Developing In Vitro-In Vivo Correlations (IVIVCs) for In Vitro Permeation Test and In Vivo Pharmacokinetic Studies to Evaluate the Effects of Heat on Nicotine Transdermal Delivery Systems

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Introduction

The clinical safety and efficacy of Transdermal Delivery Systems (TDS) may be altered by their exposure to heat. In Vitro Permeation Tests (IVPT) have been widely used for evaluating the rate and extent of bioavailability of drugs from topical and transdermal formulations. In this study, the results of two separate IVPT studies and one in vivo pharmacokinetic (PK) study (all performed under harmonized study conditions at three test facilities by two independent research groups) were used to establish in vitro - in vivo correlations (IVIVCs). The IVIVC models were used to predict the effect of transient exposures to an elevated temperature on the in vivo bioavailability of nicotine from two different nicotine TDS.

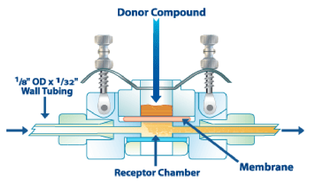
Methods

Two matrix-type nicotine TDS (Nicoderm CQ® and Aveva) were investigated in two separate IVPT studies with excised human skin, and in one PK study with 10 healthy human subjects. Studies were performed with 1 h of transient heat (42 ± 2°C at the skin surface) at both early and late times during the period of wear, and compared to a baseline temperature (32 ± 1°C).

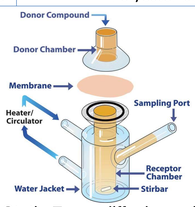
In the first IVPT study design (n=4 donors, 4 replicates/donor) at the University of Maryland (UMB), a flow-through In-Line diffusion cell system with an automated fraction collector was used; heat was applied by increasing the temperature of water circulating in the jackets surrounding the diffusion cell. The second IVPT study design (n=4 donors, 3 replicates/donor) at the University of Cincinnati (UC), used static Franz diffusion cells and a manual sampling technique; heat was applied using an infrared heat lamp. In the in vivo study at UMB, a pre-heated heating pad was applied on the TDS to increase the skin temperature during the same time periods, in a manner similar to what was done in both IVPT study designs.

IVPT samples were analyzed using a validated HPLC method and serum samples from the in vivo study were analyzed using a validated LC-MS/MS method. All data are expressed as mean ± SD.

Nicotine TDDS 14 mg/24h	Patch size (cm^2)	Rate/Area ($\mu g/h/cm^2$)	Adhesive type	Other inactive ingredients
Nicoderm CQ®	15.75	37	Polyisobutylene	Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backing
Aveva	20	29	Polyacrylate/Silicone	Polyester backing

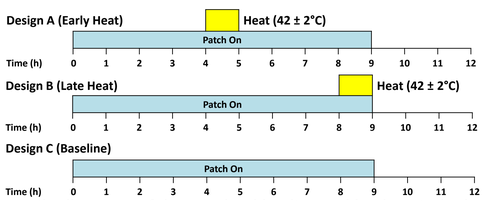


Flow-through In-Line diffusion cell system



Static Franz diffusion cells

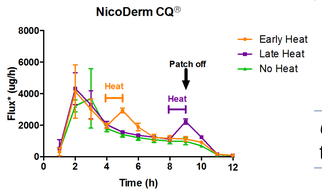
Diffusion cell images from PermeGear: www.permegear.com



Schematic diagrams of harmonized in vitro and in vivo study designs

Level A IVIVC: Approach I

IVPT flux profile (shown in figure below), PK-based mathematical equations and in vitro heat effect coefficient (H_i) were used to predict in vivo concentrations.



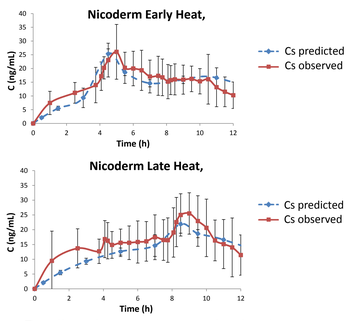
$$C_s = \frac{R_{in} \cdot H_i}{CL} \cdot (1 - e^{-kt})$$

$C_s = C_0 \cdot e^{-kt}$ is used for the duration that the TDS was removed (9-12h)

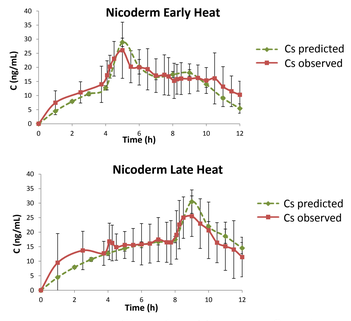
In Vitro Heat Factor (H_i) = $\frac{Jmax\ Reached\ due\ to\ increased\ temprature}{Corresponding\ baseline\ J}$

C_s: Predicted in vivo serum concentration
R_{in}: Rate of input (mean flux during steady-state from IVPT experiments)
CL: Population-based total body clearance [72 L/h]
k: Elimination rate constant [0.2475 $^{-}$h]
t: Time after application of TDS/ removal of TDS
C_0: Initial concentration after TDS removal

UC



UMB



Predicted vs. observed nicotine serum concentration profiles for Nicoderm® using **Approach I**. Similar results were observed for Aveva (graphs not shown).

Level C IVIVC

$$C_{ss} = J_{ss} \times A / CL$$

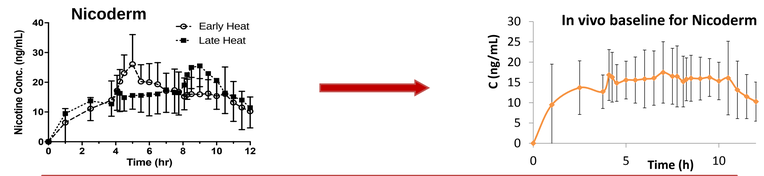
C_{ss}: Predicted in vivo serum concentration at steady state
J_{ss}: In vitro flux at steady state
A: Area of the TDS
CL: Population total body clearance [72 L/h]

UMB	Observed C_{ss} *in vivo* (ng/mL)	Estimated C_{ss} from IVPT late heat (ng/mL)	Estimated C_{ss} from baseline IVPT (ng/mL)
Nicoderm	17.46 ± 7.58	17.15± 1.43	14.95± 2.54
Aveva	11.16 ± 5.21	12.00 ± 1.34	10.05 ± 3.44

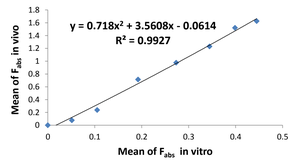
UC	Observed C_{ss} *in vivo* (ng/mL)	Estimated C_{ss} from IVPT late heat (ng/mL)	Estimated C_{ss} from baseline IVPT (ng/mL)
Nicoderm	17.46 ± 7.58	14.69 ± 1.52	17.37 ± 2.35
Aveva	11.16 ± 5.21	8.95 ± 1.64	11.88 ± 1.13

Level A IVIVC: Approach II

1. Reconstruct in vivo baseline (without heat)



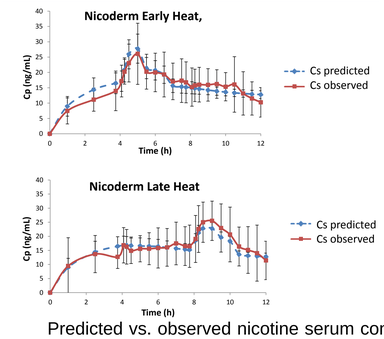
2. Deconvolute the in vivo baseline PK and construct IVIVC model



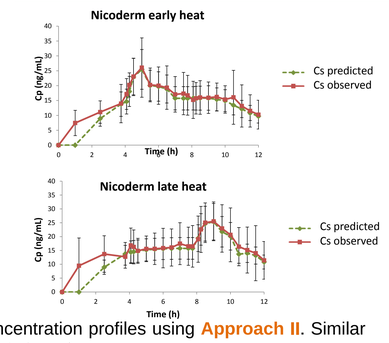
3. Convolute the predicted in vivo fraction absorbed data and apply the in vivo heat effect coefficient (H_{ii}) to the predicted in vivo profile

In Vivo Heat Factor (H_{ii}) = $\frac{Cmax\ Reached\ due\ to\ increased\ temperature}{Corresponding\ baseline\ C}$

UC



UMB



Predicted vs. observed nicotine serum concentration profiles using **Approach II**. Similar results were observed for Aveva (graphs not shown).

$$\%\ \boldsymbol{Prediction\ Error\ (PE)} = \frac{Observed\ value - Predicted\ value}{Observed\ value} \times 100$$

Conventionally, acceptable % PE for each formulation should not exceed 15%.

UMB	Point Estimate	Nicoderm – Early Heat	Nicoderm – Late Heat	Aveva – Early Heat	Aveva – Late Heat
Approach I	Total AUC	7.0	3.3	12.4	1.7
	C_{max}	7.6	18.3	10.6	0.1
Approach II	Total AUC	10.6	13.1	12.4	8.1
	C_{max}	6.6	5.6	16.9	1.5

UC	Point Estimate	Nicoderm – Early Heat	Nicoderm – Late Heat	Aveva – Early Heat	Aveva – Late Heat
Approach I	Total AUC	4.6	16.2	3.7	17.6
	C_{max}	18.4	5.2	17.1	36.0
Approach II	Total AUC	3.4	11.5	15.5	12.0
	C_{max}	3.3	11.5	23.5	12.0

Conclusions

There have been relatively few reports which demonstrated Level A IVIVCs for transdermal drug products. The results described here demonstrate two Level A IVIVCs, for each of the two nicotine TDS, each under normal temperature and elevated skin surface temperature conditions. A novel aspect of this work is that it additionally provides a corroboration of the results between two independent research groups. Despite technical and procedural differences between the in vitro (IVPT) study protocols at UMB and UC, key parameters for both of the in vitro study designs were harmonized with corresponding parameters for the in vivo study. Qualitatively, the predicted PK profiles using either in vitro dataset (UC or UMB) were similar to the observed results in vivo, for both products. Quantitatively, the prediction errors using either in vitro dataset (UC or UMB) were typically less than 15%, or slightly higher, with only two exceptions. This work, therefore, suggests that IVPT study results can correlate with and be predictive of in vivo bioavailability for the nicotine TDS products evaluated here.

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