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Evaluation of Heat Effects on Transdermal Delivery Systems Using an *In Vitro* Permeation Test (IVPT) Strategy

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BACKGROUND & PURPOSE

- Many transdermal delivery systems (TDS) exhibit altered performance under conditions of elevated temperature, which may lead to unanticipated toxicity and drug dosing complications.
- Currently, there is no standard *in vitro* test method to evaluate and compare the performance of TDS under the influence of elevated temperature.
- The purpose of the study was to develop an experimental model, an *in vitro* permeation test (IVPT), to assess the effect of heat on drug delivery by using nicotine TDS and fentanyl TDS.

METHODS

Different heating protocols (application time and duration) were examined to identify the conditions that can characterize the effect of elevated temperature on drug delivery from TDS.

In vitro permeation test (IVPT) with TDS

- The experimental model used excised human skin mounted in a modified Franz diffusion cell which allowed for precise control of skin temperature when external heat was applied from an infrared lamp.
- Temperatures between the skin and the TDS were monitored by thermocouples.
- The target skin surface temperature for heat application was 42°C , which was determined in a separate *in vivo* study (not reported here) to be approximately the maximum tolerable skin surface temperature for human subjects. The target skin surface temperature for baseline IVPT experiment (the control condition) was 32°C.
- The products investigated in the study are listed below. (Table 1)

TDS (Strength)	Nicotine (21 mg/day)	Fentanyl (50 µg/h)
Alza	22 cm²	23 cm²
Aveva	28 cm²	21 cm²
Mylan		13 cm²

Table 1. Measured size of nicotine TDS (21 mg/day) and fentanyl TDS (50 µg/h), products used in the study.

- IVPT method was used to determine the effects of heat on TDS flux under different heat application regimens. (Table 2)

Nicotine	Fentanyl
0-24h	0-72h
4-24h	6-72h
8-24h	11-12h
4-5h	18-19h
8-9h	24-72h
	48-72h
	Multiple heat applications

Table 2. Heat application protocols for nicotine and fentanyl, respectively. The multiple heat application protocol for fentanyl involved successive heating at 6-7, 18-19, and 48-72h

- Nicotine and fentanyl TDS were removed at the end of the study (at 24 and 72 h, respectively). With short heat application regimens, the TDS was removed at 9 h (nicotine) and 19 h (fentanyl).

Skin permeation experiments without TDS

- The activation energies for nicotine and fentanyl were obtained by conducting skin permeation experiments without TDS in side by side diffusion cells under 32°C and 42°C.

RESULTS

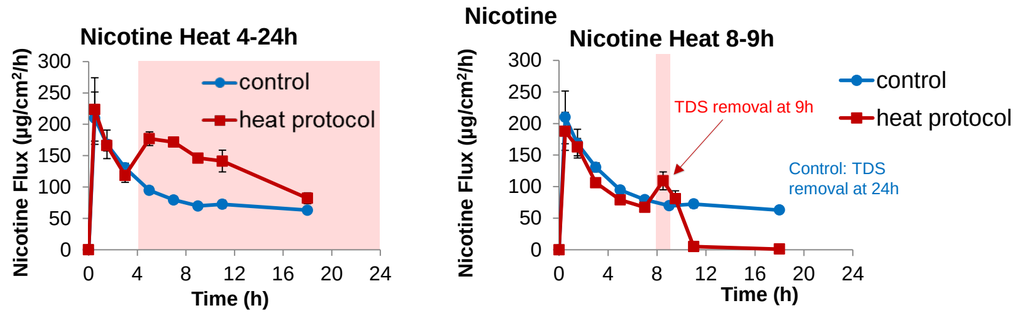

Figure 1. Flux profiles for nicotine TDS 21 mg/day (Alza) when heat was applied from 4-24h or 8-9h, respectively (see shaded red bands indicating durations of heat application). Significant heat induced flux increase was observed for both heating protocols (*t*-test, $P < 0.05$). No appreciable nicotine fluxes were observed after TDS removal at 9h. Similar results were observed for nicotine (Aveva) (data not shown). (n=4 donors, at least 3 replicates for each donor, Mean ± SEM).

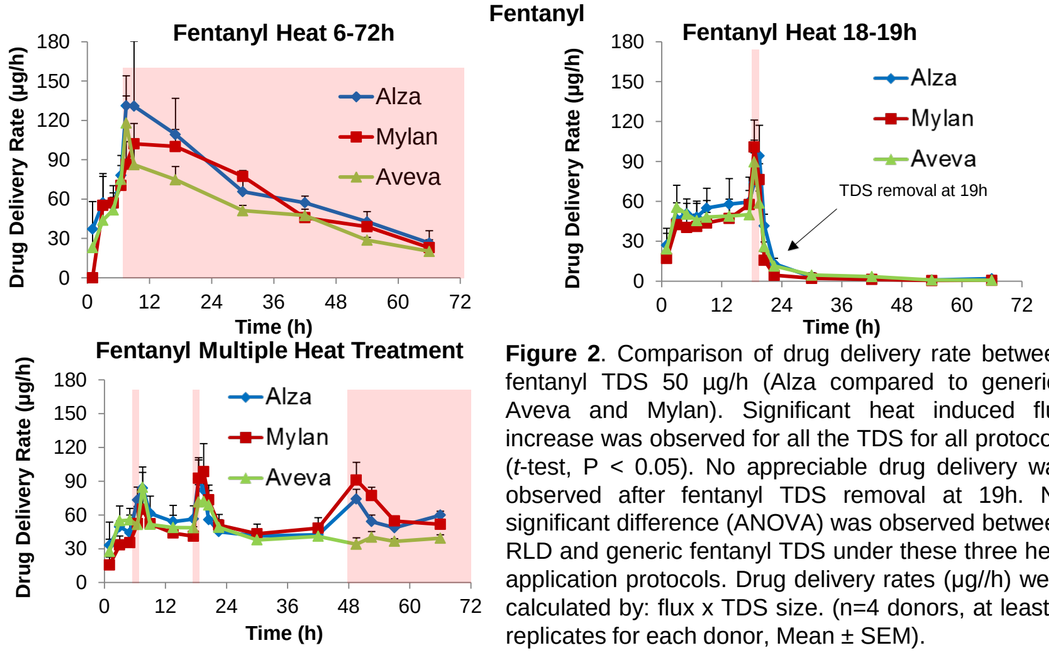

Figure 2. Comparison of drug delivery rate between fentanyl TDS 50 µg/h (Alza compared to generics Aveva and Mylan). Significant heat induced flux increase was observed for all the TDS for all protocols (*t*-test, $P < 0.05$). No appreciable drug delivery was observed after fentanyl TDS removal at 19h. No significant difference (ANOVA) was observed between RLD and generic fentanyl TDS under these three heat application protocols. Drug delivery rates (µg//h) were calculated by: flux x TDS size. (n=4 donors, at least 3 replicates for each donor, Mean ± SEM).

Table 3. Peak flux during heat application for nicotine TDS (Mean ± SD). An average of ~1.8 fold increase in flux was observed for both TDS at elevated temperature.

Nicotine	Peak Flux During Heat (µg/cm²/h)	
Heating Protocol	**Alza**	**Aveva**
0-24h	266 ± 41	126 ± 37
4-24h	177 ± 22	114 ± 21
8-24h	123 ± 28	56 ± 18
4-5h	172 ± 24	85 ± 25
8-9h	109 ± 28	58 ± 17

Table 4. Peak flux during heat application for fentanyl TDS* (Mean ± SD). An average of ~2 fold increase in flux was observed for all the fentanyl TDS under elevated temperature.

Fentanyl	Peak Flux During Heat (µg/cm²/h)		
Heating Protocol	**Alza**	**Aveva**	**Mylan**
0-72h	4.7 ± 1.8	4.2 ± 1.2	8.2 ± 1.9
6-72h	5.9 ± 1.4	5.5 ± 1.9	7.7 ± 2.4
11-12h	4.1 ± 2.2	4.3 ± 2.2	6.2 ± 2.4
18-19h	4.1 ± 1.4	4.2 ± 1.5	7.6 ± 3.1
24-72h	4.8 ± 1.3	3.4 ± 0.7	10.0 ± 3.7
48-72h	3.8 ± 1.1	2.7 ± 0.5	7.2 ± 2.5
6-7h of multiple heat	3.6 ± 0.9	3.9 ± 1.7	5.0 ± 3.0
18-19h of multiple heat	3.9 ± 1.1	3.3 ± 1.1	7.5 ± 3.8
48-72h of multiple heat	3.2 ± 0.5	1.9 ± 0.5	6.9 ± 2.4

*The peak flux values in Table 4 were not adjusted using the size of TDS represented in Table 1

Table 5. Experimentally-determined activation energy for nicotine and fentanyl in drug solution (not TDS), respectively.. The increase in flux at 42°C was consistent with the experimentally obtained activation energy (E_A) values.

E_A (kJ/mol)	Nicotine	Fentanyl
Experiment without TDS	65.9	62.1

CONCLUSION

- Drug permeation across human skin *in vitro* is higher at 42°C than that of 32°C, with flux increases occurring shortly after exposure of the TDS to heat, for both nicotine TDS and fentanyl TDS.
- Maximum flux was observed when heat was applied earlier or with sustained heat application for both nicotine TDS and fentanyl TDS. This may be related to drug depletion in TDS and drug transport lag time, respectively.
- The results suggest that TDS can behave differently under heat exposure due to different TDS designs and their interactions with skin.
- An IVPT protocol with heat application at an early time may be better to identify the maximum delivery rates of nicotine and fentanyl from TDS at an elevated temperature.

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