Evaluation of Bioavailability and In Vitro/In Vivo Correlation of Nicotine Transdermal Drug Delivery Systems Under the Influence of Heat

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Introduction

Drug release and absorption from transdermal delivery systems (TDS) can be affected by multiple factors, from physiological and pathological factors to physiochemical properties of drug/drug products and environmental factors. Among these factors, effect of heat on drug release and absorption from TDS has been of significant interest following multiple life-threatening incidents involving fentanyl patches exposed to elevated temperature. In fact, there are many possible exposures to elevated temperature while wearing TDS since most of these products are for a relatively long duration of use. Possible sources of heat in commonplace include heating pads, saunas, hot tubs, sunbathing and prolonged activity under direct sunlight.

Today, TDS represent a considerable size of drug market and consequently, various products (reference listed drug and generics) are available with different compositions and formulations. The purpose of the current study was to compare the effect of heat on drug delivery from two nicotine TDS, NicoDerm CQ® and Aveva, with the same intended dose delivery (14 mg/day) but with different formulations. Both *in vitro* permeation tests (IVPT) and *in vivo* human pharmacokinetic studies with matched designs and conditions of exposure to heat were performed and *in vitro/ in vivo* correlation was evaluated.

Methods

In Vitro Studies

A six-way crossover *in vitro* study using two nicotine TDS (Table 1) was performed: no heat exposure and 1h heat exposure after either 4h or 8h of patch application. TDS was removed after 9h for all designs, with IVPT 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 with a flow rate of ~5 mL/h. Immediately prior to the initiation of the experiment, nicotine TDS were cut into circular discs 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 TDS to prevent the lifting of the TDS disc during the experiment. 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 and a typical heat exposure temperature, respectively. Skin temperature was monitored using a traceable® infrared thermometer. After TDS was removed from skin surface, 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

	NicoDerm CQ®	Aveva
TDS 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. At least a one-week washout period separated each study visit. Heat was applied using a Theratherm® heating pad for 1h either 4h or 8h post TDS application, with a target skin temperature of 42 ± 2°C. The skin temperature was monitored using an Oakton™ FEB insulated 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 concentrations using a validated LC-MS/MS method. The residual amount of nicotine remaining in the TDS was determined after TDS was removed from each subject utilizing the same method used for *in vitro* study.

Data Analysis

A non-compartmental analysis was performed using a Phoenix® WinNonlin® software (Pharsight Corporation, San Diego, California). Analysis of variance (ANOVA) followed by an appropriate post-hoc test for multiple pair comparisons or t-test to compare PK parameters and residual amount of nicotine in the TDS from the four treatment days.

Results

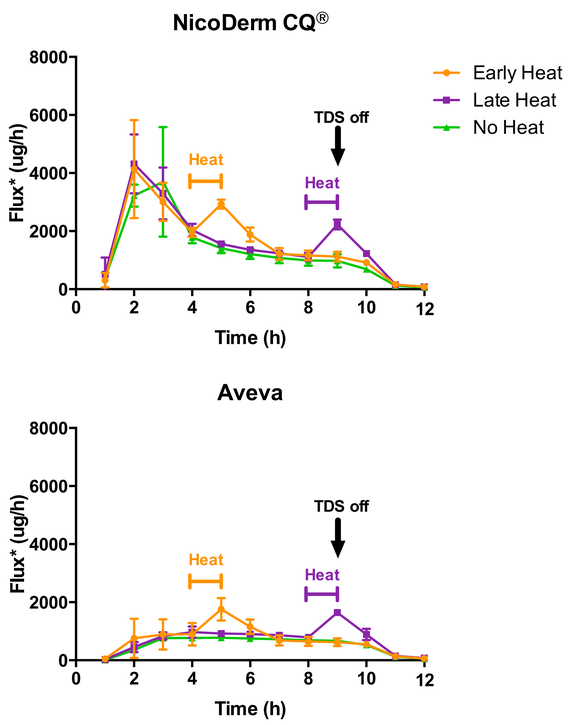

Figure 1. Flux profiles of a) NicoDerm CQ® and b) Aveva nicotine TDS with either early, late, or no heat exposure. TDS was removed after 9 hours for all of the study designs. *Flux values were corrected for patch size. (Mean ± SD from 4 donors with n=4 skin sections per donor)

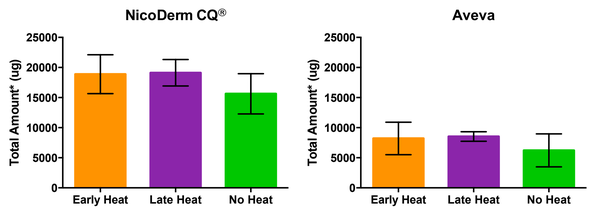

Figure 2. Total amount of nicotine permeated through *ex vivo* human skin over 12h with either early, late, or no heat exposure. No significant difference ($p > 0.05$) was found within the three treatment groups for both nicotine TDS. There were significant differences ($p < 0.05$) of total amounts of nicotine permeated between NicoDerm CQ® and Aveva TDS in all of the three treatment groups. *Values were corrected for TDS size. (Mean ± SD from 4 donors with n=4 skin sections per donor)

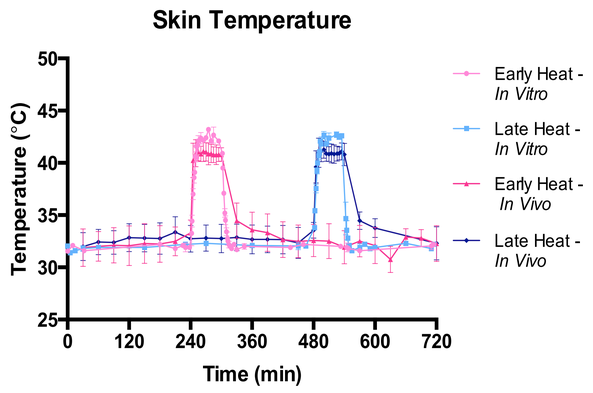

Figure 3. Mean ± SD skin surface temperature throughout the entire study periods from both *in vitro* and *in vivo* studies. Values were obtained from 4 donors with 4 replicates per donor for *in vitro* and 10 human subjects for *in vivo*.

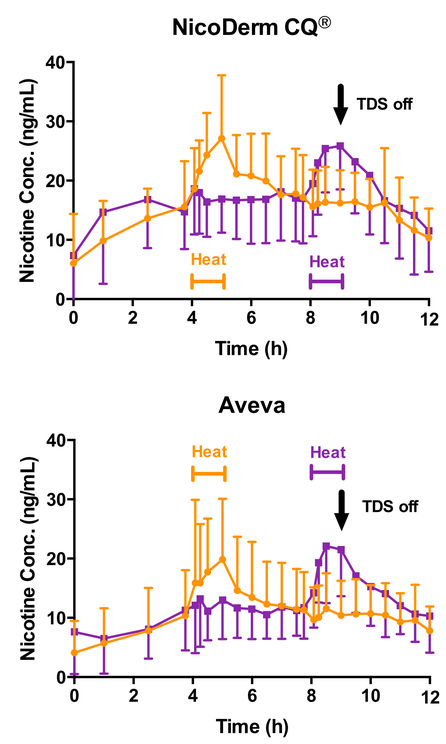

Figure 4. Serum nicotine concentrations obtained from 10 adult smokers after applying NicoDerm CQ® or Aveva nicotine TDS with 1h of either early or late heat exposure. TDS was removed after 9 hours for every study design. (Mean ± SD from 10 human subjects)

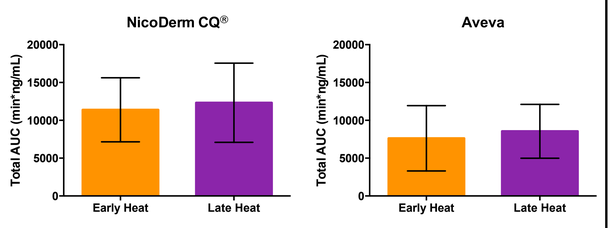

Figure 5. Total AUC from clinical study serum sample analysis for both nicotine TDS. No statistical difference ($p > 0.05$) was found between early and late heat treatments for both TDS, whereas the total AUC from the two TDS showed a significant difference ($p < 0.05$) (Mean ± SD from 10 human subjects)

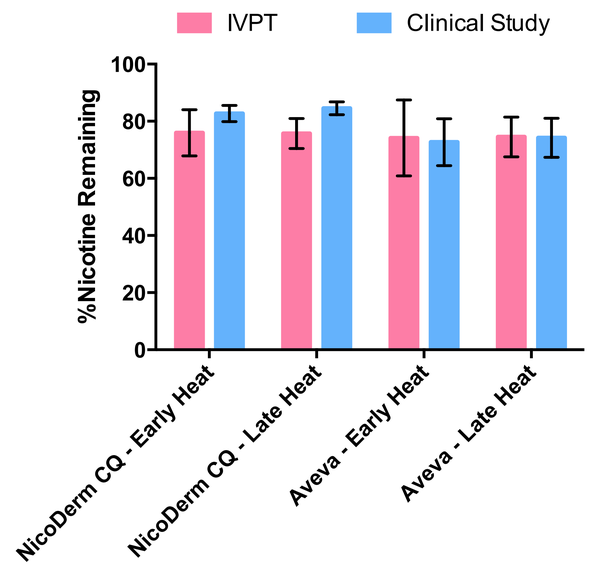

Figure 6. Residual TDS analysis from both *in vitro* and *in vivo* studies. The amount of nicotine extracted from the TDS after 9h was compared to the amount extracted from the new, unused TDS from the same lot (data not shown). No significant differences were found between IVPT and clinical study results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

R_{in} (ng/hr) = J (ng/cm^2/hr) x Area (cm^2)
R_{in} = CL x C_{ss}
CL = total clearance of nicotine (72000 mL/h)[1]

NicoDerm CQ®

Mean flux at 6h: 0.08602 ± 0.00538 µg/cm^2/h
Estimated C_{ss} = (0.08602 ng/cm^2/h)*(15.75 cm^2)/(72000 mL/h)
= **18.81 ± 1.18** ng/mL
C_{ss} from Clinical Study = **15.86 ± 7.13** ng/mL

Aveva

Mean flux at 6h: 0.04506 ± 0.00463 µg/cm^2/h
Estimated C_{ss} = (0.04506 ng/cm^2/h)*(20.12 cm^2)/(72000 mL/h)
= **12.59 ± 1.29** ng/mL
C_{ss} from Clinical Study = **10.54 ± 4.77** ng/mL

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

Figure 7. 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. ($p > 0.05$).

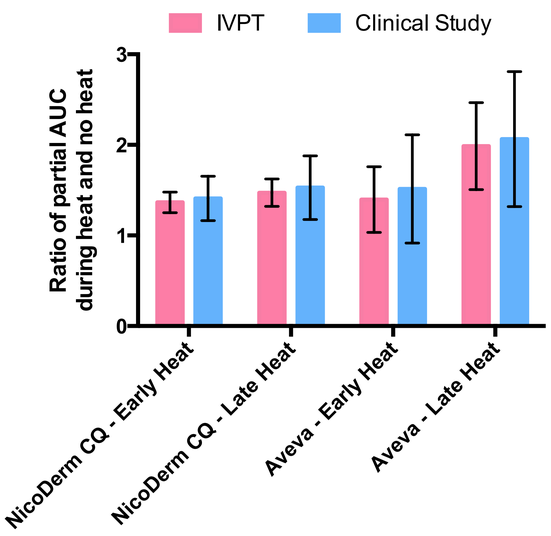

Figure 8. IVIVC of heat-induced increase in drug delivery from nicotine TDS, determined by the ratio of AUC during heat (1h) and AUC during no heat from the same donor/subject. No significant differences were found between IVPT and clinical study results ($p > 0.05$).

Conclusions

The total amounts of nicotine permeated through human skin *in vitro* were significantly different between the two nicotine TDS for both early and late heat exposure conditions (Fig. 2). Likewise, the difference was also found from the clinical *in vivo* study, evaluated by the total AUC values. However, no significant difference was found between early and late heat exposure in the same TDS. Such results were seen consistently for both *in vitro* and *in vivo studies*. Furthermore, analysis of residual 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.

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 temporary heat exposure. Such correlations existed for the entire duration of study for all of the four treatment groups, as well as for the heat-induced increase of nicotine delivery from TDS. The results indicate that IVPT can be a powerful tool in assessing and/or predicting the behaviors of comparative transdermal drug delivery systems *in vivo*, even under the influence of external factors such as heat.

Acknowledgments

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