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Evaluation of Level A In Vitro-In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure by 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. Even though 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, 14 mg/24h (NicoDerm CQ® and Aveva) and three fentanyl TDS, 25 µg/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:

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

- Eq. 2 Prediction after TDS removal:

$$C_s = C_0 \cdot e^{-\left(\frac{\ln 2}{t_{1/2,TDS}}\right)t}$$

C_s: Predicted in vivo serum concentration
F: Absolute bioavailability for TDS ; $\frac{AUC_{0-\infty,TDS} \times Dose_{IV}}{AUC_{0-\infty,IV} \times Dose_{TDS}}$
R_{in}: Rate of input (mean delivery rate during steady-state in IVPT experiments)
H_i : In vitro heat effect coefficient (composite heat effect during and after heat exposure); ratio of flux values with heat and without heat
CL: Total body clearance obtained from literature/product package information
k: Elimination rate constant obtained from literature/product package information
t: Time after administration of TDS for Eq.1 and time after removal of TDS for Eq. 2
C_0: Predicted Initial concentration after TDS removal
$t_{1/2,TDS}$: half-life after TDS removal

Approach II and III:

1. Reconstruct baseline (32°C) profile by combining the non-heat (32°C) portion of each profile from the early and late heat study designs (Fig. 1)
2. Deconvolute the in vivo baseline conc. vs time profile using Phoenix®
3. Construct an IVIVC model by plotting the fraction permeated in vitro vs. the fraction absorbed in vivo
4. Predict the in vivo fraction absorbed using the IVIVC model and IVPT data
5. Convolute the predicted in vivo fraction absorbed data
6. Apply the in vitro heat effect coefficient H_i (**Approach II**) or the 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.

	API Amt (mg)	Size (cm^2)	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	Isopropyl myristate, octyldodecanol, polybutene, polyethylene/ aluminum/ polyester film backing
Mylan	2.55	6.25	Silicone	Dimethicone NF, polyolefin film backing

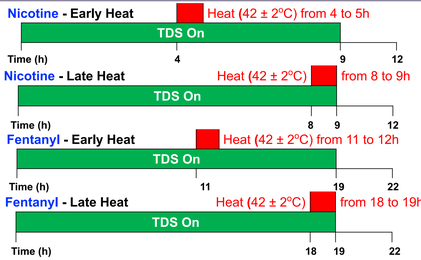
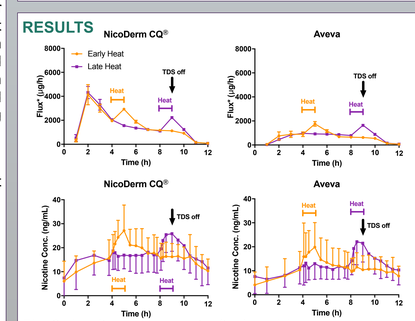


Fig 1. Schematic diagrams (not to scale) of study designs.

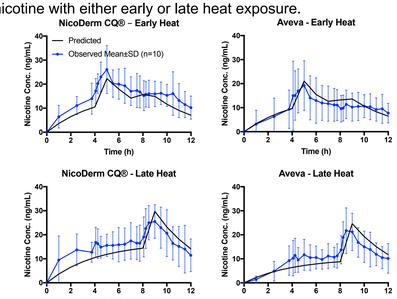
RESULTS



In vitro: Mean ± SEM; 4 donors with n=4 replicates per donor

In vivo: Mean ± SD; n=10 subjects

Fig 2. In vitro delivery rate (top) and in vivo serum concentrations (bottom) of nicotine with either early or late heat exposure.



PK parameters of nicotine used for Approach I, II, and III were obtained from:

- Hukkanen et al. Pharmacol Rev 2005
- Gupta et al. Br J Clin Pharmcol 1993
- F of 0.825 was used for both NicoDerm CQ® and Aveva.

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

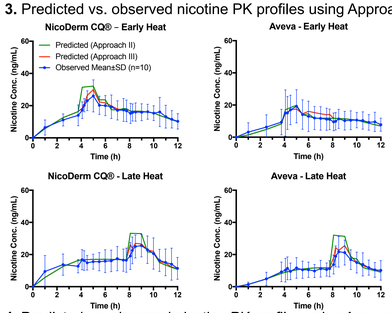


Fig 4. Predicted vs. observed nicotine PK profiles using Approach II & III.

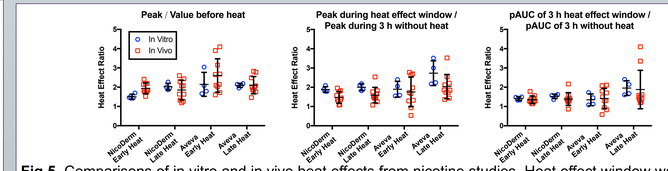


Fig 5. Comparisons of in vitro and in vivo heat effects from nicotine studies. Heat effect window was defined as 4-7 h for early heat and 8-11 h for late heat. No statistically significant difference ($p > 0.05$) was found between in vitro and in vivo heat effects.

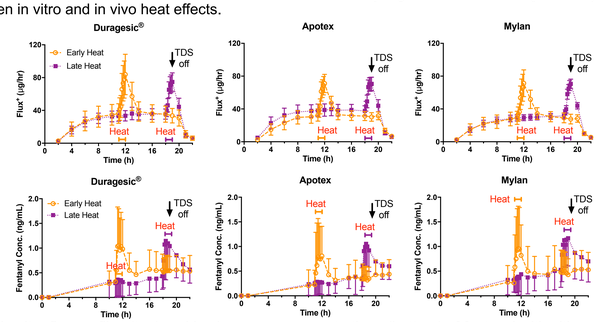
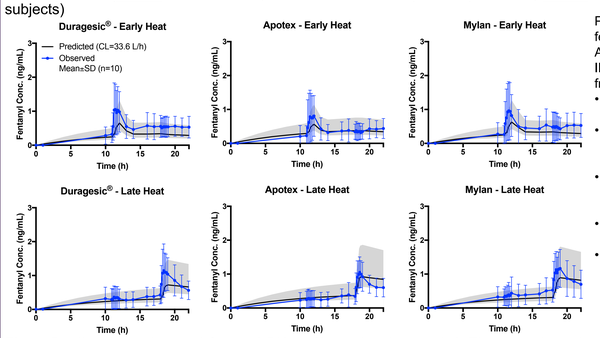


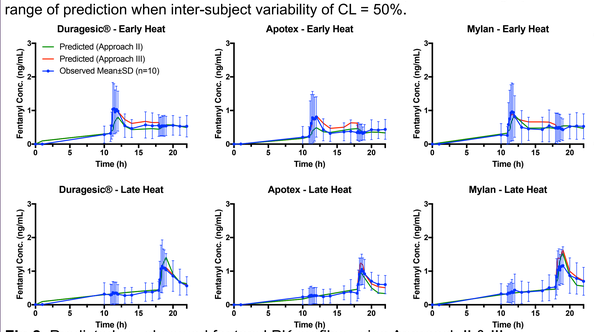
Fig 6. In vitro flux profiles (top) and in vivo serum concentrations (bottom) of fentanyl with either early or late heat exposure. (In vitro: Mean ± SEM; 4 donors with n=4 replicates per donor; In vivo: Mean ± SD, n=10 subjects)



PK parameters of fentanyl used for Approach I, II, and III were obtained from:

- Bower et al. Br J Anaesth 1982
- McClain et al. Clin Pharmacol Ther 1980
- Scott et al. J Pharmacol Exp Ther 1986
- Fung et al. J Clin Pharmacol 1980
- Unpublished study at Univ. of MD, Baltimore

Fig 7. Predicted vs. observed fentanyl PK profiles using Approach I. The grey shaded area represents the range of prediction when inter-subject variability of CL = 50%.



- F for Duragesic® (0.36) and Mylan (0.42) were each determined from an unpublished study at the Univ. of MD, Baltimore.
- F for Apotex was estimated (0.39) by the mean of 0.36 and 0.42, due to lack of available data.

Fig 8. Predicted vs. observed fentanyl PK profiles using Approach II & III.

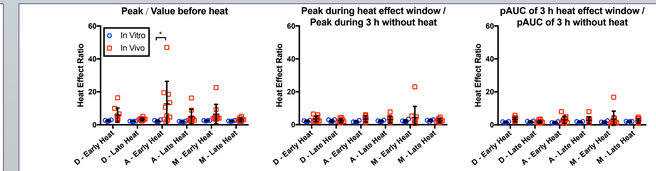


Fig 9. Comparisons of in vitro and in vivo heat effects from fentanyl studies. The heat effect window was defined as 11-14 h (early heat) and 18-21 h (late heat). In vivo heat effects were higher compared to in vitro heat effects, with higher variability. (* $p \leq 0.05$, Two-way ANOVA with Bonferroni's post-hoc)

Table 2. Prediction error, PE (%), for nicotine TDS.

$$PE\,(\%) = \frac{|Observed - Predicted|}{Observed} \times 100$$

Nicotine TDS	NicoDerm CQ®		Aveva	
	Early Heat	Late Heat	Early Heat	Late Heat
Approach I (prediction with in vitro data only)				
Total AUC	20.3	12.9	7.5	5.0
C_{max}	14.4	16.6	9.8	13.5
Approach II (using the in vitro heat effect coefficient, H_i)				
Total AUC	10.3	5.0	1.5	13.3
C_{max}	23.3	30.2	3.5	47.5
Approach III (using the in vivo heat effect coefficient, H_{ii})				
Total AUC	5.1	1.2	1.1	4.5
C_{max}	15.0	5.8	8.9	17.7

Table 3. Prediction error, PE (%) for fentanyl TDS.

Fentanyl TDS	Duragesic®		Apotex		Mylan	
	Early Heat	Late Heat	Early Heat	Late Heat	Early Heat	Late Heat
Approach I (prediction with in vitro data only)						
Total AUC	31.7	17.5	4.0	19.3	24.3	18.4
C_{max}	37.7	36.8	29.8	12.4	34.1	23.2
Approach II (using the in vitro heat effect coefficient, H_i)						
Total AUC	3.3	13.1	10.2	11.8	5.1	0.6
C_{max}	23.4	23.6	39.6	11.2	11.4	31.5
Approach III (using the in vivo heat effect coefficient, H_{ii})						
Total AUC	15.2	10.1	11.9	0.8	18.1	8.3
C_{max}	0.5	2.3	4.4	18.7	7.7	40.5

* Area Under the concentration vs. time Curve (AUC) and maximum concentration (C_{max})

CONCLUSIONS

The results of the in vitro and in vivo TDS heat effects studies, and the different approaches to establish a Level A correlation, illustrate that carefully designed IVPT studies with nicotine and fentanyl TDS can be correlated with and predictive of the in vivo rate and extent of drug delivery, including 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. For Approach I, 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 to 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. The relatively higher PE% associated with C_{max} using Approach II can be attributed to use of an in vitro heat effect coefficient, H_i, to the in vivo data. When H_{ii} from the in vivo study was applied in Approach III, the PE% decreased with good predictions for both total AUC and C_{max}. Due to the high inter-subject variability observed in the fentanyl dataset, especially for heat effects, applying the in vivo heat effect coefficient might still result in a higher PE% compared to nicotine, as seen from the PE% of C_{max} for fentanyl TDS from Mylan, Late Heat study design. Comparability of results obtained using the three different IVIVC approaches and usefulness of each approach requires further consideration.

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