Level A In Vitro/In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure, Evaluated using Multiple Approaches

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Purpose

An in vitro model that exhibits IVIVC is a powerful tool in biopharmaceutical drug development because it can efficiently predict drug product performance *in vivo*. While the concept of IVIVC has been utilized most often for oral dosage forms, demonstrations of IVIVC with in vitro models used for other dosage forms are emerging. The present investigation used multiple approaches to develop a Level A IVIVC for Transdermal Delivery Systems (TDS). Additionally, the effect of transient heat exposure on the rate and extent of TDS drug delivery was concurrently evaluated. Two model drug molecules, nicotine and fentanyl, with different physicochemical characteristics (e.g. log P) were evaluated in the current study.

Methods

In Vitro and In Vivo Studies

In vitro permeation tests (IVPT) using dermatomed ex vivo human skin and in vivo pharmacokinetic (PK) studies in healthy subjects were performed under harmonized study designs, including harmonized conditions of transient exposure to elevated temperatures for two nicotine TDS, 14mg/24h (NicoDerm CQ® and Aveva) and three fentanyl TDS, 25µg/h (Duragesic®, Apotex and Mylan). The TDS were exposed to one hour (h) of transient heat (target skin temperature of 42 ± 2°C) at either 4 h (early) or 8 h (late) for nicotine TDS and at 11 h (early) or 18 h (late) for fentanyl TDS. Temperature was monitored using an infrared thermometer in vitro and a temperature probe in vivo.

IVIVC

Approach I: IVPT data, PK-based mathematical equations and in vitro heat effect coefficient (H_i) were used to predict in vivo concentrations.

- Eq. 1 Prediction while TDS was worn:

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

- Eq. 2 Prediction after TDS removal:

$$C_s = C_0 \cdot e^{-kt}$$

C_s: Predicted in vivo serum concentration
R_{in}: Rate of input (mean flux during steady-state in IVPT experiments)
H_i : In vitro heat effect coefficient (composite heat effect during and after heat exposure); ratio of flux value and R_{in} until H_i becomes 1 or less
CL: Population total body clearance obtained from literature[1,2]
k: Elimination constant obtained from literature[2,3]
t: Time after administration of TDS for Eq.1 and time after removal of TDS for Eq. 2
C_0: Initial concentration after TDS removal

Approach II and III:

1. Reconstruct of baseline (without heat) profile by combining non-heat portion of profiles from two study designs (Fig. 1)
2. Deconvolute in vivo baseline PK data using the Wagner-Nelson method and PK parameters obtained from literature
3. Construct IVIVC model by plotting fraction permeated in vitro vs. fraction absorbed in vivo
4. Predict in vivo fraction absorbed using the IVVIC model and IVPT data
5. Convolute the predicted in vivo fraction absorbed data
6. Apply H_i (**Approach II**) or in vivo heat effect coefficient (H_{ii}) (**Approach III**) to the predicted in vivo profile

Table 1. Characteristics of nicotine and fentanyl TDS used in the study

	Drug Load (mg)	Size (cm²)	Adhesive	Other Inactive Ingredients
Nicotine TDS (14 mg/24 h)				
NicoDerm CQ®	Unknown	15.75	PIB	Ethylene vinyl acetate-copolymer, polyester backings
Aveva	Unknown	20.12	Acrylate/ Silicone	Polyester
Fentanyl TDS (25 µg/h)				
Duragesic®	4.20	10.50	Acrylate	Polyester/ ethyl vinyl acetate backing film, copovidone
Apotex	2.76	10.70	PIB	Isopropoyl myristate, octyldodecanol, polybutene, polyethylene/ aluminum/ polyester film backing
Mylan	2.55	6.25	Silicone	Dimethicone NF, polyolefin film backing

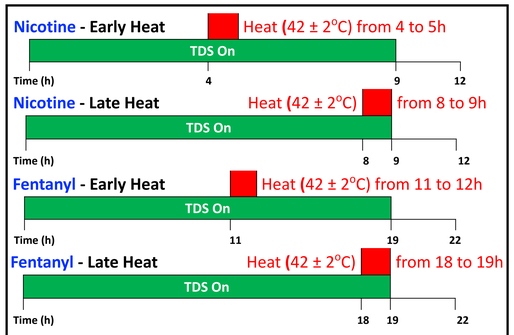

Fig 1. Schematic diagrams (not to scale) of study designs.

Results

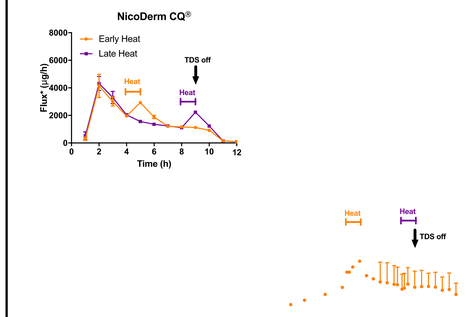

Fig 2. In vitro flux profiles (top) and in vivo serum concentrations (bottom) of nicotine with either early or late heat exposure.
(In vitro data: Mean ± SEM from 4 donors with n=4 replicates per donor; In vivo data: Mean ± SD, n=10 subjects)

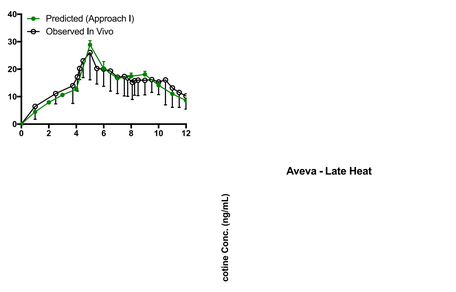

Fig 3. Predicted vs. observed nicotine profiles using Approach I.

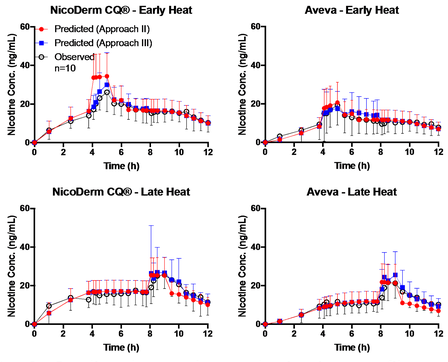

Fig 4. Predicted vs. observed nicotine profiles using Approach II and III.

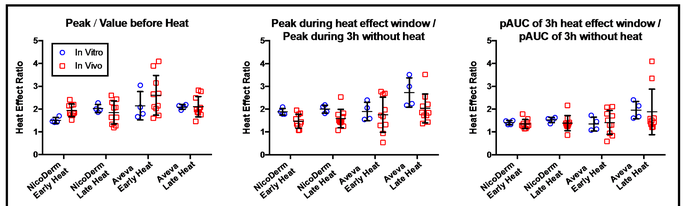

Fig 5. Comparisons of in vitro and in vivo heat effects from nicotine studies. Heat effect window was defined as 4-7 h for early heat and 8-11 h for late heat. No statistically significant difference ($p > 0.05$) was found between in vitro and in vivo heat effects.

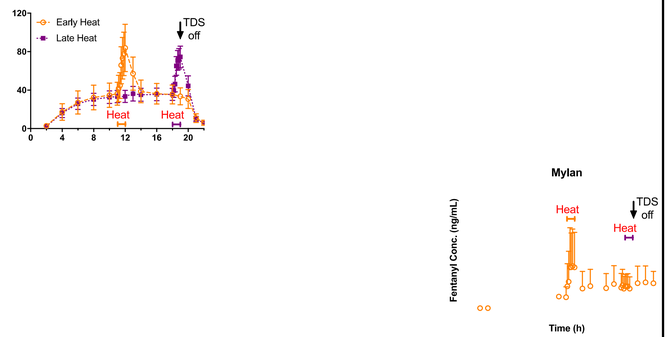

Fig 6. In vitro flux profiles (top) and in vivo serum concentrations (bottom) of fentanyl with either early or late heat exposure.
(In vitro data: Mean ± SEM from 4 donors with n=4 replicates per donor; In vivo data: Mean ± SD, n=8 subjects)

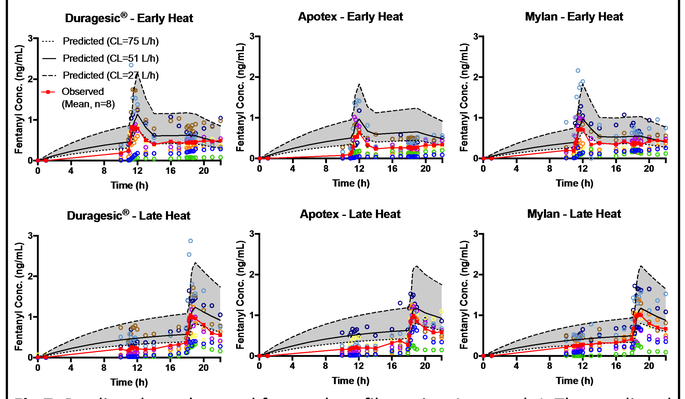

Fig 7. Predicted vs. observed fentanyl profiles using Approach I. The predicted profiles were obtained by using three CL values[2], with grey shaded area representing the range of prediction. A high inter-subject variability was observed (individual data points are shown in colored open circles).

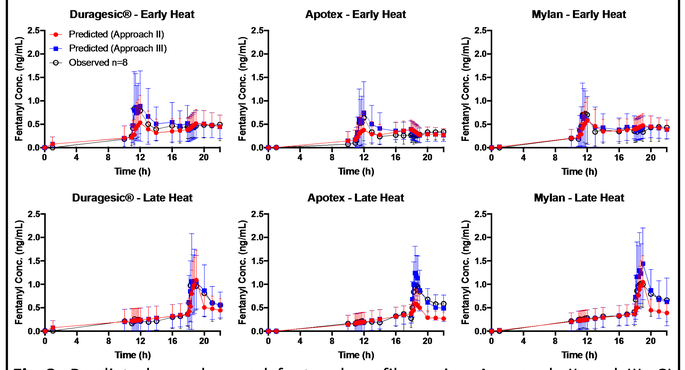

Fig 8. Predicted vs. observed fentanyl profiles using Approach II and III. CL value of 51 L/h was used for prediction.

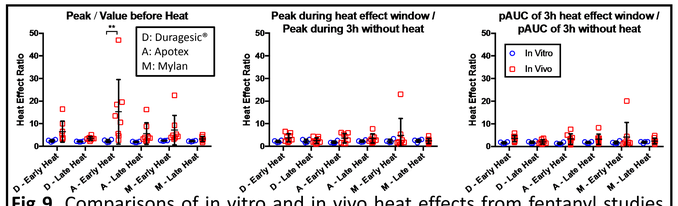

Fig 9. Comparisons of in vitro and in vivo heat effects from fentanyl studies. Heat effect window was defined as 11-14 h for early heat and 18-21 h for late heat. In vivo heat effects were higher compared to in vitro heat effects, with higher variability. (** $p \leq 0.01$, Two-way ANOVA with Bonferroni's post-hoc)

Table 2. Prediction error (%) for nicotine TDS

Nicotine TDS	NicoDerm CQ®		Aveva	
	Early Heat	Late Heat	Early Heat	Late Heat
Approach I				
Total AUC	4.5	6.4	31.2	5.5
C_{max}	10.8	8.4	38.2	6.4
Approach II				
Total AUC	10.2	4.6	0.5	6.7
C_{max}	31.8	0.4	7.6	0.4
Approach III				
Total AUC	5.1	1.2	1.1	4.5
C_{max}	15.0	5.8	8.9	17.7

Table 3. Prediction error (%) for fentanyl TDS

Fentanyl TDS		Duragesic®		Apotex		Mylan	
		Early Heat	Late Heat	Early Heat	Late Heat	Early Heat	Late Heat
Approach I							
Total AUC	CL = 75 L/h	7.5	25.3	75.8	34.0	4.9	1.8
	CL = 51 L/h	35.6	56.6	62.0	61.9	35.2	48.1
	CL = 27 L/h	193.3	335.1	396.8	395.3	191.3	264.2
C_{max}	CL = 75 L/h	32.0	23.4	22.7	14.3	9.3	21.6
	CL = 51 L/h	27.8	15.8	34.4	16.4	25.1	13.2
	CL = 27 L/h	332.7	124.2	187.8	125.9	152.3	117.6
Approach II							
Total AUC		7.0	0.8	8.4	23.3	1.2	14.7
C_{max}		35.2	4.5	39.1	40.4	20.3	2.6
Approach III							
Total AUC		16.5	10.1	29.3	1.4	6.5	6.0
C_{max}		7.8	2.0	16.9	26.7	8.6	41.3

Conclusions

The results of the in vitro and in vivo TDS heat effects studies and the different approaches to establishing a Level A correlation illustrate that carefully designed IVPT studies with nicotine and fentanyl TDS can be correlated with and predictive of in vivo heat effects for these products. The study designs, correlation approaches and analyses described here were shown to be compatible with the evaluation of multiple different TDS products.

Strong correlations were observed for the nicotine TDS, and the results with fentanyl TDS also showed good correlation albeit with a higher PE%. The relatively higher PE% for fentanyl may be attributable a more complex and highly variable clearance rate in vivo for fentanyl compared to nicotine, and may be impacted by a skin depot effect that has been postulated for transdermal fentanyl. Approach I, which relies only on in vitro data to make predictions without considering in vivo sources of variability showed the highest PE%. The other two approaches, which effectively accounted/corrected for differences in the skin permeability between the in vitro and in vivo study populations, and/or variability in the rate of clearance of the drug from the systemic circulation, generally provided a lower PE% and better predictions compared with Approach I.

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