Effect of Heat on Nicotine and Fentanyl Transdermal Delivery Evaluated *In Vitro* Using Different Skin/Membranes

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Introduction

At increased skin surface temperatures, it is intuitive based upon thermodynamic principles that drug molecules could be released from transdermal delivery systems (TDS) and permeate through skin or other membranes at a greater rate. However, the extent of such effects may also be modulated by multiple other factors, including the design of the TDS and its compositional formulation (i.e. excipients). In addition to characteristics of TDS, the effect of heat on TDS may vary depending on the types of membranes used to evaluate drug delivery.

The purpose of the current study was to examine the effect of heat on drug delivery, and to evaluate the influence of key variables with which the heat interacts including the drug (nicotine or fentanyl), the TDS formulation (see Table 1), and the membrane used in the study (see Table 2).

Methods

In vitro permeation test (IVPT) experiments were performed using a PermeGear® flow-through In-Line diffusion system at two different temperatures: 32 ± 1°C or 42 ± 2°C to mimic normal physiological skin temperature or a typical heat exposure temperature, respectively. A circulating water bath connected to the diffusion system was used to control the temperature of membrane and TDS. The temperature of individual diffusion cells was monitored using an infrared thermometer. The receiver solution was 0.9% saline with 0.005% gentamicin. The experiment duration was 24 h for nicotine and 72 h for fentanyl, in each case corresponding to the maximum recommended duration of wear for the selected TDS. Samples were analyzed using validated HPLC methods.

Conclusions

While the dataset is limited, the results suggest that heat effects on TDS drug delivery may be influenced by the skin or membrane, as well as by different TDS formulations. Among different membranes, no significant increase in J_{max} due to heat was observed when nicotine TDS with polyacrylate/silicone adhesive was applied on porcine skin (Fig. 4), unlike the other membranes. Also, the skin from human donor 2 (unlike donor 1) did not show a significant increase in J_{max} due to heat for fentanyl TDS with a polyacrylate adhesive (Fig. 4). Among TDS formulations, those with a polyisobutylene adhesive typically exhibited a lower J_{max} enhancement ratio when exposed to heat (Fig. 5).

These results suggest that reports of higher drug delivery from TDS are partially due to the effect of heat on TDS itself, and not just the skin, since significant increases of J_{max} are observed in absence of skin (Fig. 4). However, the results also suggest that differential heat effects with different TDS formulations (including various adhesives, enhancers and other excipients) may be partially due to the differential response of the skin barrier to the heat in the context of different formulations, and may not be predicted by studies using membranes like Tuffryn® (Fig. 5), which are typically used for *in vitro* release testing because they are expected not to be rate limiting. The Tuffryn® membrane exhibited the highest J_{max} for all TDS tested, and showed no significant difference(s) between nicotine TDS or among fentanyl TDS (Fig. 5).

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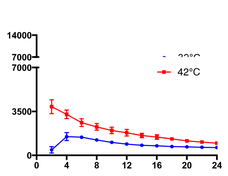
Results

Table 1. Characteristics of nicotine TDS (14mg/24h) and fentanyl TDS (25µg/h)used in the study

	(NicoDerm® CQ®)	(Aveva)	(Duragesic®)	(Apotex)	(Mylan)
	Nicotine	Nicotine	Fentanyl	Fentanyl	Fentanyl
Drug Content (mg)	Not available	Not available	4.20	2.76	2.55
Patch size (cm^2)	15.75	20.12	10.50	10.70	6.25
Rate/Area (µg/h/cm^2)	37	29	2.4	2.3	4.0
Adhesive	Polyisobutylene	Polyacrylate/ Silicone	Polyacrylate	Polyisobutylene	Silicone
Other Inactive Ingredients	Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backings	Polyester backing	Polyester/ethyl vinyl acetate backing film, copovidone	Isopropyl myristate, octyldodecanol, polybutene, polyethylene/ aluminum/ polyester film backing	Dimethicone NF, polyolefin film backing

Table 2. Membrane barriers used in the study

	Porcine Skin (Yucatan miniature)	Human Skin	EVA - 9	Tuffryn®
Thickness (µm) Range	250 ± 50 (Dermatomed)	240 ± 60 (Dermatomed)	50.8	145
TEWL ($g/m^2/h$) Mean ± S.D.	7.69 ± 1.80	Donor 1: 4.19 ± 2.07 Donor 2: 3.68 ± 1.89	-	-
Pore Size (µm)	-	-	Non-porous	0.45
Membrane Medium	Mostly epidermis with a thin layer of dermis		Ethylene Vinyl Acetate (9%)	Hydrophilic polysulfone
Anatomical Site	Dorsal & Ventral	Abdominal	-	-



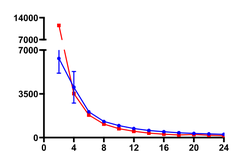


Figure 1. Flux profiles (corrected for TDS size) of two nicotine TDS at two different temperatures on various membranes. (Mean ± SD; 3-4 replicates)

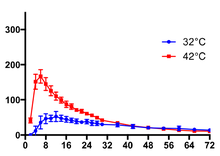


Figure 2. Flux profiles (corrected for TDS size) of three fentanyl TDS at two different temperatures on various membranes. (Mean ± SD; 3-4 replicates)

Figure 3. Comparisons of various membranes for nicotine (top two rows) and fentanyl (bottom two rows) delivery from TDS at two different temperatures.

Figure 4. J_{max} enhancement due to heat on various membranes for two nicotine (top) and three fentanyl (bottom) TDS.

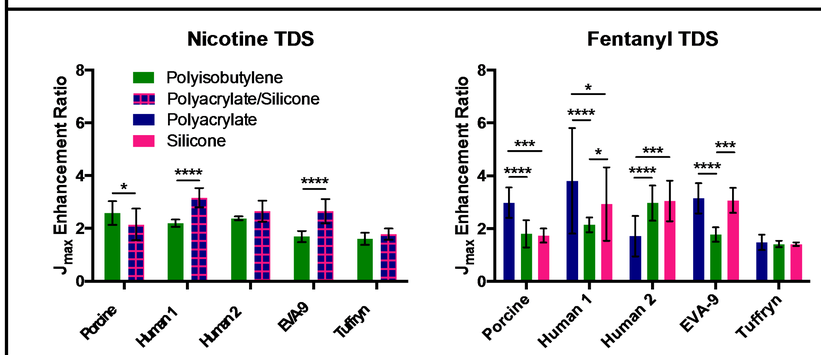


Figure 5. J_{max} enhancement ratio due to increased temperature across five membranes for two nicotine and three fentanyl TDS.