Evaluation of Level A *In Vitro In Vivo* Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems (TDS) with Transient Heat Exposure by Using Multiple Approaches

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2017 Barrier Function of Mammalian Skin (GRS)

IVIVC

- Definition by the U.S. FDA

  "a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response"

- Level A: a point-to-point correlation between in vitro and in vivo profiles
- Level B: comparison between in vitro dissolution time and in vivo residence time
- Level C: a single point correlation between in vitro and in vivo parameters (e.g. J_{max} vs. C_{max})

Level A is most informative and useful

IVIVC con't

- Value of IVIVC
  - Facilitate testing of drug candidates and optimization of formulation
  - Assist in quality control
  - Serve as a surrogate for bioequivalence studies, scale-up and postapproval changes

→ Minimize/Reduce in vivo clinical studies (Save  & )

- Currently, no formal guidance for developing IVIVC for TDS exists.
- IVIVC for TDS is not accepted by regulatory agencies to support biowaiver claims.

Why is Heat on Drug Delivery from TDS of Interst?

- Many sources of heat:
  - Heating pads
  - Saunas
  - Hot tubs
  - Sunbathing
  - Prolonged activity under direct sunlight

- Multiple life-threatening incidents when TDS was exposed to heat

- FDA required labeling change for Duragesic® fentanyl TDS (RLD) with a warning against heat

⇒ Same labeling change was required for generic fentanyl TDS

Objectives

1. Can *in vitro* permeation test (IVPT) predict the performance of TDS and heat effects on drug delivery and absorption *in vivo*?

2. Does heat affect drug delivery/absorption from TDS differently on products with different inactive ingredients (i.e. RLD vs. Generic)?

3. Does heat exposure at different TDS wear periods (early vs late) results in different effects?

Model Drugs: Nicotine & Fentanyl

Approach

I. Harmonized in vitro and in vivo study designs

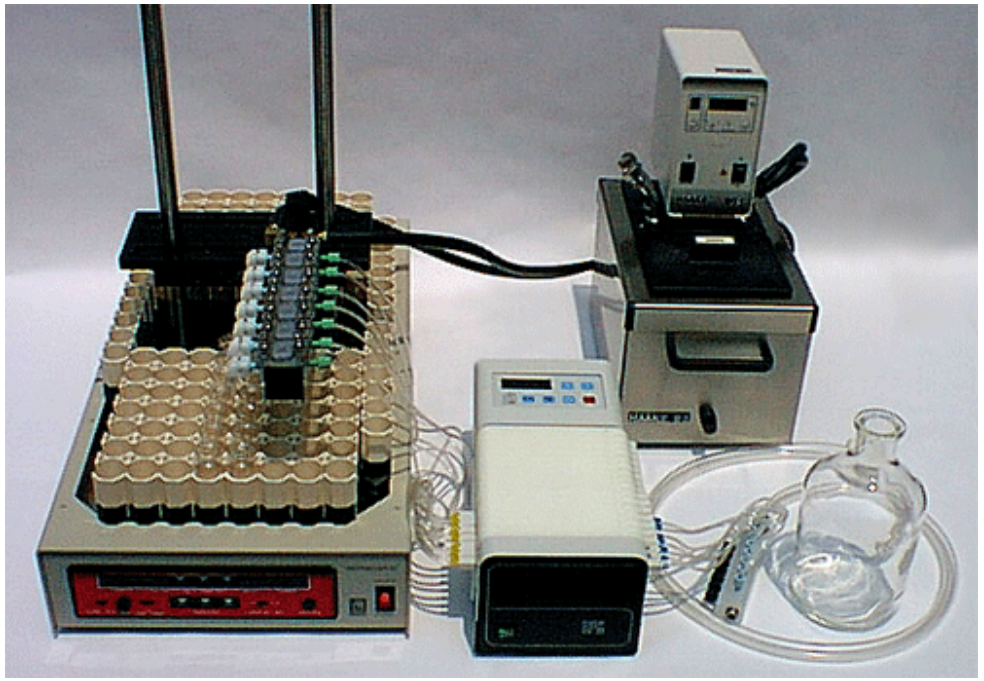
II. In vitro: IVPT studies using dermatomed human skin

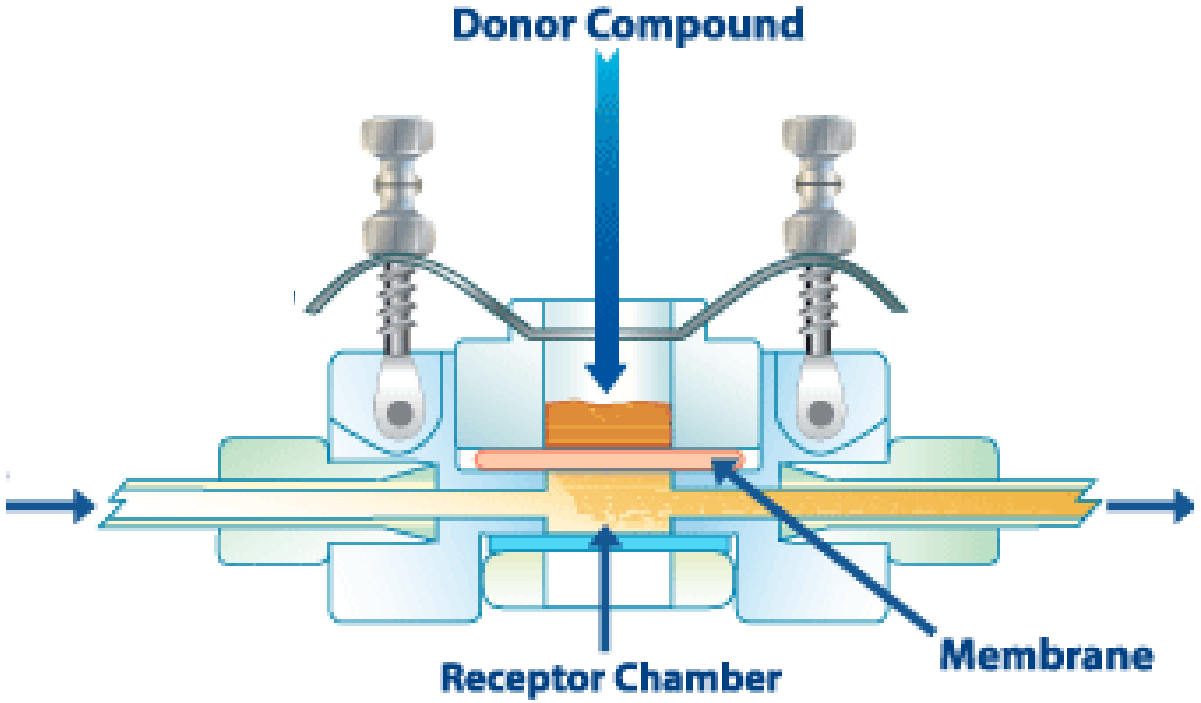
III. In vivo: pharmacokinetics (PK) study in healthy human subjects

IV. Evaluation of *in vitro* and *in vivo* correlations (IVIVC) for TDS

IVPT Setup

- Dermatomed Human Skin (~250 microns)
- In-line flow-through diffusion system
- Permeation area of 0.95 cm^2

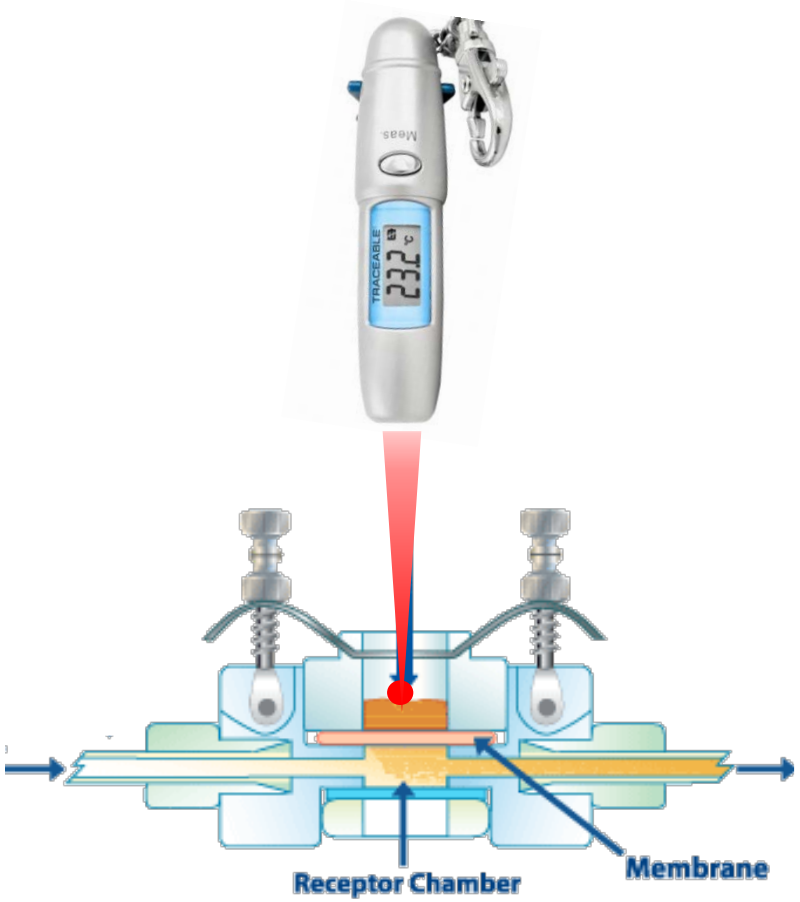


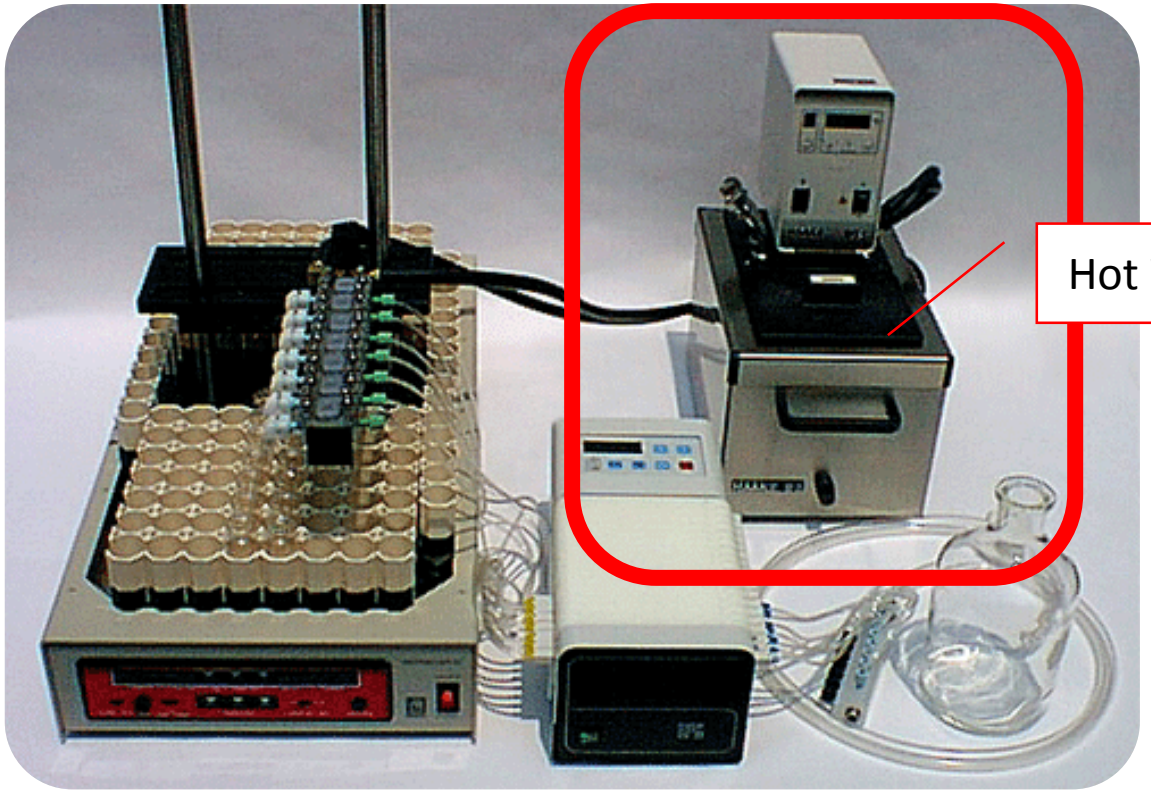


Images from www.ibric.org and www.permegear.com

Temperature Monitoring & Heat Application *In Vitro*

Infrared Thermometer





Images from https://traceable.com/products/thermometers/4480.html and www.permegear.com

Temperature Monitoring & Heat Application *In Vivo*

- Kevlar sleeve with an opening to expose TDS, while protecting skin outside the dosing area
- Thermometer probe adjacent to TDS

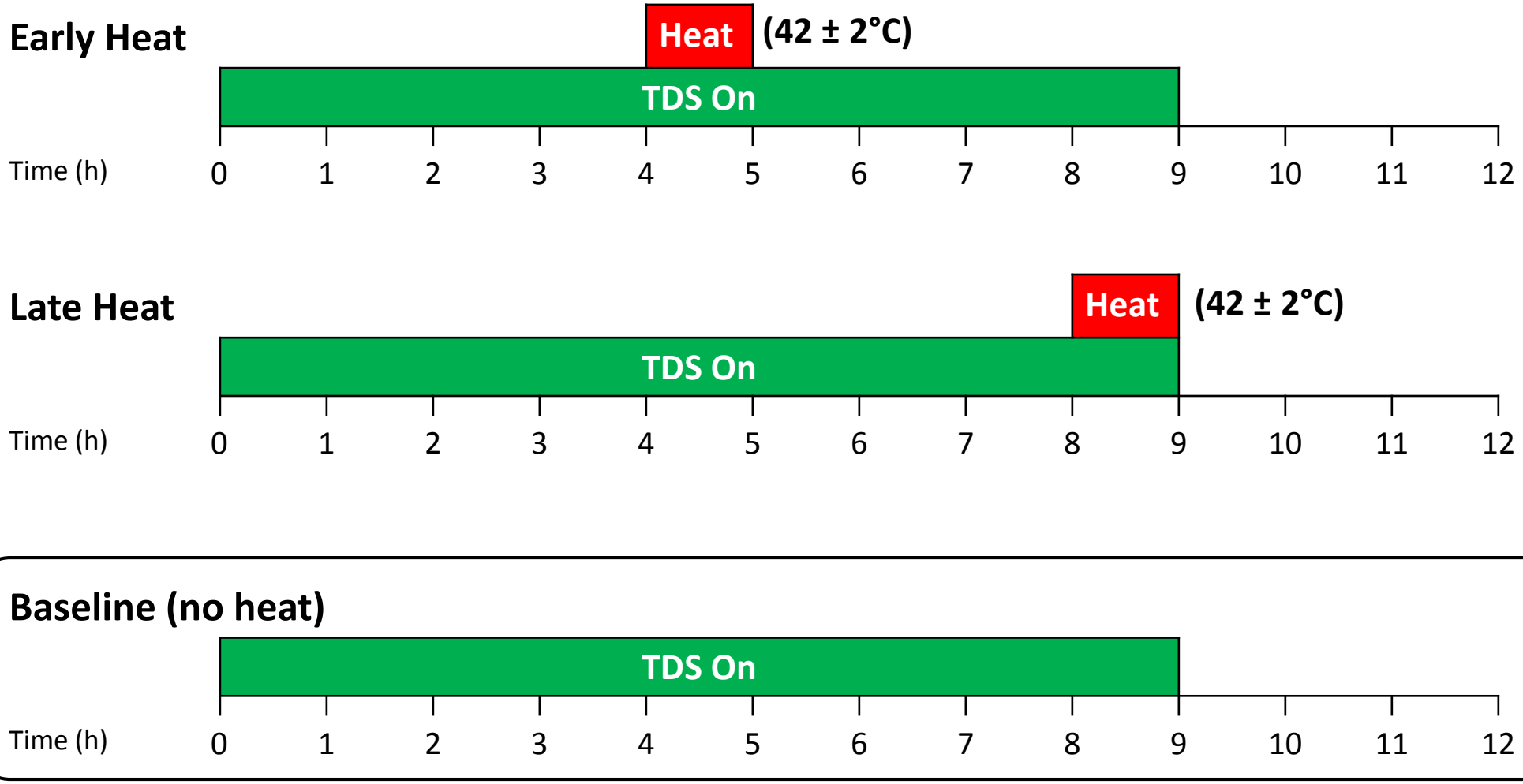
- Pre-heated heating pad
- ACE™ Bandage to ensure good contact between TDS and heating pad

Thermometer image from http://static.coleparmer.com/large_images/91427_10_5.jpg

1. Nicotine TDS, 14 mg/24 hr

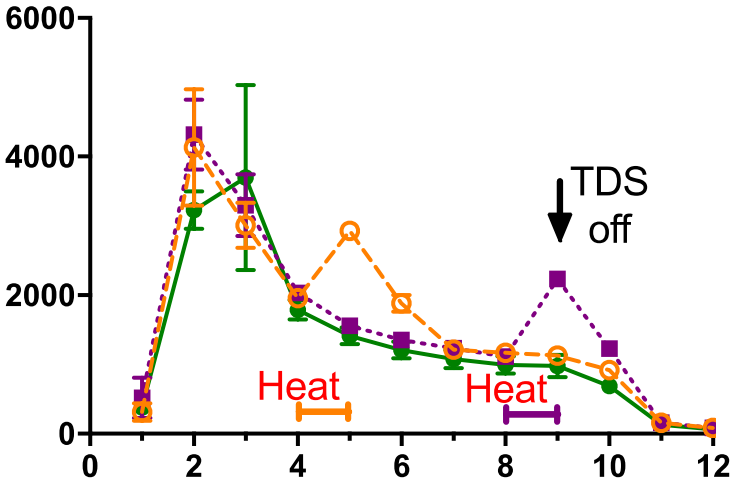
	NicoDerm CQ®	Aveva
TDS size (cm^2)	15.75	20.12
Drug content (mg)	Not available	Not available
Rate/Area ($\mu g/cm^2/h$)	37	29
Adhesive	Polyisobutene	Acrylate/Silicone
Other Inactive ingredients	Ethylene vinyl acetate-copolymer, high density polyethylene between clear polyester backing	Polyester

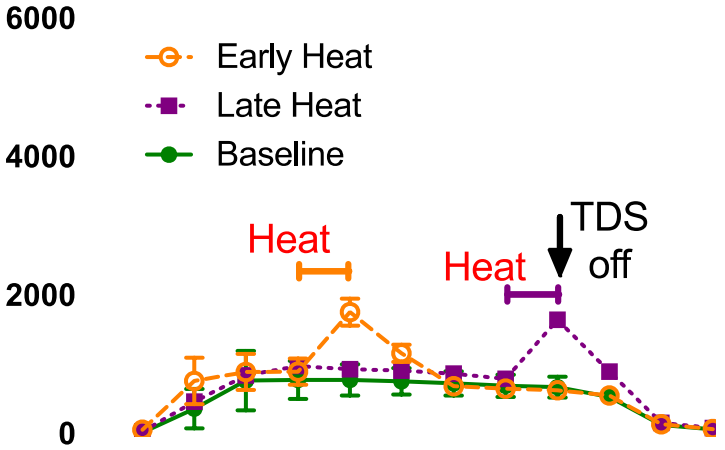
Study Designs – Nicotine TDS



In Vitro Only

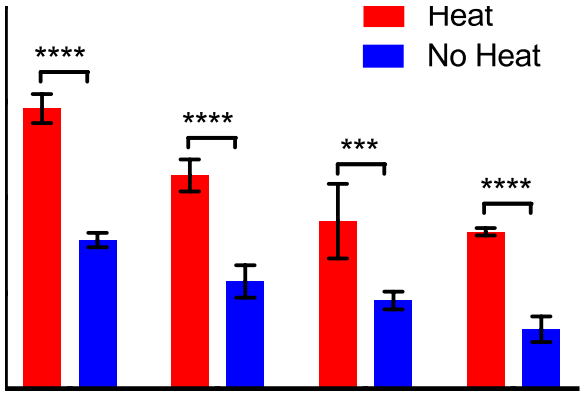
IVPT Results

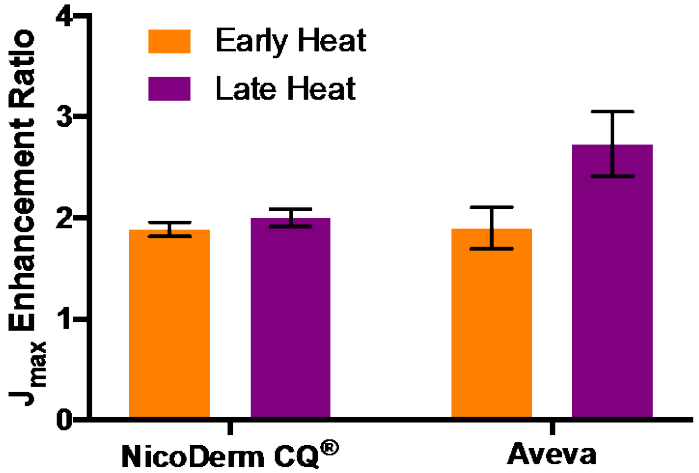




Human Skin Data

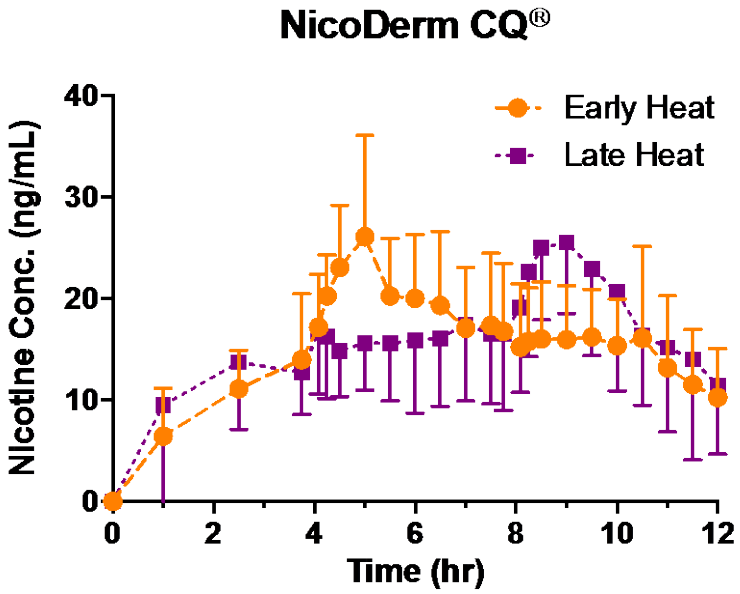
Mean ± SEM from 4 donors for Early Heat and Late Heat, 2 donors for Baseline with n=4 per donor

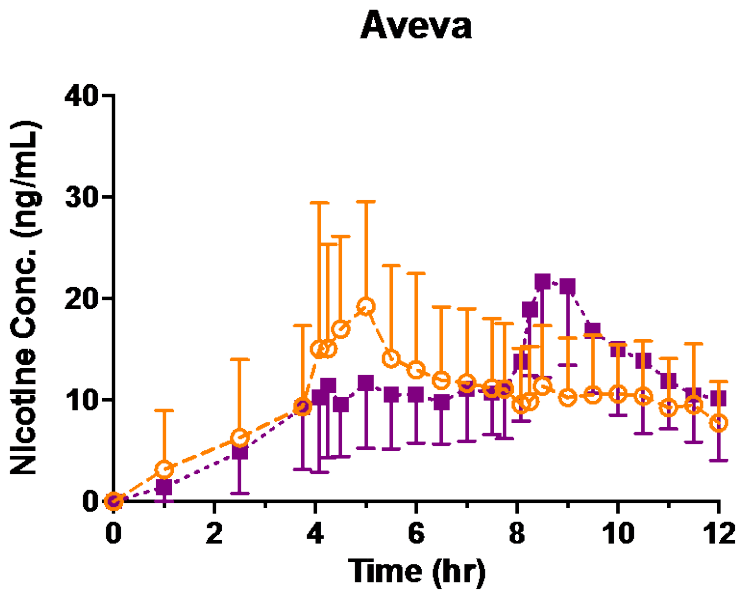




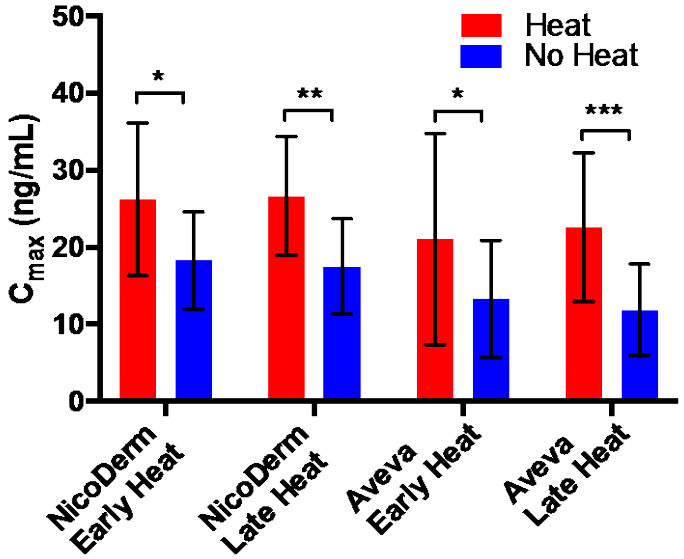
Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

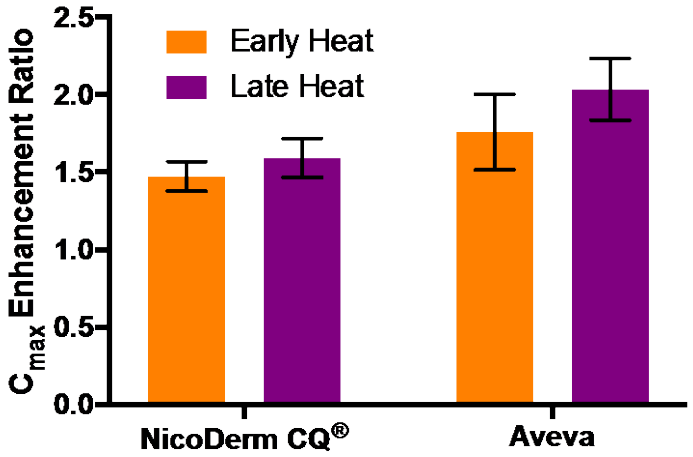
In Vivo Results





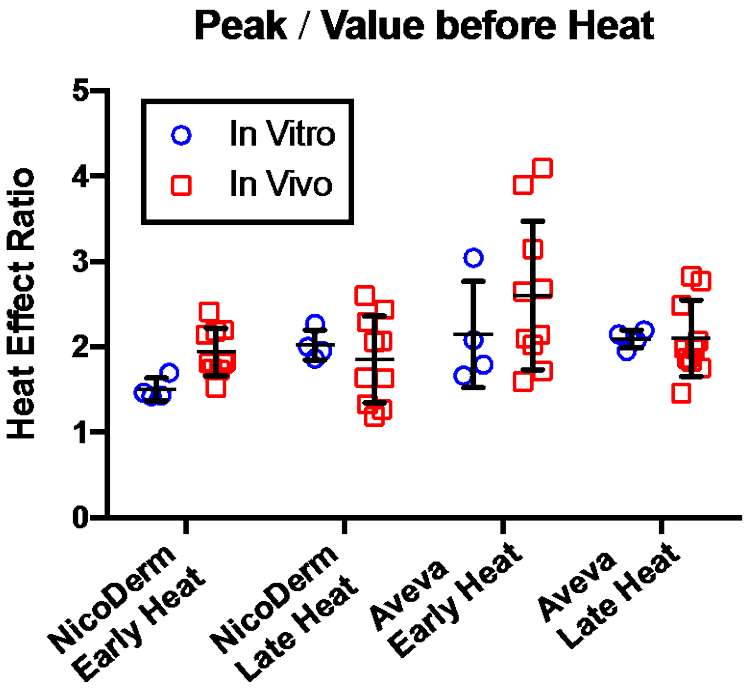
Mean ± SD
from 10 human subjects

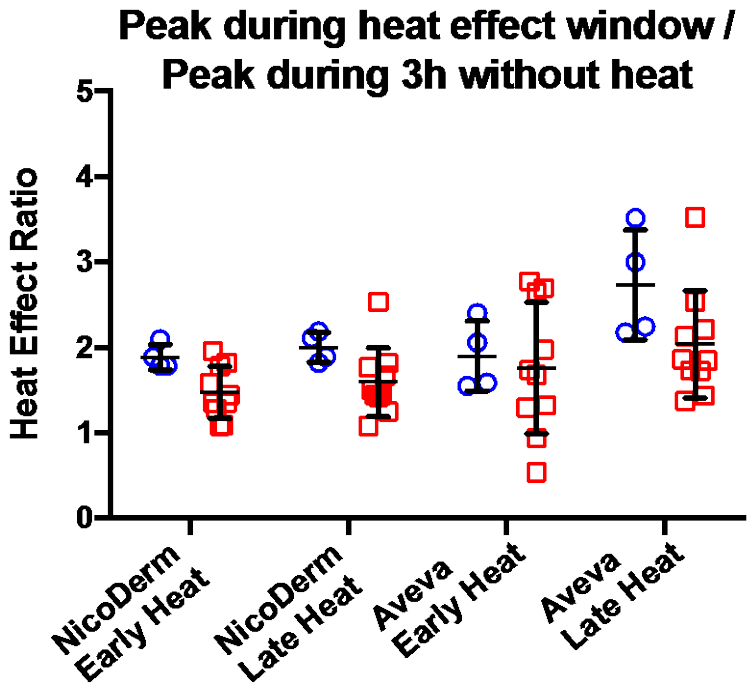


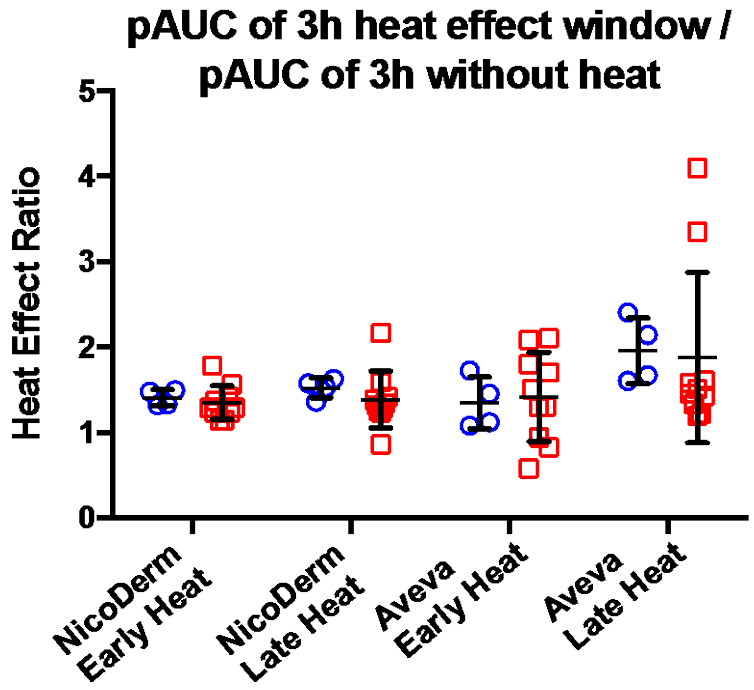


Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

IVIVC: Heat Effects







No statistically significant difference ($p > 0.05$) between in vitro and in vivo heat effects
(Two-way ANOVA, followed by Bonferroni's post-hoc multiple pair comparisons)

- In vitro data from 4 donors with n=4 replicates per donor
- In vivo data from 10 subjects

IVIVC: Level A (Approach I)

1) Prediction while TDS was worn (time points from 0 to 9 h):

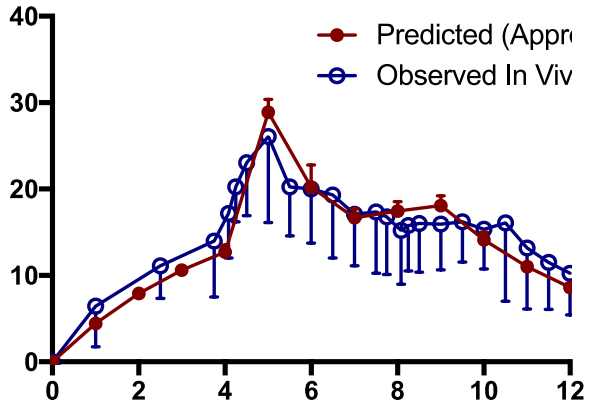
$$C_s = \frac{R_{in} \cdot H_i}{CL} \cdot (1 - e^{-kt})$$

2) Prediction after TDS removal (time points after 9 h until 12 h):

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

- C_s is the predicted serum concentration
- R_{in} is rate of input obtained from mean flux during steady-state in IVPT experiments
- H_i is the *in vitro* heat factor at the respective time point, a term describing composite heat effect during and after heat application
- *CL* is the population total body clearance of nicotine
- *k* is the elimination constant
- *t* is the time after administration of TDS for Eq.1 and the time after removal of TDS for Eq. 2
- C_0 is the initial concentration after TDS removal (the predicted C_s at 9 h)

IVIVC: Level A (Approach I)



Prediction Error (%)

$$= \frac{|Observed - Predicted|}{Observed} \times 100$$

	NicoDerm CQ®	
	Early Heat	Late Heat
Total AUC	4.5	6.4
C_{max}	10.8	8.4

Aveva – Late Heat

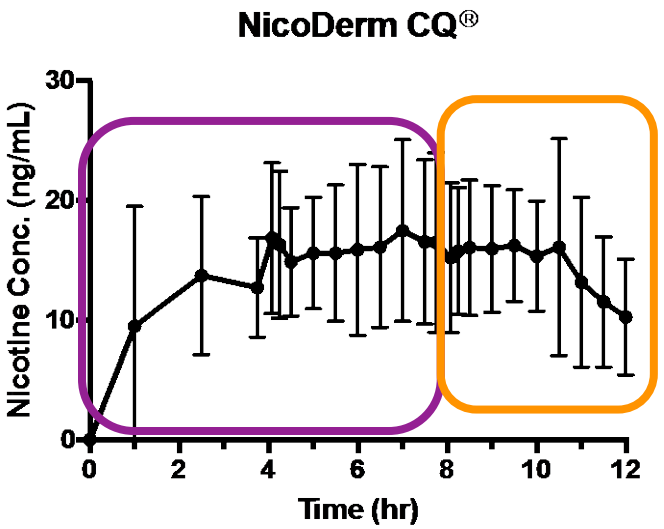
Nicotine Conc. (ng/mL)

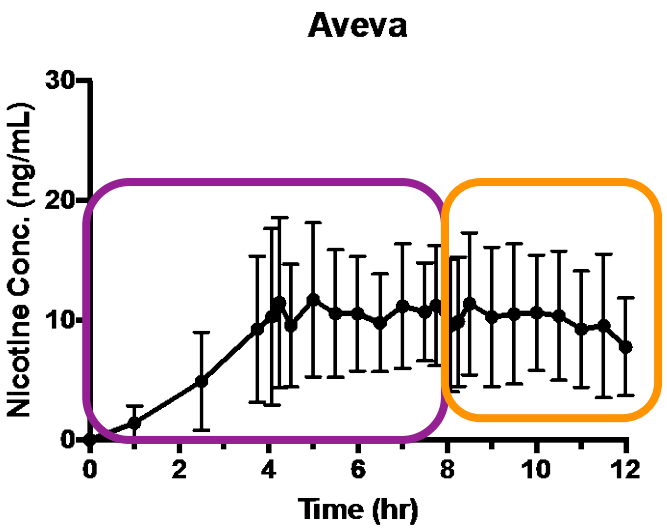
hr)

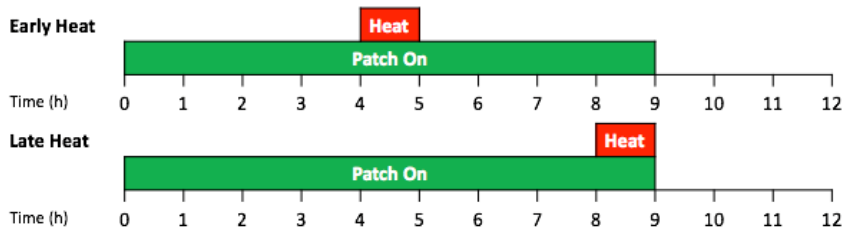
	Aveva	
	Early Heat	Late Heat
Total AUC	31.2	5.5
C_{max}	38.2	6.4

IVIVC: Level A (Approach II/III)

1) Reconstruct the baseline (no heat) *in vivo* profile
   - Late Heat data (time 0 to 7.75 hrs) + Early Heat data (time 8.08 to 12 hrs)



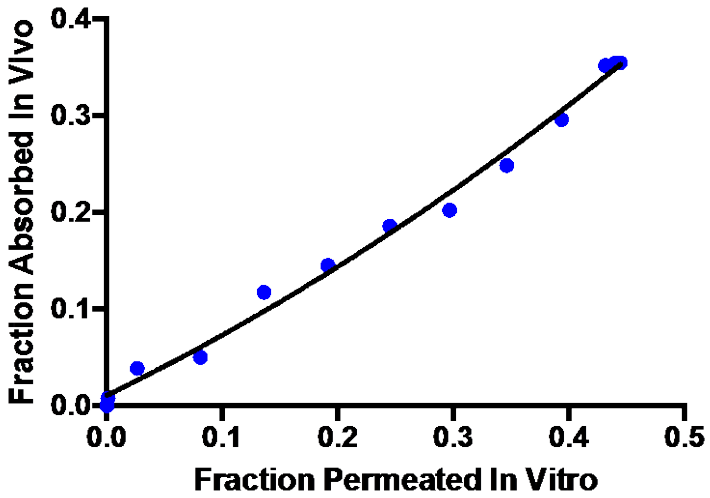




2) Deconvolute *in vivo* profile (Wagner-Nelson method) to obtain *in vivo* fraction of drug absorption

IVIVC: Level A (Approach II/III)

3) Construct IVIVC model between *in vitro* fraction of drug permeation and *in vivo* fraction of drug absorption
4) Examine and find the model with the best fit → Obtain regression coefficients



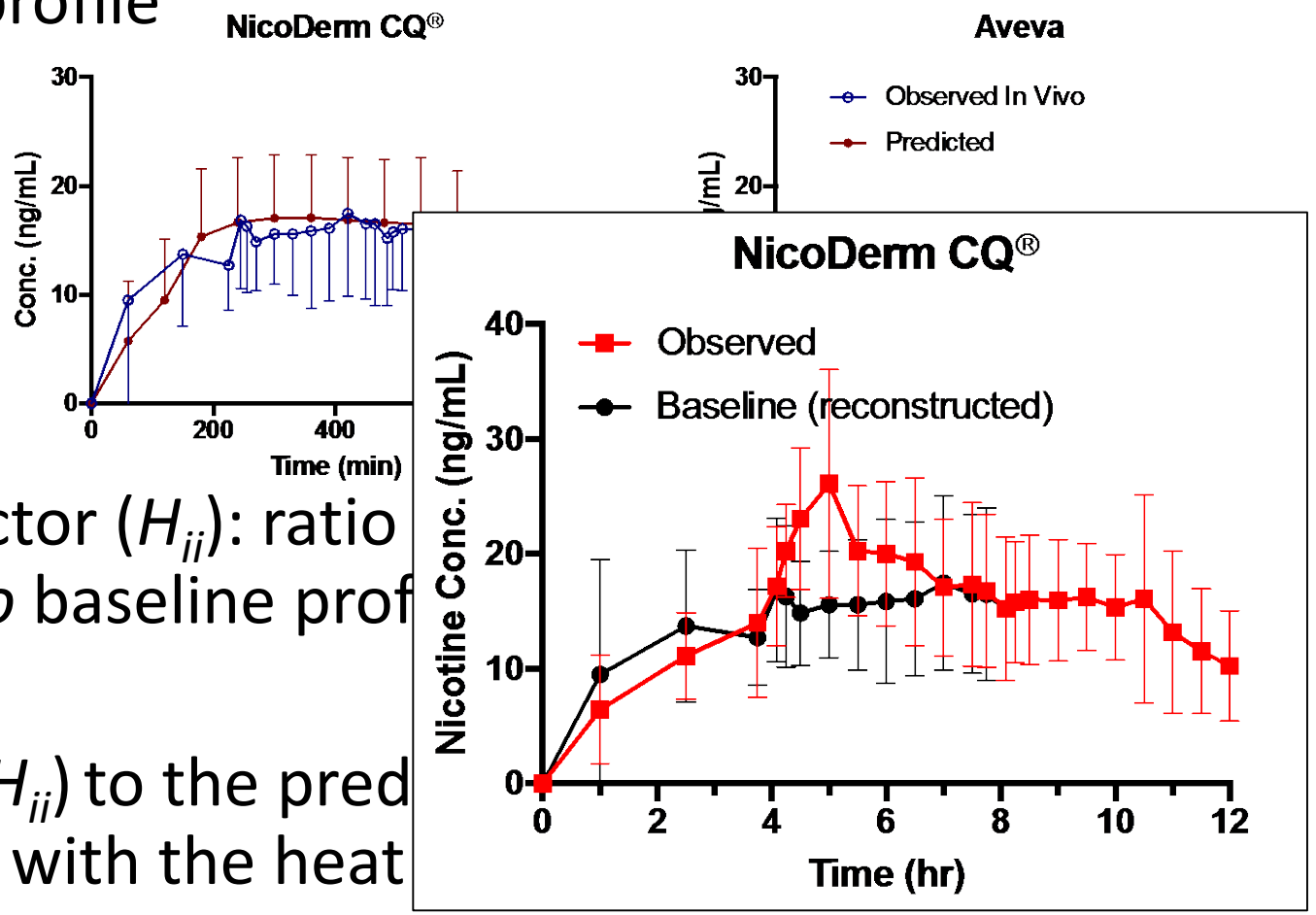
Quadratic Polynomial model

5) Predict the *in vivo* fraction of drug absorption using the regression coefficients obtained from the IVIVC model

$$F_{in\ vivo(predicted)} = B_0 + B_1 F_{in\ vitro(observed)} + B_2 F_{in\ vitro(observed)}$$

IVIVC: Level A (Approach II/III)

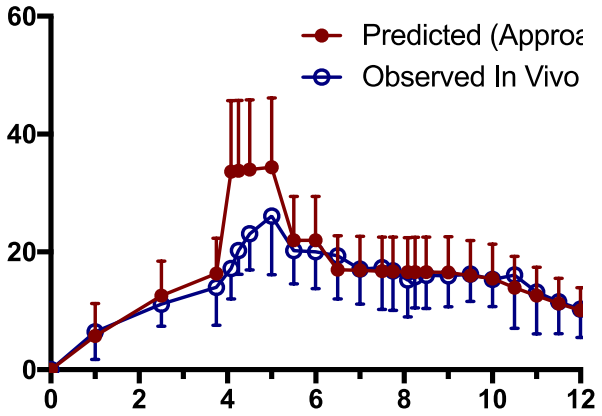
6) Convolute the predicted fraction of drug absorption vs time profile to obtain conc. vs time profile



7) Calculate *in vivo* heat factor (H_{ii}): ratio
the reconstructed *in vivo* baseline prof
exposure

8) Apply heat factor (H_i or H_{ii}) to the pred
complete the prediction with the heat

IVIVC: Level A (Approach II, $H_{i\ (in\ vitro)}$)

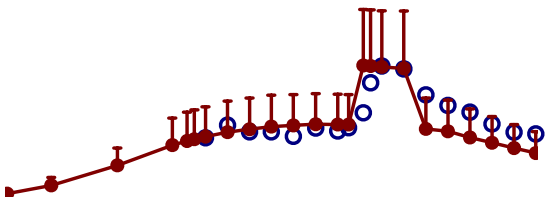


Prediction Error (%)

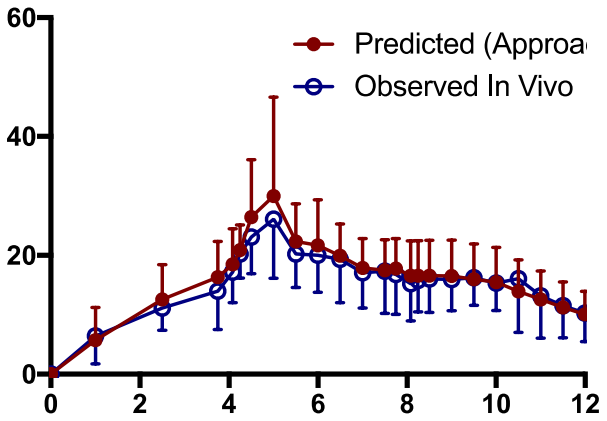
$$= \frac{|Observed - Predicted|}{Observed} \times 100$$

	NicoDerm CQ®	
	Early Heat	**Late Heat**
Total AUC	10.2	4.6
C_{max}	31.8	0.4

	Aveva	
	Early Heat	**Late Heat**
Total AUC	0.5	6.7
C_{max}	7.6	0.4



IVIVC: Level A (Approach III, $H_{ii\ (in\ vivo)}$)

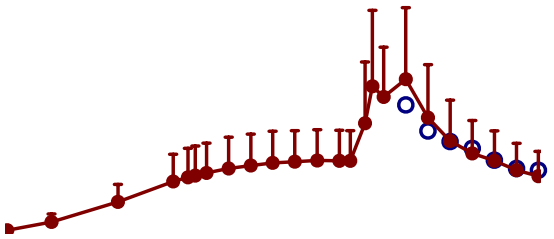


Prediction Error (%)

$$= \frac{|Observed - Predicted|}{Observed} \times 100$$

	NicoDerm CQ®	
	Early Heat	**Late Heat**
Total AUC	5.1	1.2
C_{max}	15.0	5.8

	Aveva	
	Early Heat	**Late Heat**
Total AUC	1.1	4.5
C_{max}	8.9	17.7



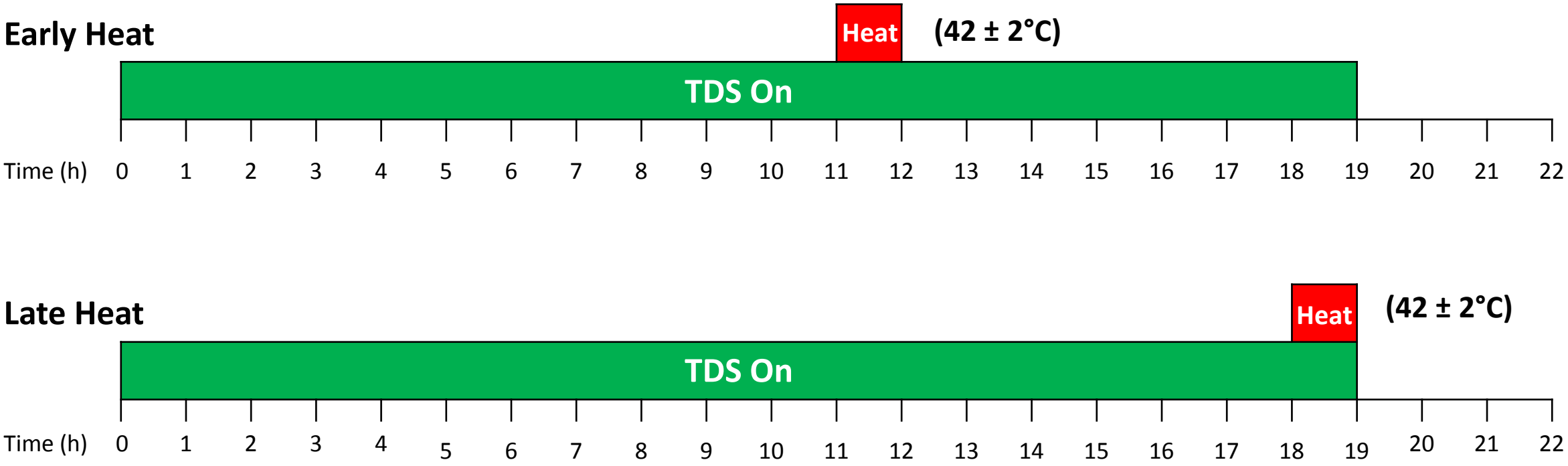
Conclusions – Nicotine

- Early vs. Late Heat effect comparable both *in vitro* and *in vivo*
- Heat effect on two differently formulated TDS comparable both *in vitro* and *in vivo*
- *In vitro* and *in vivo* heat effect ratios were comparable
- Strong IVIVCs between IVPT and clinical human PK studies under the matched study designs

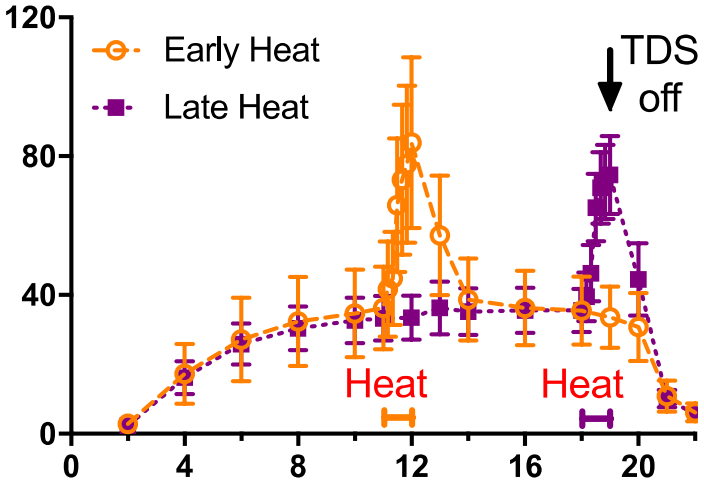
2. Fentanyl TDS, 25 µg/hr

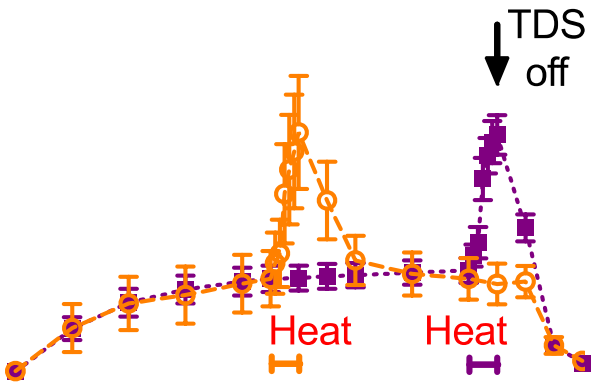
	Duragesic®	Apotex	Mylan
Drug Load (mg)	4.20	2.76	2.55
Size (cm^2)	10.50	10.70	6.25
Thickness (µm)	110	200	190
Adhesive	Polyacrylate	Polyisobutene	Silicone
Other Inactive Ingredients	Polyester/ ethyl vinyl acetate backing film, copovidone	Isopropoyl myristate, octyldodecanol, polybutene, polyethylene/ aluminum/ polyester film backing	Dimethicone NF, polyolefin film backing
Appearance			

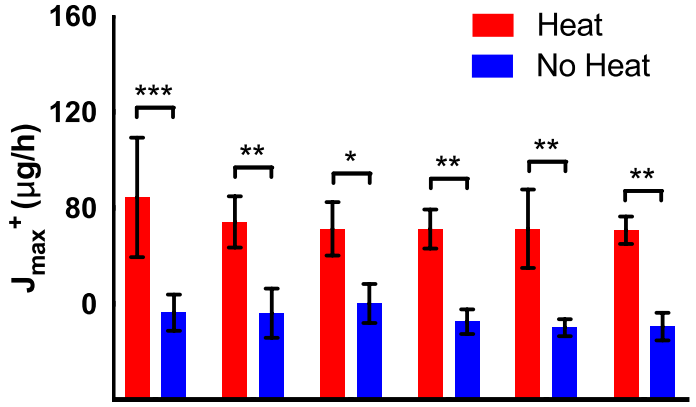
Study Designs – Fentanyl TDS

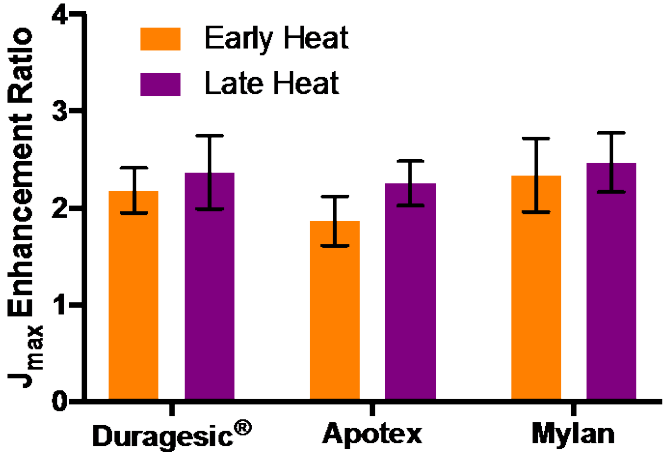


IVPT Results







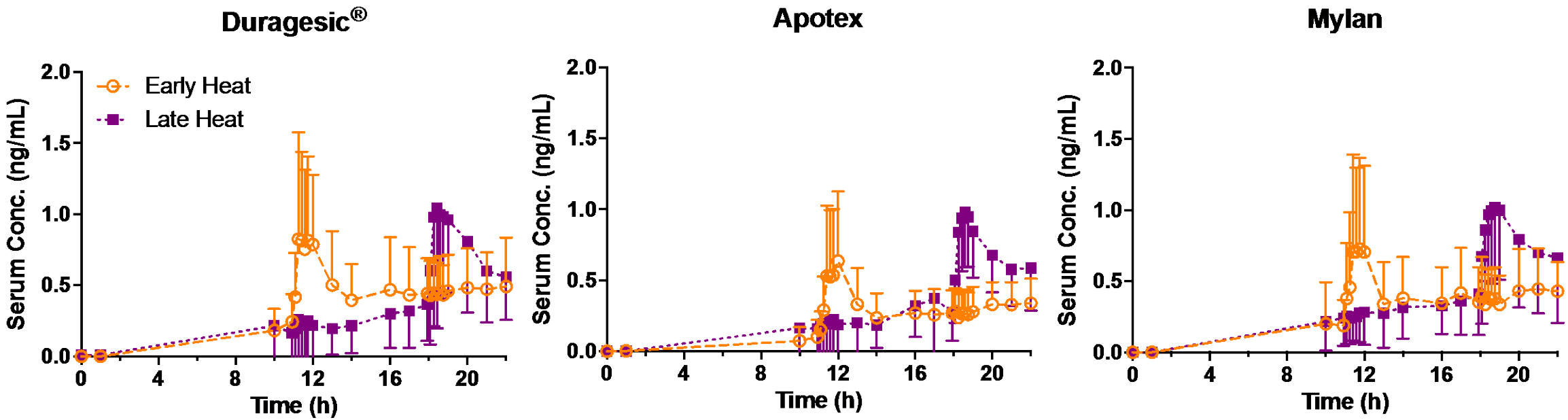


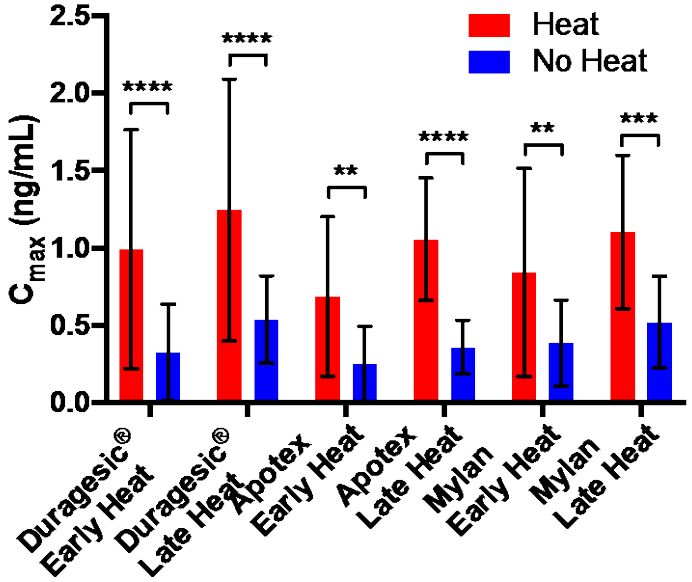
Human Skin Data

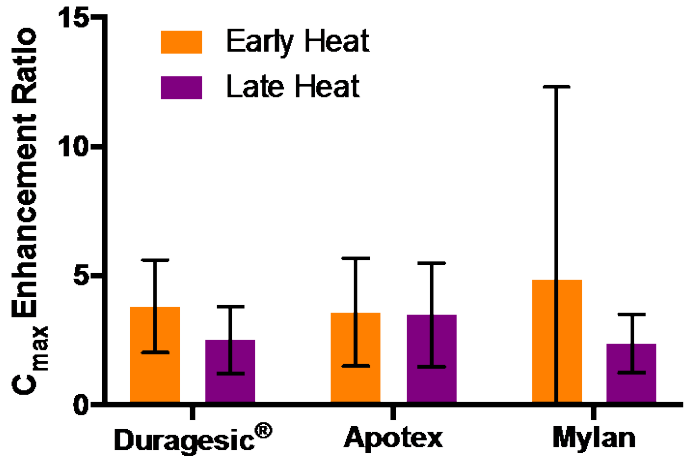
Mean ± SEM from 4 donors with n=4 per each donor

Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

In Vivo Results



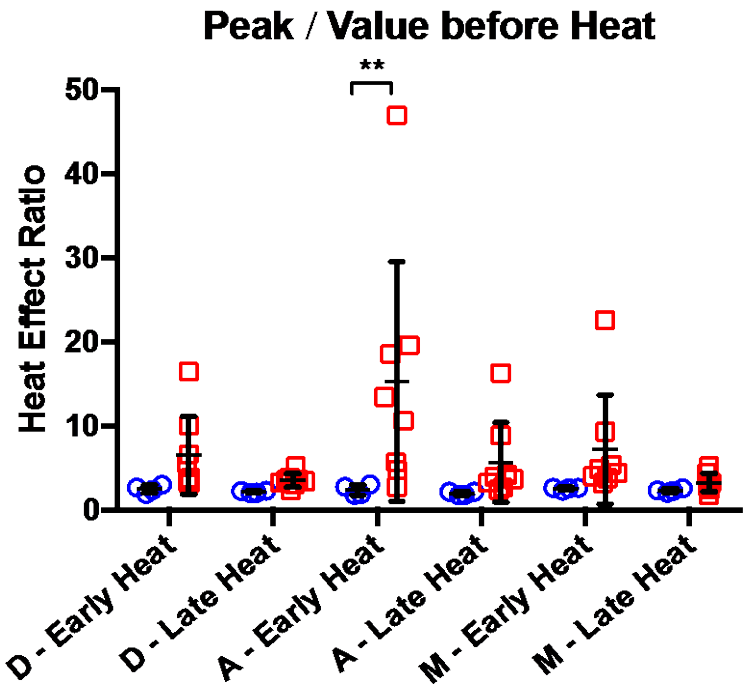


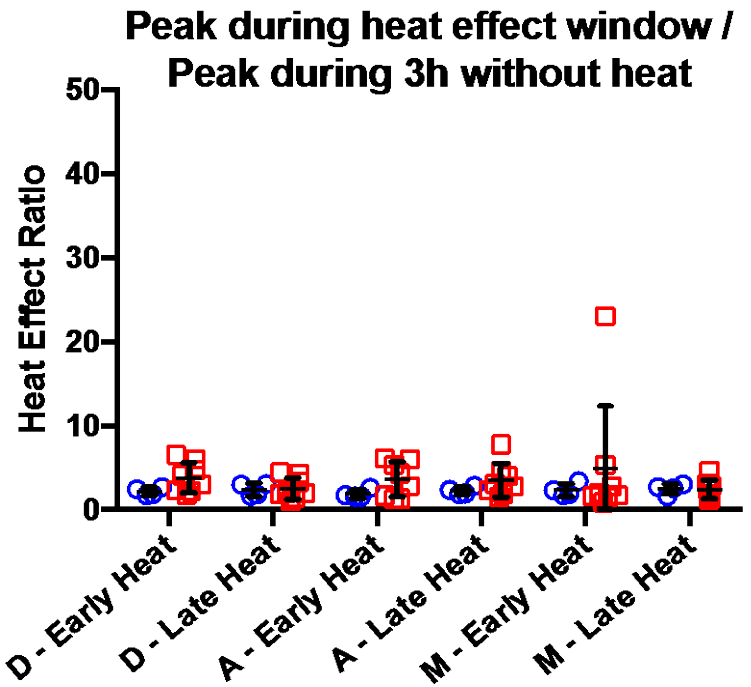


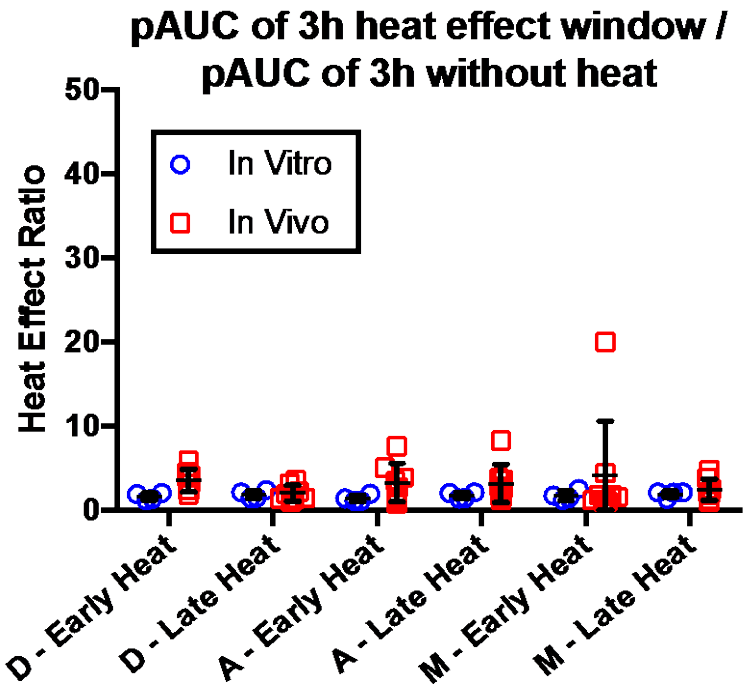
Mean ± SD
from 8 human subjects

Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

IVIVC: Heat Effects







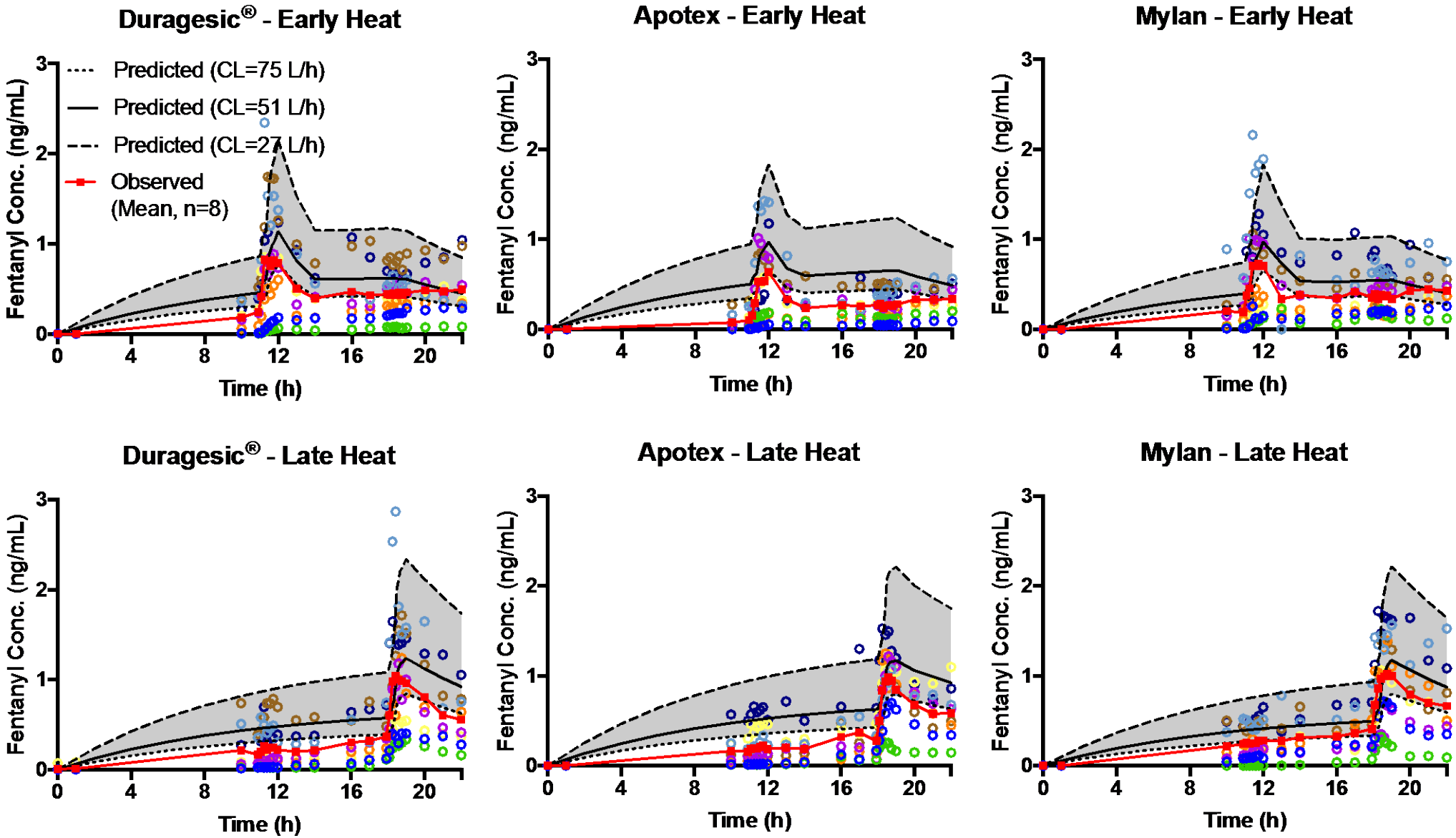
D: Duragesic®
A: Apotex
M: Mylan

In vivo heat effect is greater than in vitro, with higher variability

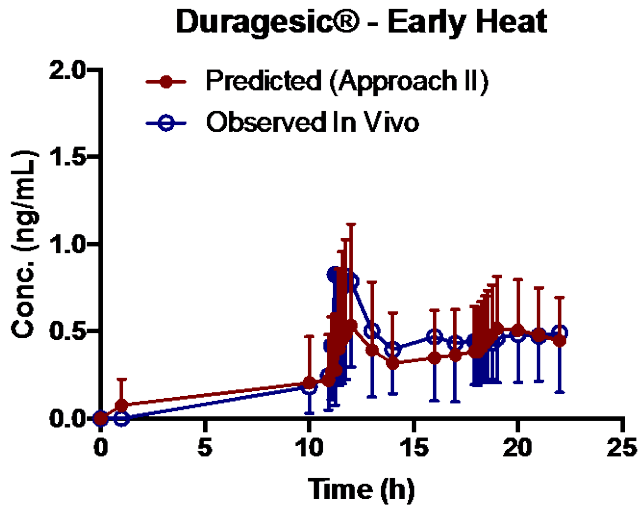
(Two-way ANOVA followed by Bonferroni's post-hoc multiple pair comparisons)

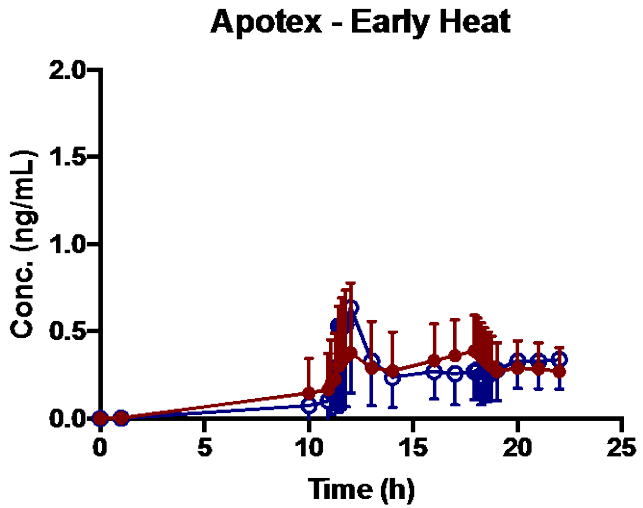
- In vitro data from 4 donors with n=4 replicates per donor
- In vivo data from 8 subjects

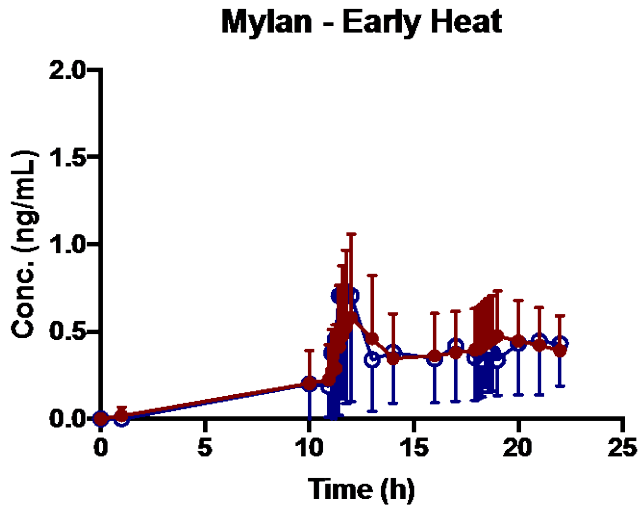
IVIVC: Level A (Approach I)

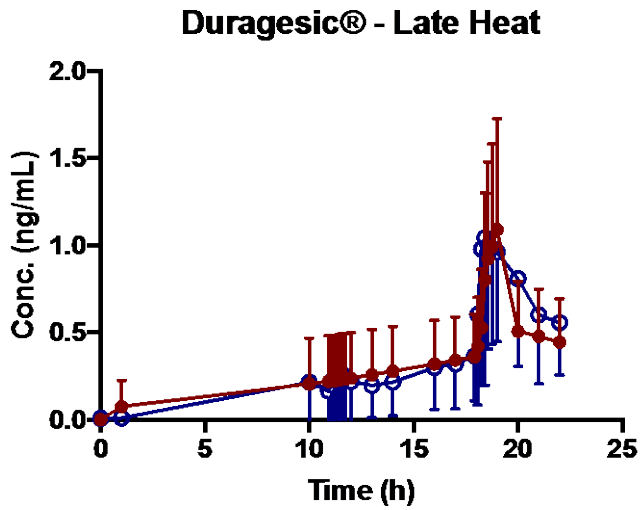


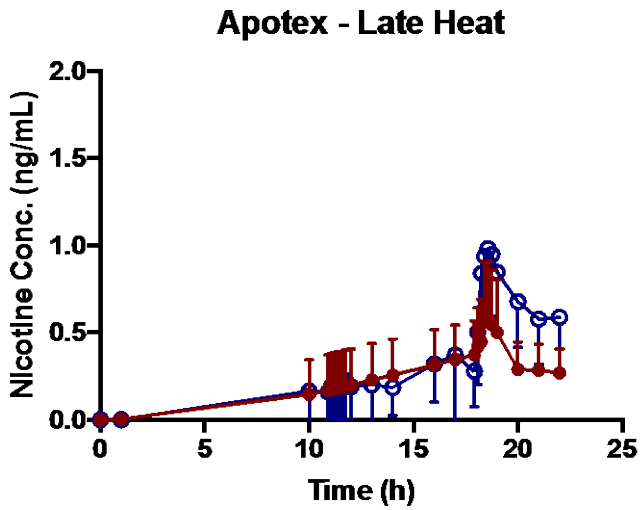
IVIVC: Level A (Approach II, $H_{i\ (in\ vitro)}$)

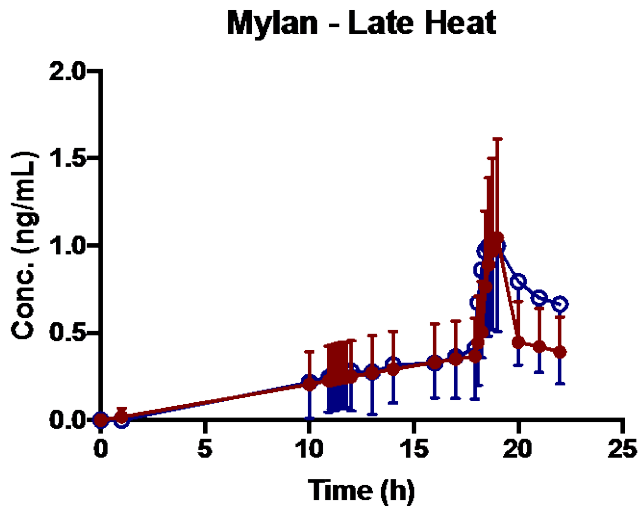




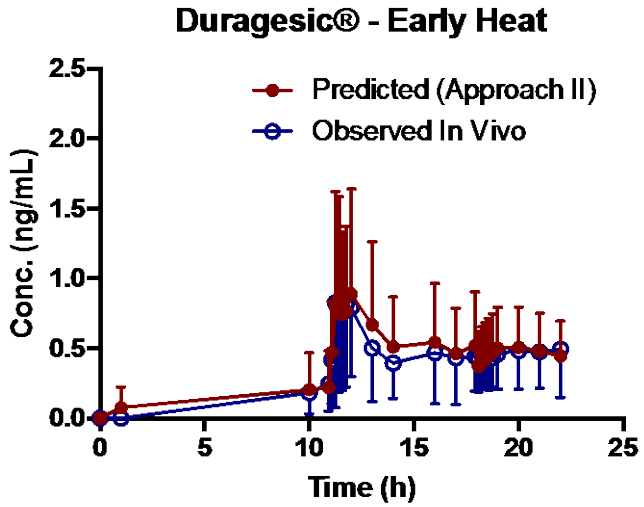


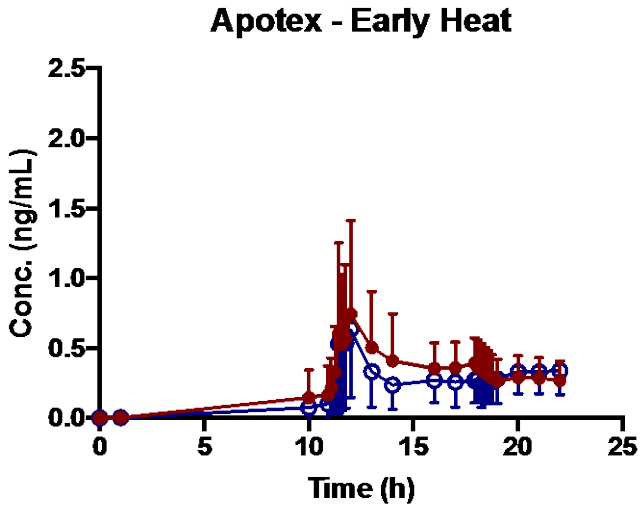


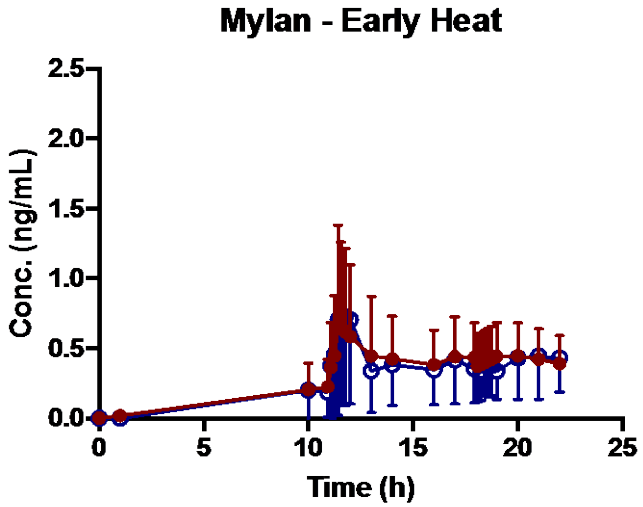


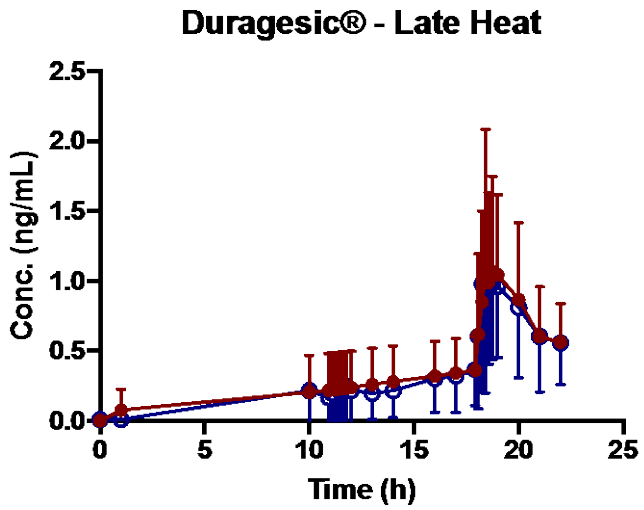


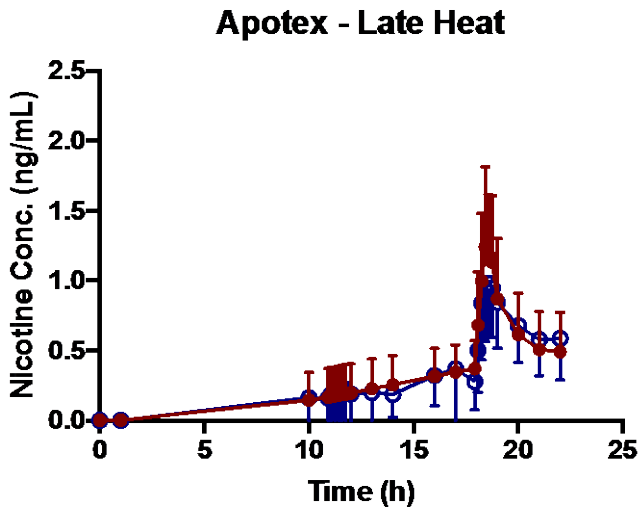
IVIVC: Level A (Approach III, $H_{ii\ (in\ vivo)}$)

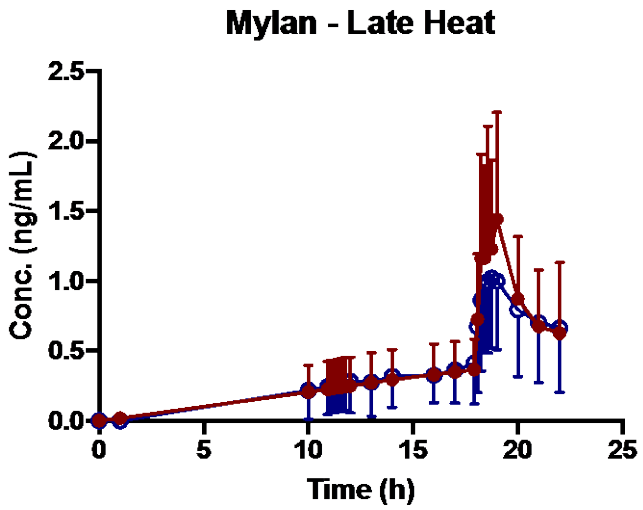












% Prediction Errors

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	5.6	19.4	48.8	40.5	4.9	1.9
	CL = 51 L/h	55.3	75.6	163.0	106.6	54.3	44.3
	CL = 27 L/h	193.3	231.5	396.8	290.3	191.3	172.6
C_{max}	CL = 75 L/h	5.8	19.3	3.6	18.7	9.2	21.7
	CL = 51 L/h	38.5	18.8	52.4	19.6	33.6	15.2
	CL = 27 L/h	161.7	124.2	187.8	125.9	152.3	117.6
Approach II (H_i)							
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 (H_{ii})							
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 – Fentanyl

- Early vs. Late Heat effect comparable both *in vitro* and *in vivo*
- Heat effect on three differently formulated TDS comparable both *in vitro* and *in vivo*
- However, in vivo heat effect seemed to be higher compared to the in vitro heat effect
- IVIVCs between IVPT and clinical human PK studies under the matched study designs

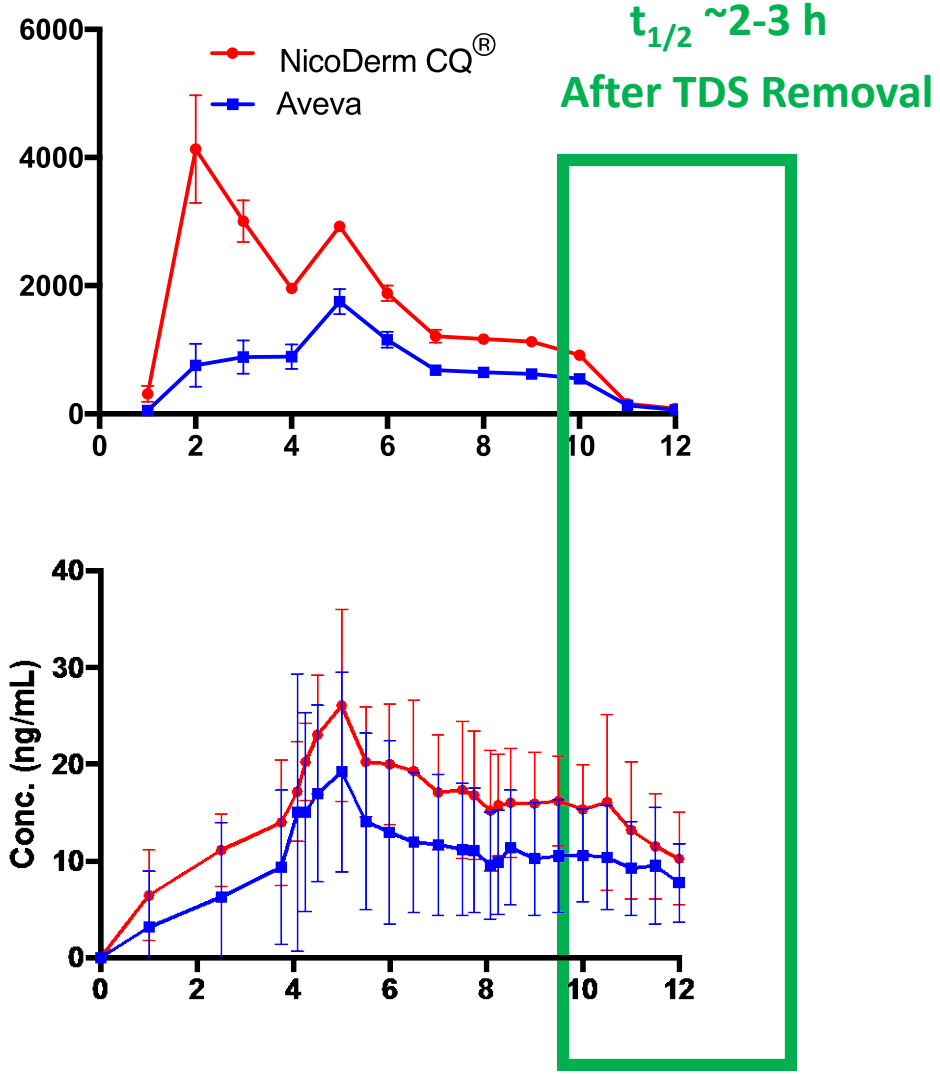
  ⇒ Less strong compared to nicotine…

Why??

1. Lipophilicity of Fentanyl

In Vitro

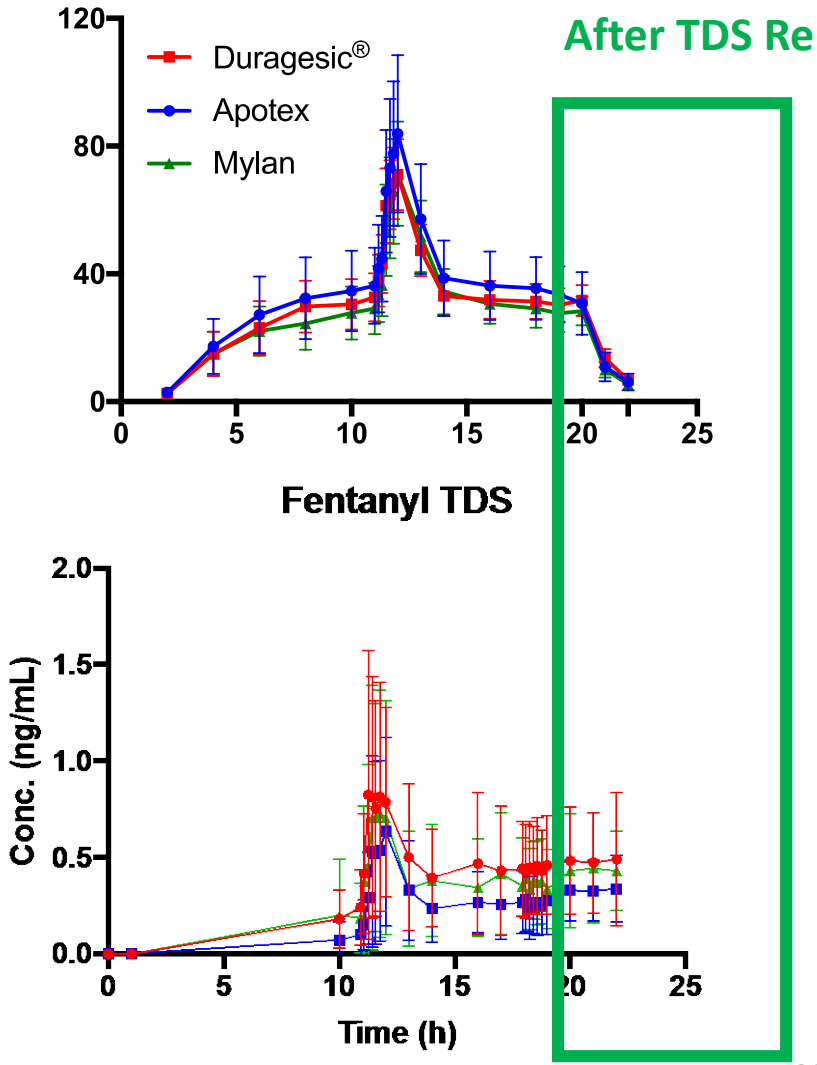
In Vivo



$t_{1/2}$ ~2-3 h
After TDS Removal

In Vitro

In Vivo

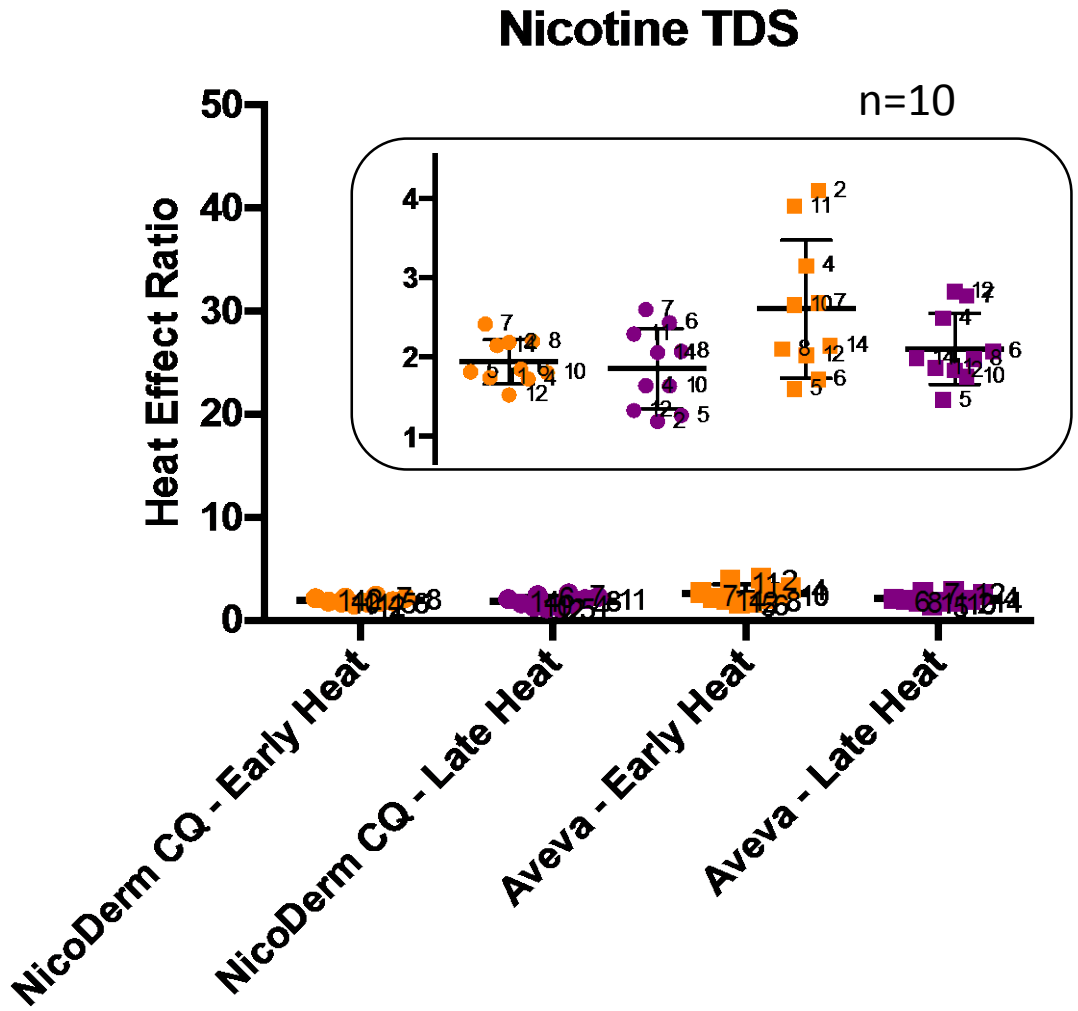


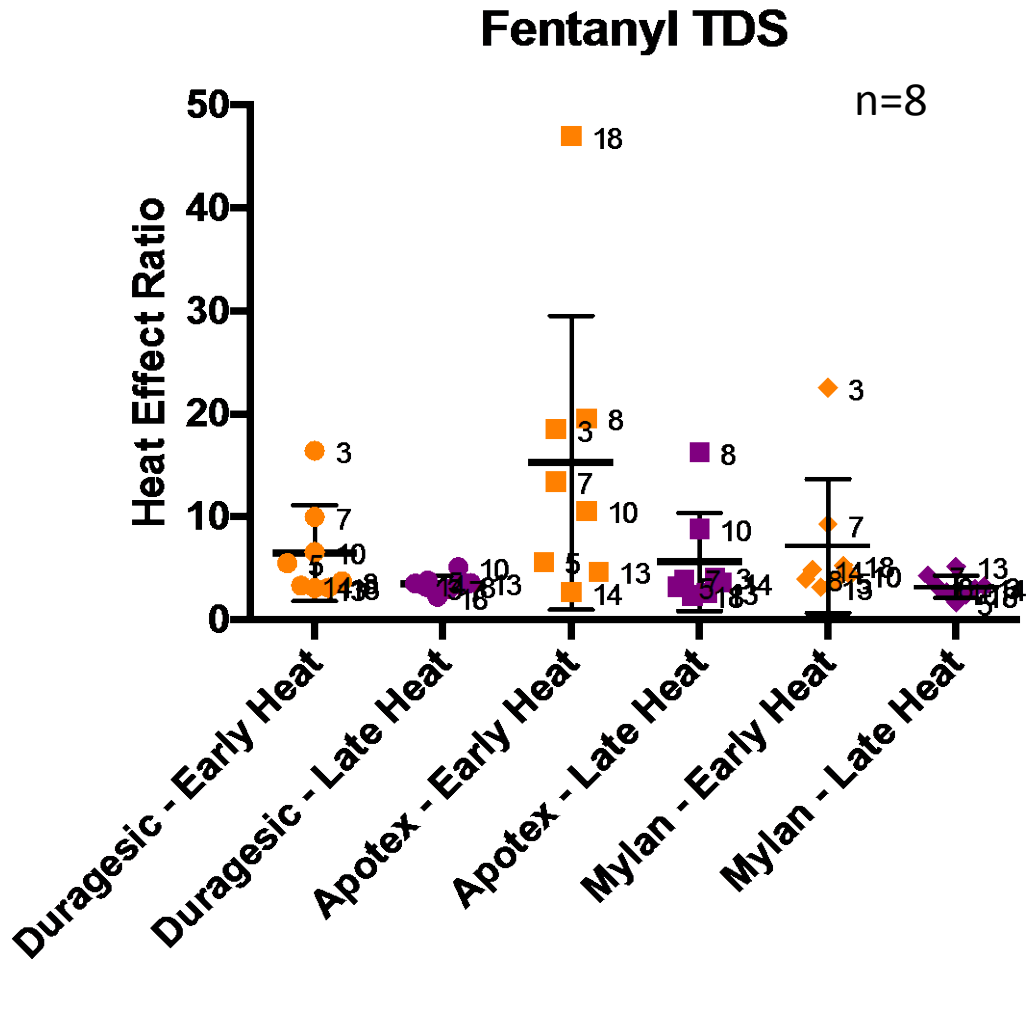
$t_{1/2}$ ~20-27 h
After TDS Removal

2. High Inter-subject Variability of Fentanyl

Reference	Subject #	Condition	Cl (L/h)
Ariano et al. J Clin Pharmacol 2001	18	Healthy	128
Bower et al. Br J Anaesth 1982	7	Healthy	92
Bentley et al. Anesth Analg 1982	5	Surgical	59
McClain et al. Clin Pharmacol Ther 1980	5	Healthy	57
Varvel et al. Anesthesiology 1989	8	Surgical	46
Shibutani et al. Anesthesiology 2004	16	Surgical	43
Haberer et al. Br J Anaesth 1982	13	Surgical	42
Scott et al. J Pharmaol Exp Ther 1986	15	Healthy	34
Hengstmann et al. Br J Anaesth 1980	5	Surgical	26
Schleimer et al. Clin Pharmacol Ther 1978	6	Surgical	12
Fung et al. J Clin Pharmacol 1980	9	Healthy	10
Univ. of Maryland, Baltimore (ongoing)	13	Healthy	10
Duragesic® Prescribing Information	?	Surgical	27 - 75

3. Higher *in vivo* heat effect for fentanyl





Conclusions - IVIVC

- Three approaches were evaluated to demonstrate Level A IVIVC for TDS
- Strong IVIVC demonstrated for nicotine TDS, including heat effect
- Weaker IVIVC found for fentanyl TDS
  - Limitation of mimicking drug reservoir in skin layers, microcirculation and subcutaneous tissue in vitro
  - High inter-subject variability for fentanyl (+ Lack of reliable PK parameters)

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

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Thank You

for your attention!

Any Questions?