In Vitro/In Vivo Correlation (IVIVC) of Bioavailability from Nicotine Transdermal Drug Delivery Systems under the Influence of Heat

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Introduction

The influence of heat on drug release and absorption from transdermal delivery systems (TDS) has been of significant interest because there are many possible sources of heat one can encounter while wearing TDS such as heating pads, saunas, hot tubs, sunbathing and prolonged activity in direct sunlight.

Today, various TDS products (reference listed drugs and generics) of many different drug classes are available on the market. All of these products are designed and formulated differently with unique inactive ingredients and hence may behave differently under the influence of heat. The purpose of the current study was to compare the effect of heat on two nicotine TDS with the same intended dose delivery (14 mg/day) but with different formulations. *In vitro* permeation tests (IVPT) and *in vivo* human pharmacokinetic studies under the matched study designs and conditions of heat exposure (illustrated in Figure 1) were performed to evaluate *in vitro/in vivo* correlations (IVIVC).

Methods

In Vitro Studies

IVPT experiments using two nicotine TDS (Table 1) were performed for three different designs on the same donor: no heat exposure or 1h heat exposure after either 4h or 8h of patch application. The TDS was removed after 9h for all designs, although sampling in the IVPT study continued until 12h. A PermeGear® flow-through In-line diffusion system was used with dermatomed *ex vivo* human skin with a thickness of 240 ± 60 µm. The receiver solution was 0.9% saline solution with a flow rate of ~5 mL/h. A circulating water bath was used to control the temperature of the diffusion cells at either 32 ± 1°C or 42 ± 2°C to mimic normal physiological skin temperature or a typical heat exposure temperature, respectively. Skin temperature was monitored using a traceable® infrared thermometer. After a TDS was removed, the residual amount of nicotine remaining in the TDS was analyzed by extracting the TDS in ethyl acetate. All *in vitro* samples were analyzed using a validated HPLC method.

Table 1. Characteristics of nicotine TDS used in the study

	Product A	Product B
Patch size (cm^2)	15.75	20.12
Rate/Area (µg/h/cm^2)	37	29
Inactive Ingredients	Ethylene vinyl acetate-copolymer, polyisobutylene and high density polyethylene between pigmented and clear polyester backings	Acrylate adhesive, polyester, silicone adhesive

In Vivo Clinical Pharmacokinetic Studies

An open-label, four-way crossover clinical study using two nicotine TDS (Table 1) was performed with 10 adult smokers. Heat was applied using a theratherm® heating pad for 1h either 4h or 8h post TDS application, with the target skin temperature of 42 ± 2°C. The skin temperature was monitored using an Oakton™ FEB probe connected to a Temp 10 Type J thermocouple thermometer. Blood samples were drawn at pre-determined time points throughout the study on each visit. Serum samples were analyzed to determine nicotine and cotinine (shown in companion poster W5222) using a validated LC-MS/MS method. The residual amount of nicotine in the TDS was analyzed by HPLC once the TDS was removed from a study subject.

Prediction of Nicotine Concentrations In Vivo from IVPT Data

The flux values obtained from IVPT at each time point were used as the input rate to predict nicotine concentrations *in vivo* assuming the drug elimination followed first-order kinetics. The equations used for prediction while the TDS was worn and after the TDS removal are $C_p = (R_{input}/CL) * (1\text{-}e^{-kt})$ and $C_p = C_0 * e^{-kt}$, respectively.

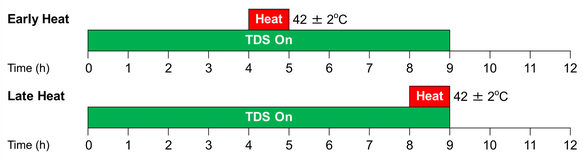

Figure 1. Schematic diagram representing the duration of the study, duration of TDS application and when early and late standardized heat was applied.

Results

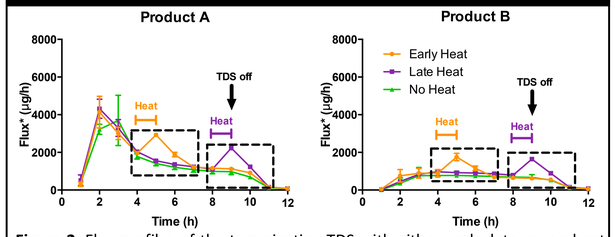

Figure 2. Flux profiles of the two nicotine TDS with either early, late, or no heat exposure. The partial AUCs during and after heat (3h; in square dotted boxes) were significantly higher ($p < 0.05$) compared to the 3h AUCs without heat treatment. The partial AUCs (3h) of the two nicotine TDS were significantly ($p < 0.05$) different, for both Early and Late Heat designs. *Flux values corrected for TDS size. (Mean ± SE from 4 donors for Early and Late Heat designs and 2 donors for No Heat design with n=4 replicates per donor)

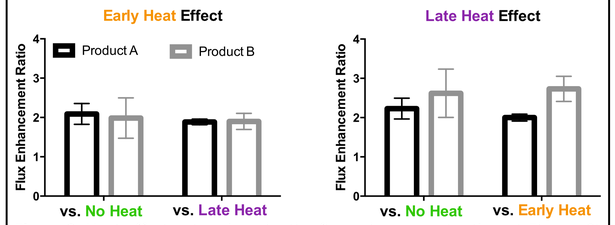

Figure 3. Heat effect determined by the flux enhancement ratios, at 5h and 9h for Early and Late Heat designs, respectively. The enhanced flux values were compared to values obtained from the other two study designs. No significant differences ($p > 0.05$) were found between the two nicotine TDS for both Early Heat and Late Heat effects. (Mean ± SE from 4 donors for Early and Late Heat designs and 2 donors for No Heat design with n=4 replicates per donor)

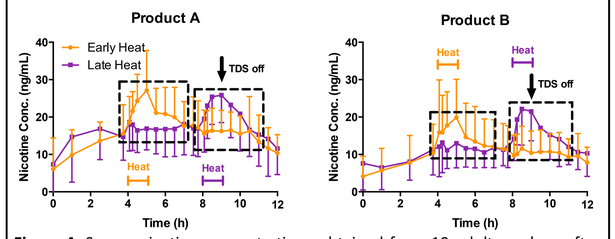

Figure 4. Serum nicotine concentrations obtained from 10 adult smokers after applying the two nicotine TDS with 1h of either early or late heat exposure. The partial AUCs during and after heat (3h; in square dotted boxes) were significantly higher ($p < 0.05$) compared to the 3h AUCs without heat treatment, except for Early Heat design for Product B. The partial AUCs (3h) of the two nicotine TDS were significantly ($p < 0.05$) different for Early Heat design. (Mean ± SD)

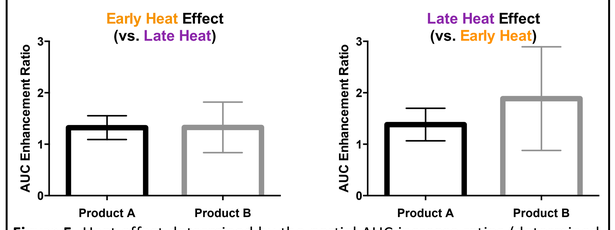

Figure 5. Heat effect determined by the partial AUC increase ratios (determined by the partial AUCs from the orange and purple curves on Fig. 4) during heat (4 to 7h for Early Heat and 8 to 11h for Late Heat). No significant differences ($p > 0.05$) were found between the two nicotine TDS products for both Early Heat and Late Heat effects. (Mean ± SD)

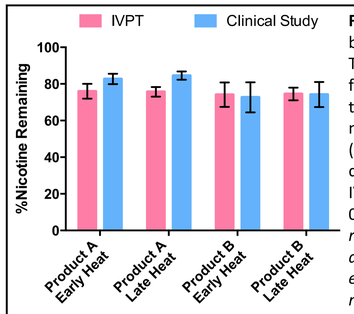

Figure 6. Residual TDS analysis from both *in vitro* and *in vivo* studies. The amount of nicotine extracted from TDS after 9h was compared to the amount extracted from the new, unused TDS from the same lot (data not shown). No significant differences were found between IVPT and clinical study results ($p > 0.05$). *No significant differences in residual amounts were found among Early, Late, and No Heat exposures from IVPT studies (data not shown).*

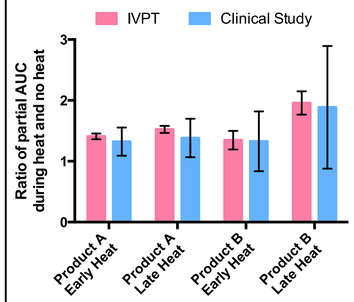

Figure 7. IVIVC of heat-induced increases in drug delivery from nicotine TDS, determined by the ratio of AUC during heat (3h) and AUC during no heat (3h) from the same donor/ subject. No significant differences were found between IVPT and clinical study results ($p > 0.05$).

Table 2. Estimation of steady-state concentration (C_{ss}) *in vivo* from IVPT results. IVPT result correctly estimated clinical C_{ss} without a significant difference for both nicotine TDS.

	Observed C_{ss}[a] *in vivo* (ng/mL)	Estimated C_{ss}[b] from IVPT (ng/mL)	p-value (unpaired t-test)
Product A	15.86 ± 7.13	18.82 ± 1.02	0.4359
Product B	10.54 ± 4.77	12.59 ± 1.12	0.4237

a. C_{ss} values obtained from serum concentration at 6h

b. C_{ss} values estimated by using flux values at 6h from IVPT data and the following equations below.
R_{in} (ng/h) = J (ng/cm^2/h) x Area (cm^2)
$R_{in} = CL \times C_{ss}$
CL = total clearance of nicotine (72000 mL/h)[1]

1. Hukkanen J, Jacob P III, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005c;57(1):79-115.

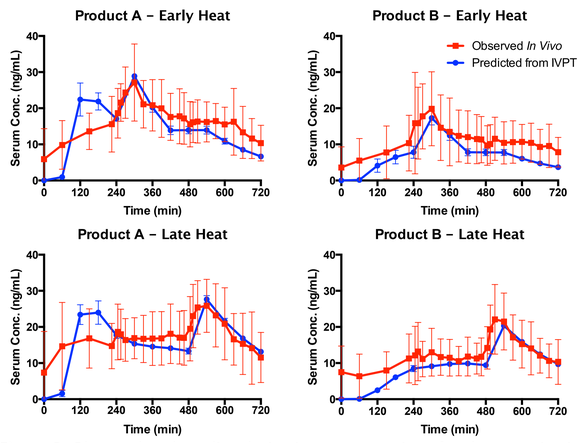

Figure 8. Observed and predicted nicotine concentrations for the two nicotine TDS products.

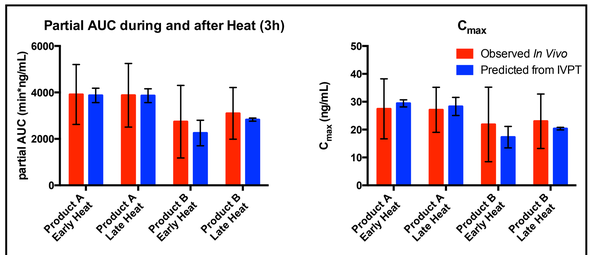

Figure 9. Observed and predicted partial AUC during and after heat (3h) and C_{max} for the two nicotine TDS products. No significant differences were found between the observed and predicted values ($p > 0.05$).

Table 3. The mean ratios between the observed and predicted partial AUC during and after heat (3h) and C_{max} for the two nicotine TDS products. The ratios are within the range of 0.80 - 1.25, except for Product A – Early Heat (C_{max}).

	Product A – Early Heat	Product A – Late Heat	Product B – Early Heat	Product B – Late Heat
Partial AUC	1.010	1.005	1.216	1.095
C_{max}	0.933	0.957	1.263	1.130

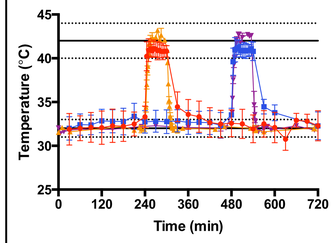

Figure 10. Mean ± SD skin surface temperature throughout the entire study periods from both *in vitro* and *in vivo* studies.

Conclusions

While both of the two nicotine TDS products exhibited a significant heat effect, the observed heat effect on the two differently formulated nicotine TDS was not significantly different. In addition, no significant difference was found between early and late heat exposure in the same TDS. Such results were seen consistently from both *in vitro* and *in vivo* studies. Furthermore, analysis of residual drug remaining in TDS after *in vitro* and *in vivo* studies resulted in comparable residual amounts suggesting that residual drug content in TDS may be a potential surrogate measure of the extent of drug delivery and/or absorption. Additional experiments are required to verify the potential and usefulness of a TDS residual drug analysis approach.

The present study demonstrated a strong IVIVC between IVPT and clinical human PK studies under the matched study conditions and designs, with an external factor of transient heat exposure. In addition, the IVPT data was able to predict the *in vivo* performance of TDS (partial AUC during and after heat and C_{max}) within a reasonable range despite different subject/donor populations. The results indicate that IVPT studies may be of value when evaluating the potential response of TDS to the influence of heat *in vivo*.

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