning labels against heat application during drug administration. Studies were performed to identify *in vitro* parameters to aid in providing regulatory guidance to evaluate heat effects on branded and generic TDDS. Specifically determined were:

a. skin temperature under TDDS with and without heat application *in vivo*,
b. skin surface temperature to be used in *in vitro* testing of TDDS,
c. the thermal properties of skin *in vivo* so *in vitro* test conditions that best identify heat effects on TDDS could be developed.

Methodology

Human *In Vivo* Studies (25-60 yr male/female)
Ultrafine IT-Series Flexible Micro thermocouple probes (Physitemp Instruments) were attached to single (1-layer) and multilayer (5-layer) drug-depleted nicotine TDDS, and the TDDS was placed on the volunteer. The temperatures at the skin surface under the TDDS and at the surface of the TDDS were monitored. Temperatures were recorded at room temperature (baseline) and at elevated temperatures maintained by a PID-thermostatically controlled heat lamp (Physitemp HL-1, TCAT-2).

***In Vitro* Studies** (split-thickness cadaver skin)
Temperatures were measured in Franz diffusion cells using the same methodology as described above. The receiver chamber temperature was controlled by a water-bath, and heat was applied to the TDDS and maintained by the PID-thermostatically controlled heat lamp.

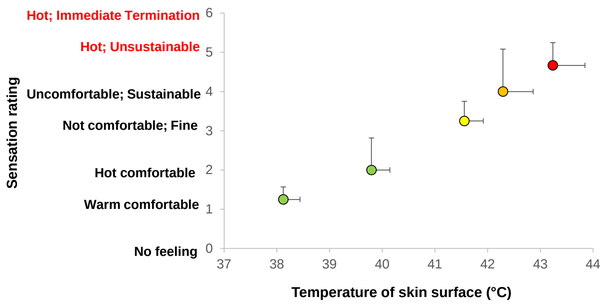
Results

(1) Skin temperature under transdermal patch without heat application in vivo (n = 6)

	Skin surface temperature under TDDS	TDDS surface temperature	Temperature difference between skin and TDDS
1-layer patch			
Forearm	32.8 ± 1.2 °C	32.5 ± 1.1 °C	0.2 ± 0.1 °C
Upper arm	32.2 ± 0.7 °C	32.0 ± 0.7 °C	0.2 ± 0.1 °C
Abdomen	32.3 ± 1.6 °C	32.2 ± 1.6 °C	0.04 ± 0.08 °C
5-layer patch			
Forearm	32.4 ± 0.6 °C	31.8 ± 0.6 °C	0.6 ± 0.2 °C
Upper arm	32.3 ± 1.0 °C	31.8 ± 1.0 °C	0.5 ± 0.1 °C
Abdomen	32.8 ± 1.5 °C	32.3 ± 1.5 °C	0.6 ± 0.1 °C

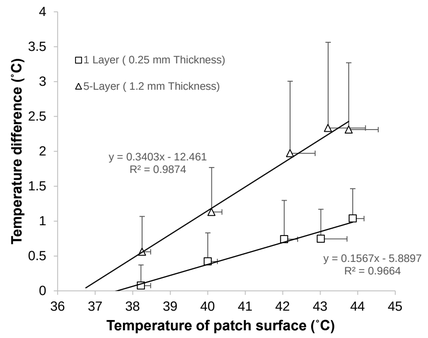
- The average baseline skin surface temperatures in the body regions measured under 1-layer and 5-layer systems was 32.2-32.8 °C.
- The resistance of the thermal barrier (i.e., thickness of the patches) did not significantly affect the skin surface temperature.
- Transdermal system with higher thermal resistance leads to a larger difference between the skin and patch surface temperatures.

(2) Sensation rating during heat application on a transdermal patch. Mean ± SD (n = 6 subjects).



- Sensation rating increased when the skin surface temperature was increased that heat sensation became unbearable when the local skin surface temperature under the patch approached 42-43 ˚C.
- This temperature is therefore recommended as the upper value of the temperature range at the skin surface in Franz diffusion cell testing *in vitro*.

(3) Temperature difference between patch and skin surfaces as a function of temperature at the patch surface in vivo: 1-layer patch (squares) and 5-layer patch (triangles). Mean ± SD (n = 6 subjects).



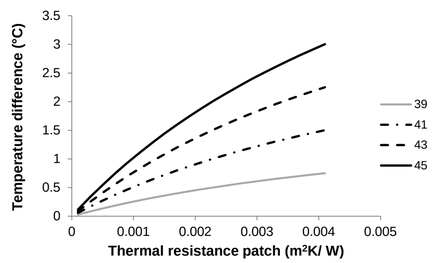
- Using the following heat transfer equation derived from the theory[1]:

$$T_{patch} - T_{patch:\,skin} = \frac{R_p}{R_p + R_z}\left(T_{patch} - T_{derm}\right)$$

the average effective thermal resistance of the skin was found to be approximately 8 times of the thermal resistance of the nicotine TDDS. The thermal resistance of TDDS was 0.00091 m^2K/W measured by ThermTest TPS 2500 S Thermal Constants Analyzer.

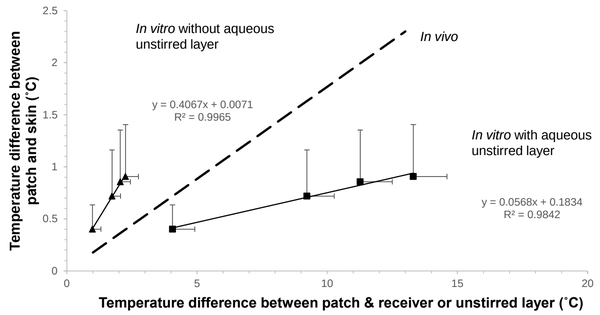
- The average effective thermal resistance of the skin was 0.0068 m^2K/W *in vivo*. This thermal resistance value is more than 10 times higher than that of the epidermis tissue *ex vivo*,[2] suggesting a significant contribution of the dermis to the total thermal resistance of skin in our study.

(4) Temperature difference between patch and skin surfaces as a function of patch thermal resistance and skin temperature in vivo



- Higher patch thermal resistance leads to an increase in the temperature difference between skin and patch surfaces *in vivo* (ranging from less than 1˚C to 3 ˚C).

(5) Temperature difference between patch and skin surfaces as a function of temperature difference between patch and receiver. Mean ± SD (n = 7).



- A comparison of the *in vivo* human and *in vitro* Franz diffusion cell data shows that the thermal resistance of skin *in vivo* is higher than that *in vitro* without the unstirred boundary layer but lower than that with the layer, suggesting stirring can affect the skin and patch temperature profiles in the diffusion cell *in vitro*.

Conclusions

- There are no significant differences among the skin temperatures on the forearm, upper arm, and abdomen under the TDDS without heat application.
- The maximum tolerable skin surface temperature for human using the TDDS was approximately 42-43 ˚C under the heat lamp *in vivo*.
- The skin and patch temperature profiles are a function of thermal resistance of the TDDS.

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