Influence of Heat on Reference and Generic Transdermal Drug Delivery Systems

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Introduction

Multiple factors, including exposure to heat and the presence of different inactive ingredients can influence drug release and absorption from transdermal drug delivery systems (TDDS). Possible exposures to elevated temperature include heating pads, saunas, and prolonged activity under direct sunlight. Since generic TDDS and the corresponding reference listed drug (RLD) products are not required to be qualitatively (Q1) and quantitatively (Q2) similar, the effect of elevated temperature on the extent of drug delivery from a generic product and its RLD can be different. Consequently, when the extent of heat effect on drug release rate and absorption from TDDS is greater in the generic as compared to its RLD, the generic TDDS can potentially expose users and patients to increased amounts of active pharmaceutical ingredients (APIs), leading to safety concerns.

The purpose of the current study was to develop *in vitro* skin permeation methods and investigate the effect of heat on nicotine and fentanyl TDDS.

Methods

In vitro permeation test (IVPT) experiments were performed using a PermeGear® flow-through in-line diffusion system. Dermatomed Yucatan minipig skin samples with transepidermal water loss readings below 15 g/m^2/h were utilized as the barrier. Receiver solution was 0.9% saline solution (with 5% ethanol for 72h fentanyl experiments) and the flow was set to 5 mL/h for nicotine and 0.7 mL/h for fentanyl. Immediately prior to the initiation of the experiment, TDDS was cut into a circular disc with area of 0.95 cm^2 to match the permeation area of the skin in the diffusion cell. A piece of polypropylene knitted mesh was used to cover the skin and patch to prevent the lifting of the transdermal patch disc during the experiment. A circulating water bath was used to control the temperature of the diffusion cells at either 32°C or 42°C to mimic normal physiological skin temperature and a typical heat exposure temperature, respectively. Skin temperature was monitored using an Oakton™ FEB insulated probe connected a Temp 10 Type J Thermocouple Thermometer or a Traceable® Infrared Thermometer. All samples were analyzed by HPLC.

Table 1. Characteristics of nicotine TDDS used in the study.

	Nicoderm CQ®	Aveva
Patch size (cm^2)	15.75	20.12
Rate/Area (µg/h/cm^2)	37	29
Adhesive type	Polyisobutylene	Polyacrylate/Silicone
Other inactive ingredients	Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backing	Polyester backing

Table 2. Characteristics of fentanyl TDDS used in the study.

	Duragesic®	Mylan	Apotex
Patch size (cm^2)	10.5	6.25	10.7
Fentanyl (mg)	4.2	2.55	2.76
Rate/Area (µg/h/cm^2)	2.4	4.0	2.3
Adhesive type	Polyacrylate	Silicone	Polyisobutylene
Other inactive ingredients	Polyester/ethyl vinyl acetate backing film, copovidone	Dimethicone NF, polyolefin film backing	Isopropyl myristate, octyldodecanol, polybutene, polyethylene/aluminum/polyester film backing

The influence of heat was investigated in two different ways: 1) In an extreme condition where skin was exposed to heat for entire duration of patch wear, 24h for nicotine and 72h for fentanyl 2) In a real-life relevant setting in which heat exposure was for a short duration of time, 1h for nicotine and 2h for fentanyl. In the latter case, heat exposure was introduced at two different times, according to Figure 3 for nicotine TDDS and Figure 8 for fentanyl TDDS.

Results - Nicotine

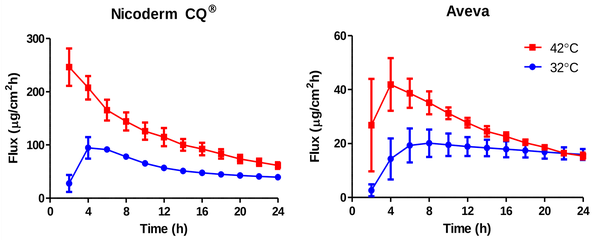

Figure 1. Flux profiles of Nicoderm CQ® (RLD) and Aveva nicotine TDDS over 24h at normal and elevated temperatures. J_{max} increased by 2.6-fold for Nicoderm CQ® and 2.1-fold for Aveva at the elevated temperature.

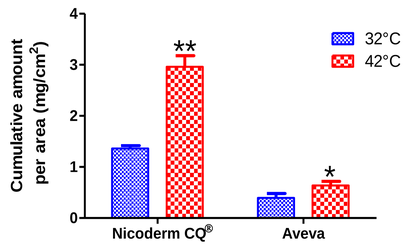

Figure 2. Cumulative amount of nicotine permeated over 24h from the RLD and generic nicotine TDDS products at normal and elevated temperatures. There were 2.2-fold and 1.6-fold increases for the RLD and generic TDDS upon heat exposure, respectively. (**p ≤0.01; *p ≤0.05)

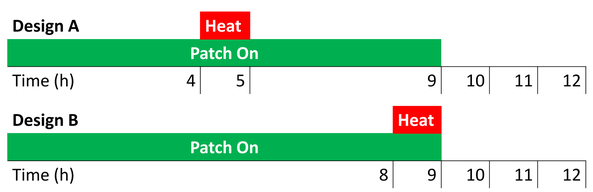

Figure 3. *In vitro* diffusion experimental Design A and B for nicotine TDDS.

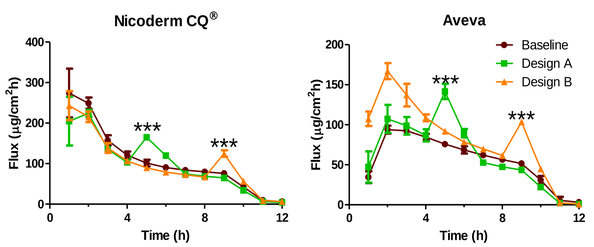

Figure 4. Flux profiles of the RLD and generic nicotine TDDS products from experimental Design A and B, compared to Baseline experiment without heat exposure. Flux during heat exposure was significantly higher compared to that of no heat exposure for both TDDS for both designs. (***p ≤0.001)

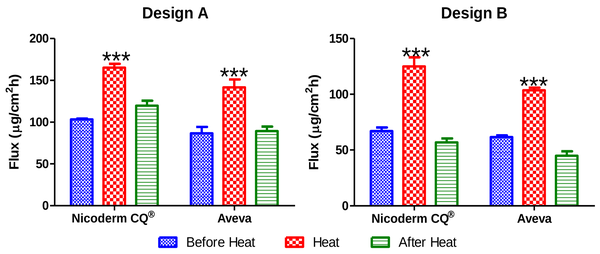

Figure 5. Flux changes upon heat exposure from experimental Design A and B. The increase of the flux during heat exposure, compared to the flux before heat exposure was significant for both the RLD and generic nicotine TDDS products for both experimental designs. (***p ≤0.001)

Results - Fentanyl

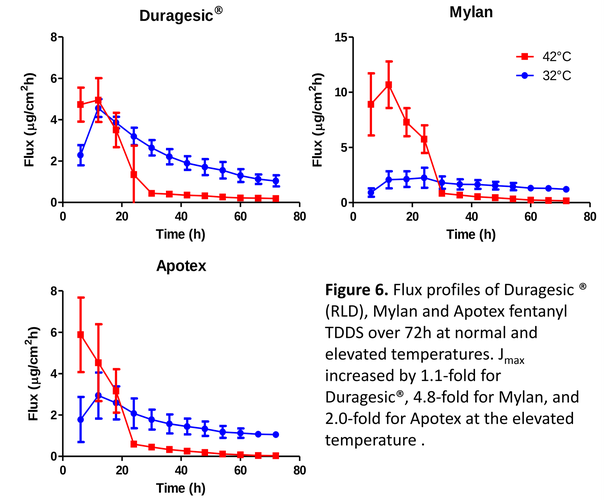

Figure 6. Flux profiles of Duragesic ® (RLD), Mylan and Apotex fentanyl TDDS over 72h at normal and elevated temperatures. J_{max} increased by 1.1-fold for Duragesic®, 4.8-fold for Mylan, and 2.0-fold for Apotex at the elevated temperature .

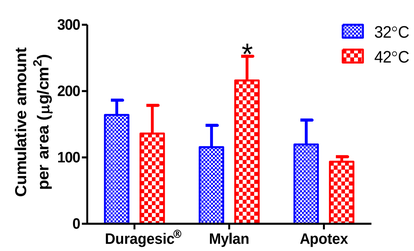

Figure 7. Cumulative amount of fentanyl permeated over 72h from the RLD and generic TDDS products at normal and elevated temperatures. Significant increase in amount of fentanyl permeated was observed in Mylan TDDS. No statistically significant difference was found in Duragesic ® and Apotex TDDS. (*p ≤0.05)

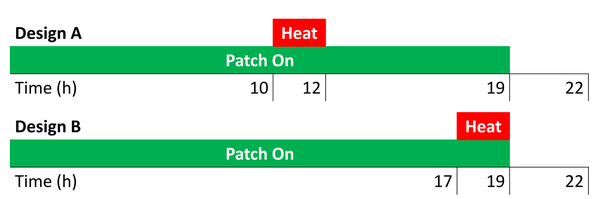

Figure 8. *In vitro* diffusion experimental Design A and B for fentanyl TDDS.

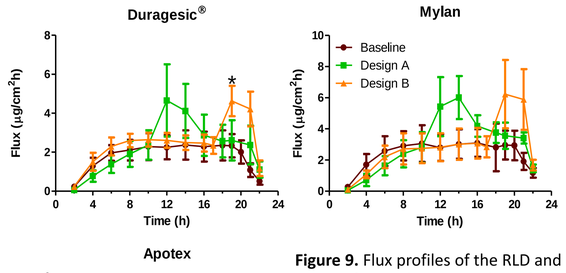

Figure 9. Flux profiles of the RLD and generic fentanyl TDDS products from experimental Design A and B, compared to Baseline experiment without heat exposure. Significant increase of flux was observed in the RLD and Apotex TDDS in experimental Design B. (*p ≤0.05; **p ≤0.01)

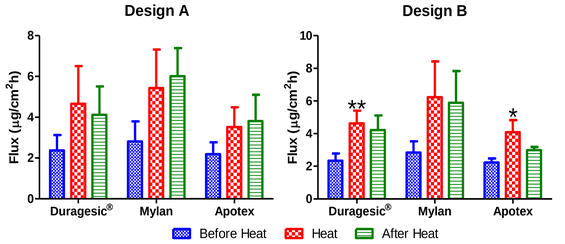

Figure 10. Flux changes upon heat exposure from experimental Design A and B. The increase of the flux during heat exposure, compared to the flux before heat exposure was significant for the RLD and Apotex fentanyl TDDS in Design B. (*p ≤0.05; **p ≤0.01)

Conclusions

The results from this study showed that different TDDS designs with varying inactive ingredients behave differently under heat exposure. For nicotine TDDS, the influence of heat was greater on the RLD product, releasing higher amounts of nicotine compared to its generic, Aveva. However, the opposite was observed for fentanyl. Mylan TDDS was affected the most among the three fentanyl TDDS products. It was also noted that the influence of heat was more significantly pronounced for nicotine products than fentanyl products in general, likely due to the rapid permeation characteristic of its API, nicotine. Furthermore, the data suggest that TDDS with a higher nominal delivery rate per area, such as Nicoderm CQ® and Mylan TDDS, might be affected to a greater extent upon exposure to heat.

The results from this study suggest that reference and generic transdermal patches can behave differently under heat exposure. Future studies are planned to evaluate these findings *in vivo* and better understand the clinical implications. However, the results from this study underscore the need for additional evaluation of risk when generic TDDS contain different inactive ingredients from their reference counterparts and indicate the importance of product labels that warn about exposing TDDS to heat.

Acknowledgment

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