Heat Effects and IVIVC in Transdermal and Topical Drug Delivery

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The views expressed in this presentation do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

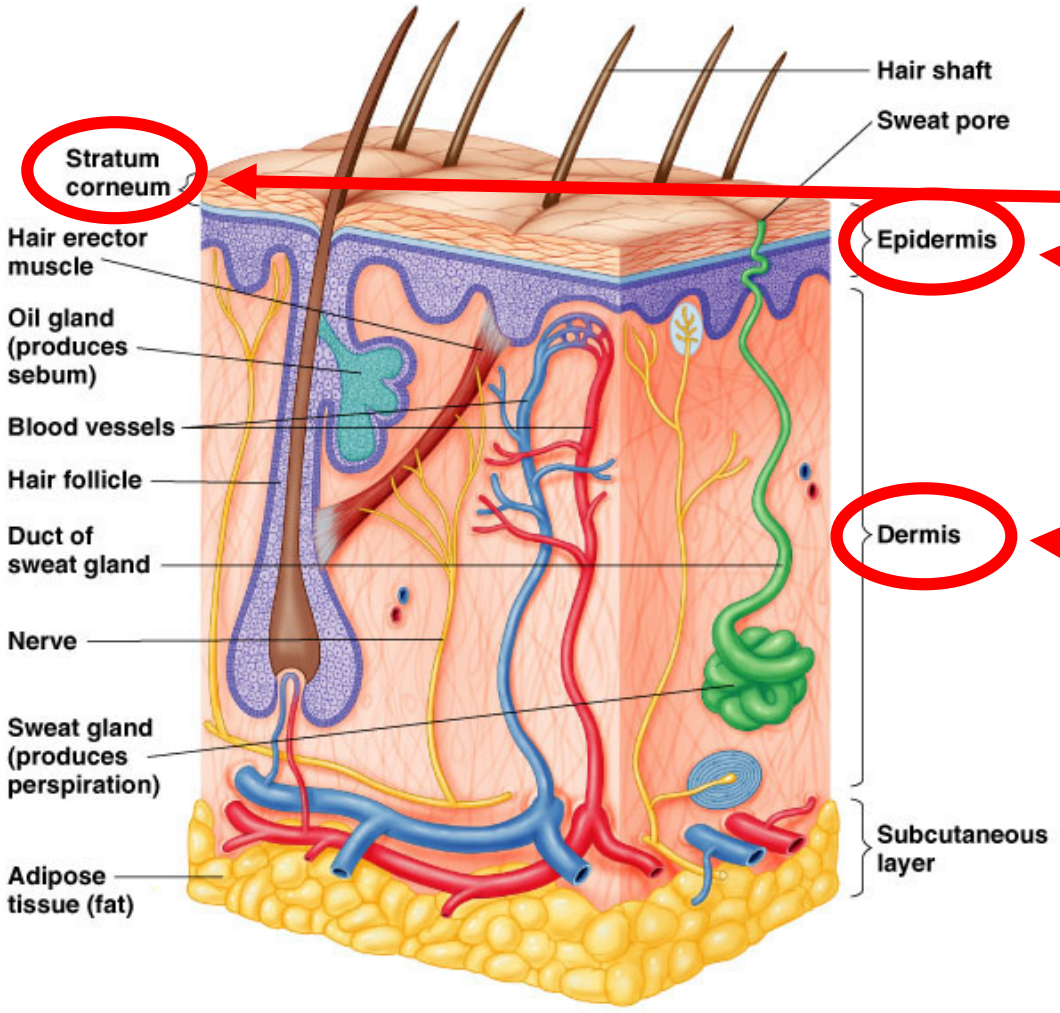
IVIVC

- 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

Skin Structure



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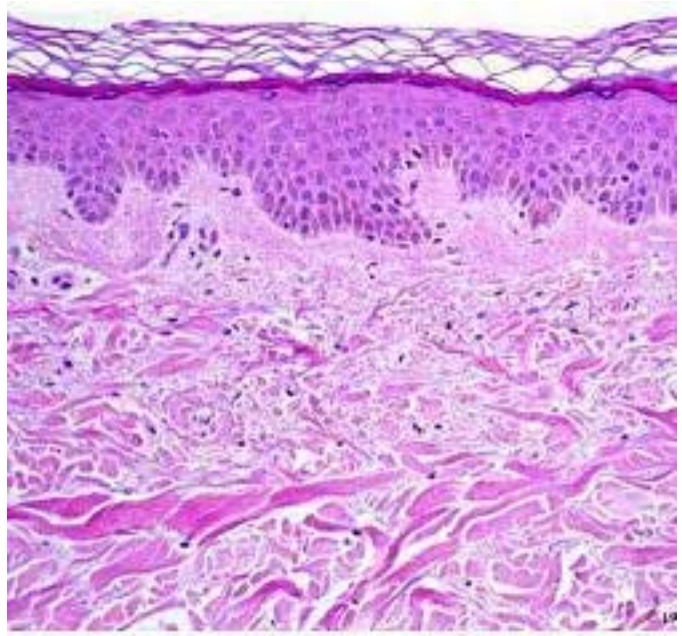


Images from http://classes.midlandstech.edu/carterp/courses/bio225/chap21/ss1.htm and http://www.scienceprog.com/skin-structure/

Factors affecting Percutaneous Absorption

Drug

- M.W. < 500 Dalton
- Suitable log $P_{oil/water}$
  - High log P (very lipophilic) -> too much retention in the skin
  - Low log P (very hydrophilic) -> difficult to cross the SC
- Unionized molecules cross SC at faster rate

Vehicle/Formulation

(Inactive Ingredients)

- Partition coefficient, $k_{membrane/vehicle}$
- pH

Skin

- Hydration level
- Age
- Gender
- Race
- Species
- Disease state

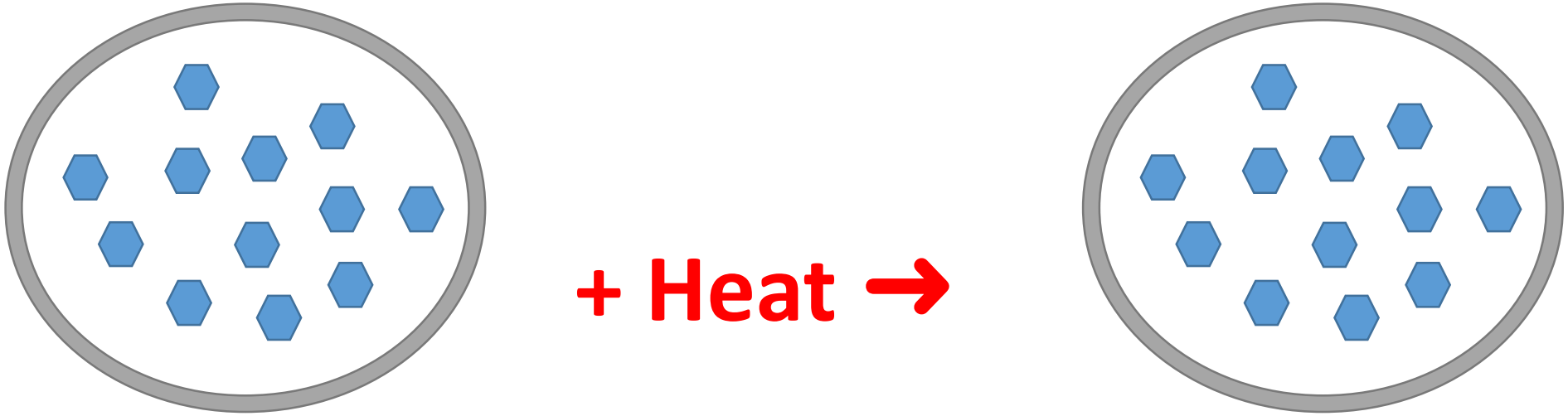
Environmental factors

- Humidity
- Occlusion
- Heat (high temperature)

Flynn G.L. (2002). Cutaneous and Transdermal Delivery – Processes and Systems of Delivery. In *Modern Pharmaceutics* (pp. 187-235).
Barry B.W. (2007). Transdermal Drug Delivery. In *Aulton's Pharmaceutics: The Design and Manufacture of Medicines* (pp. 565-597).

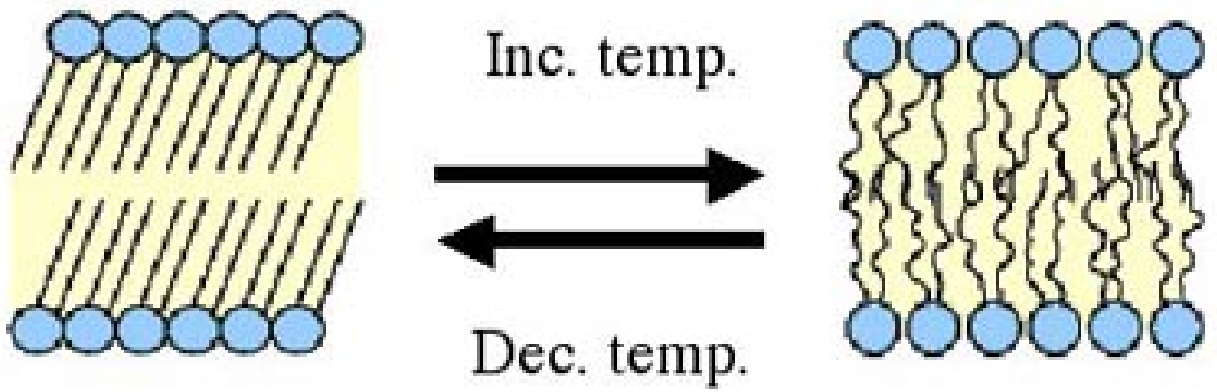
Influence of Heat on Percutaneous Absorption

1) ↑ Diffusivity of Drug from its Vehicle



Influence of Heat on Percutaneous Absorption

2) ↑ Fluidity of Stratum Corneum Lipids



Very regular,
Ordered structure

Less tightly packed,
Hydrocarbon tails
Disordered.

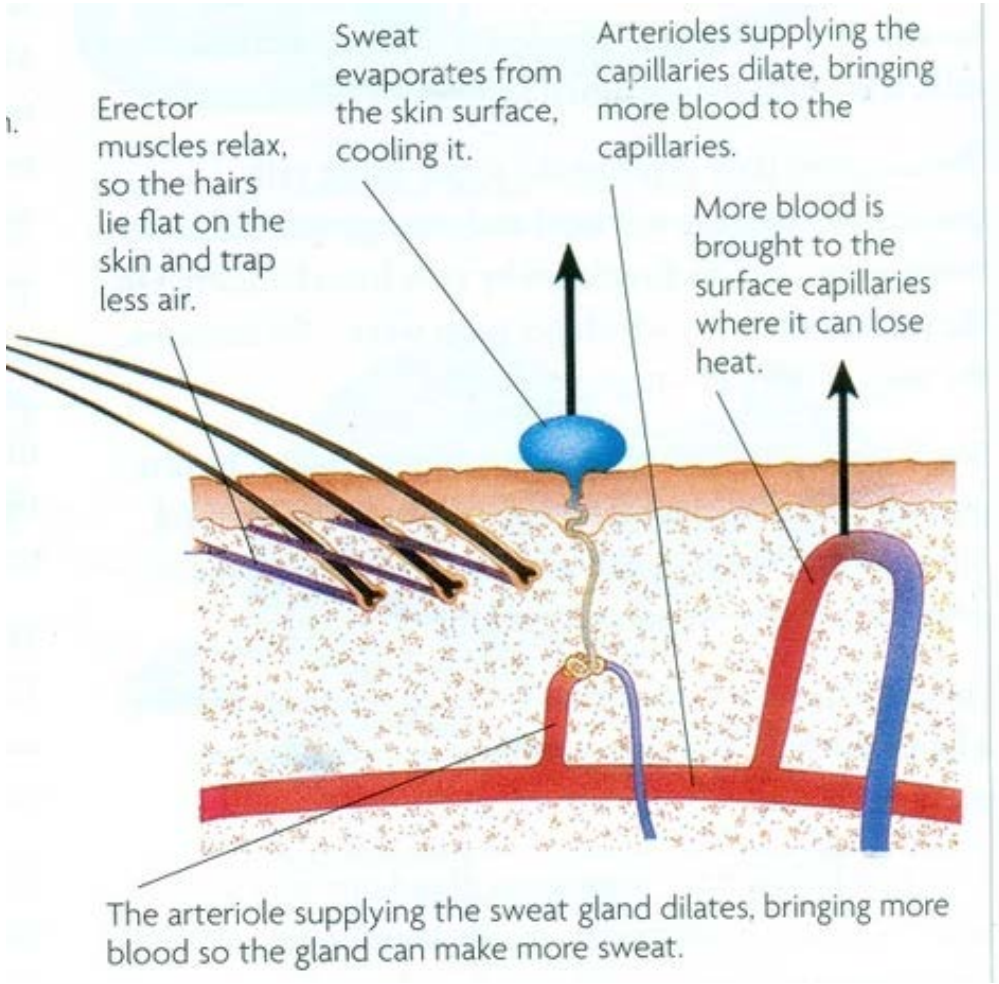
https://biochemistry3rst.wordpress.com/tag/phosphodiate/

Influence of Heat on Percutaneous Absorption

3) ↑ Cutaneous Vasodilation

Body temperature regulation

When the body is too hot



NDC 50458-091-05 **Five** (25mcg/h) **Systems**

DURAGESIC® 25 mcg/h
(FENTANYL TRANSDERMAL SYSTEM)

CII

In vivo delivery of 25mcg/h fentanyl for 72 hours

Because it can cause trouble breathing which can be fatal, DO NOT USE DURAGESIC®:

- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

Each transdermal system contains: 4.2mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

PriCara

Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

ONLY for pain requiring opioid medicine around-the-clock

DURAGESIC® 25 mcg/h (FENTANYL TRANSDERMAL SYSTEM)

Inactive Ingredients: polyester/ethyl vinyl acetate, polyacrylate adhesive

Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from pouch and after removal of the protective liner. Do not expose area to heat. Store in original unopened pouch. Store up to 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F).

See Medication Guide for important safety information.

For your convenience in recording narcotic use,

INITIAL/DATE

1._____ 2._____ 3._____

4._____ 5._____

For questions about DURAGESIC®, call the Ortho-McNeil-Janssen Scientific Affairs Customer Communications Center at 1-800-526-7736. If this is a medical emergency, please call 911.

Manufactured by:
ALZA Corporation
Vacaville, CA 95688

Manufactured for:
PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869

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Revised May 2009 0017965-2

PriCara

Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

ONLY for pain requiring opioid medicine around-the-clock

Questions

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

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

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

Model Drugs: Nicotine & Fentanyl

Specific Aims

I. Evaluation of the influence of transient heat (1h) on the release and permeation of drug from TDS using the in vitro permeation test (IVPT)

II. Evaluation of the influence of transient heat (1h) on the TDS pharmacokinetics *in vivo* by conducting PK studies in human subjects

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

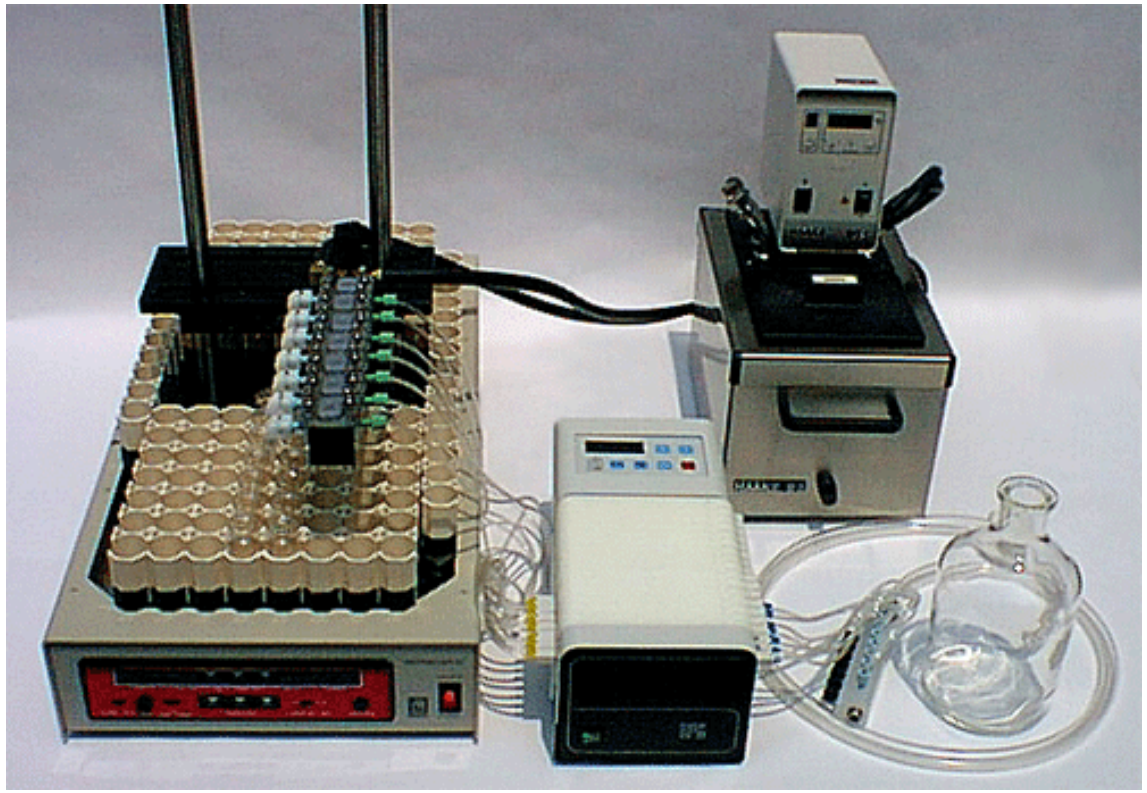
Methods: Skin Preparation

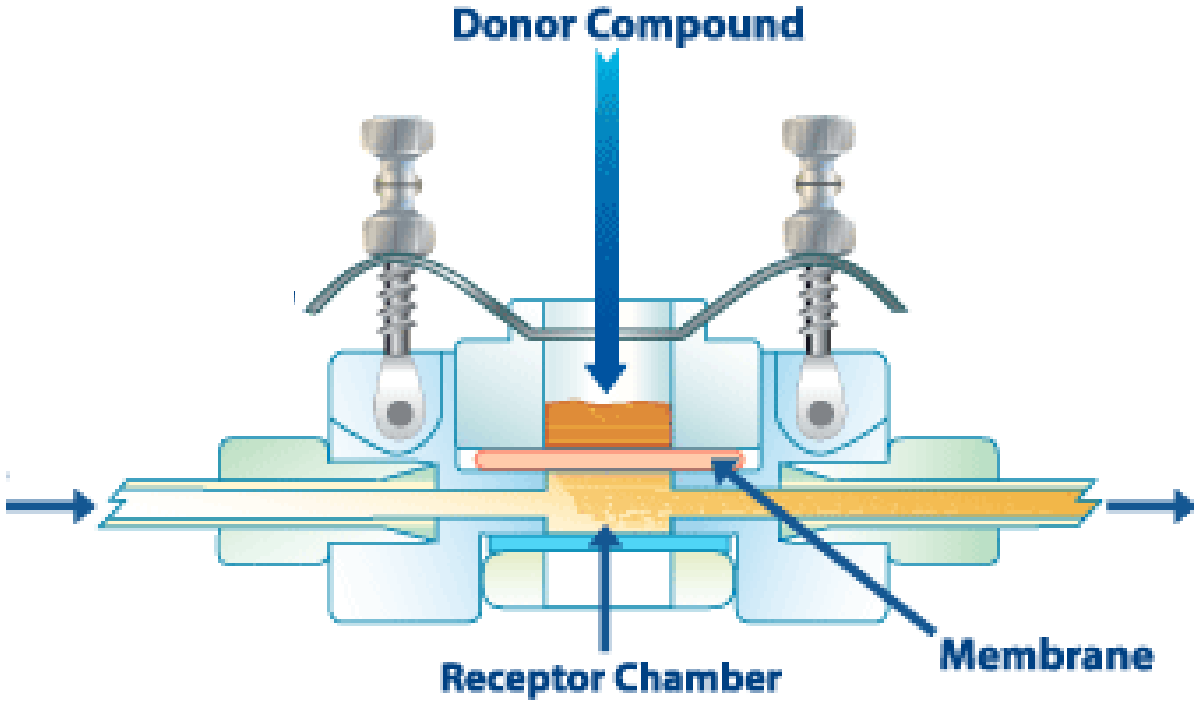
- Fresh human skin samples obtained post abdominoplasty surgery
- Dermatomed to ~250 microns
- Frozen until the day of experiment

Image obtained from the Stinchcomb Lab's SOP

IVPT Setup

- In-line flow-through diffusion system
- Permeation area of 0.95 cm^2

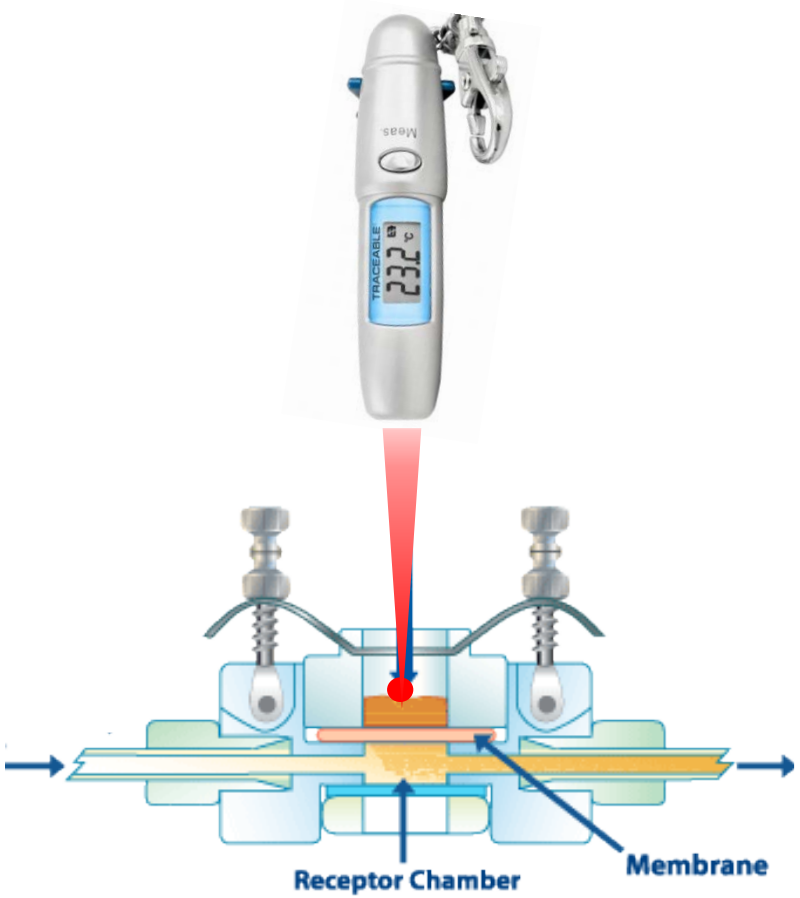


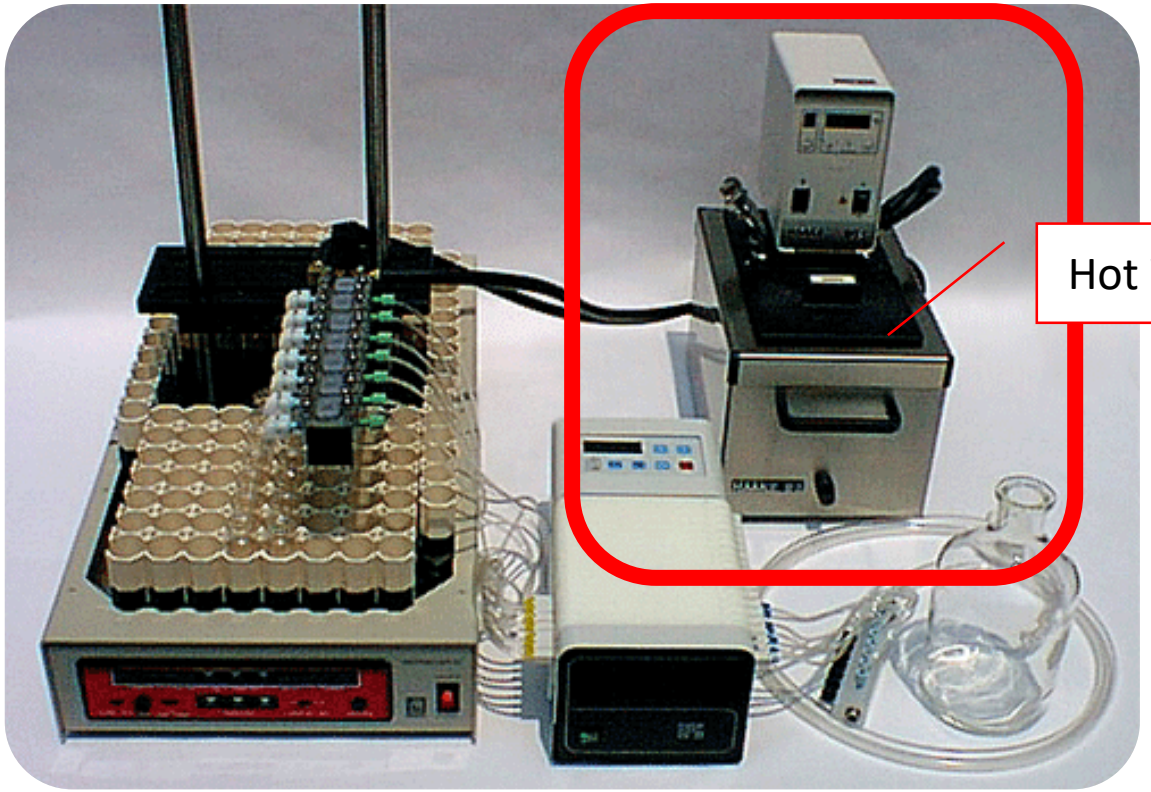


Images from www.ibric.org and www.permegear.com

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

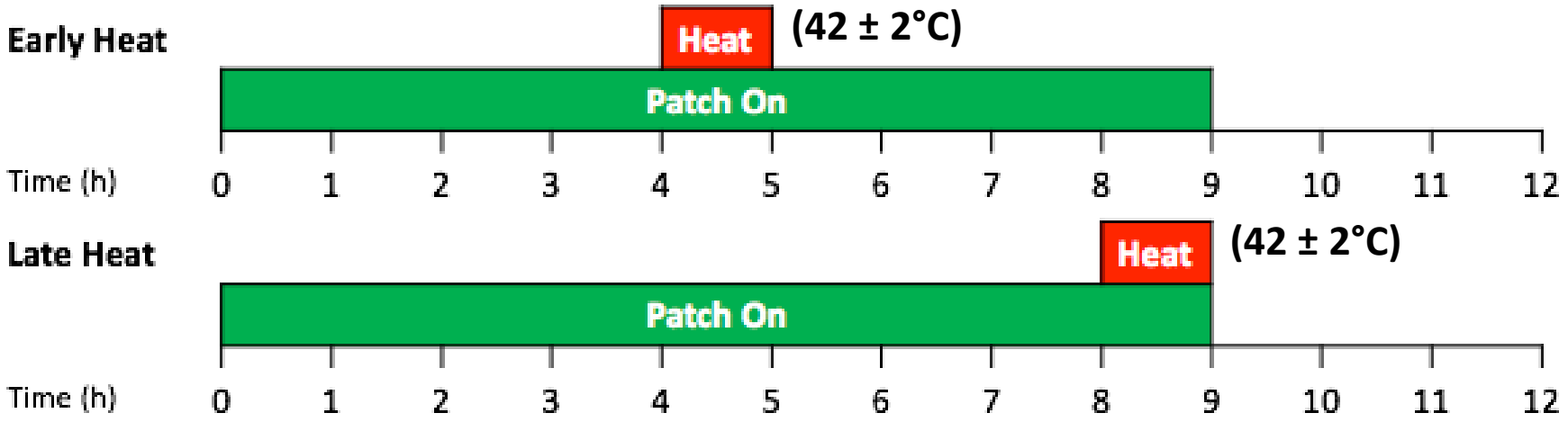
- Pre-heated heating pad
- ACE™ Bandage to ensure good contact between TDS and heating pad

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

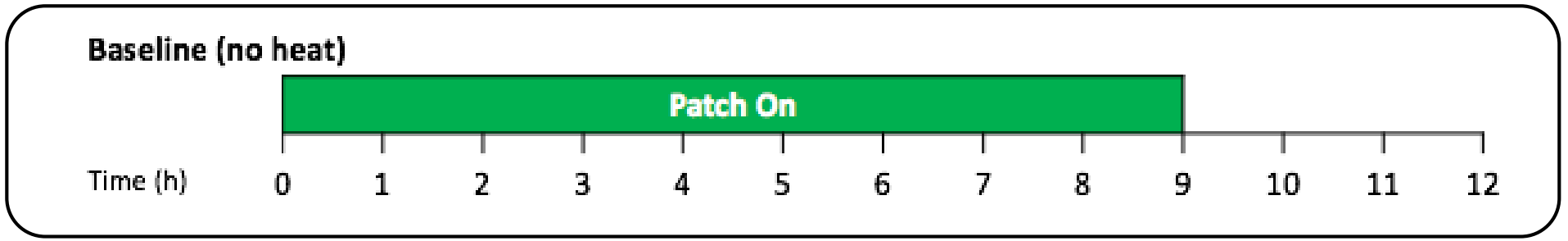
Nicotine TDS, 14 mg/24 hr

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

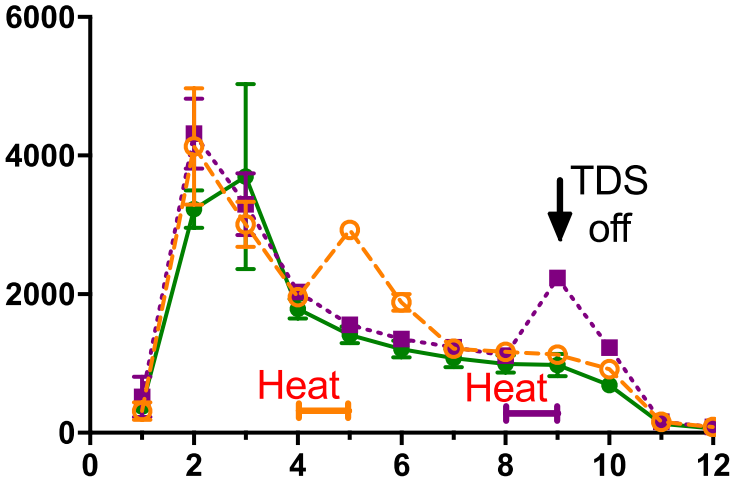
Study Designs

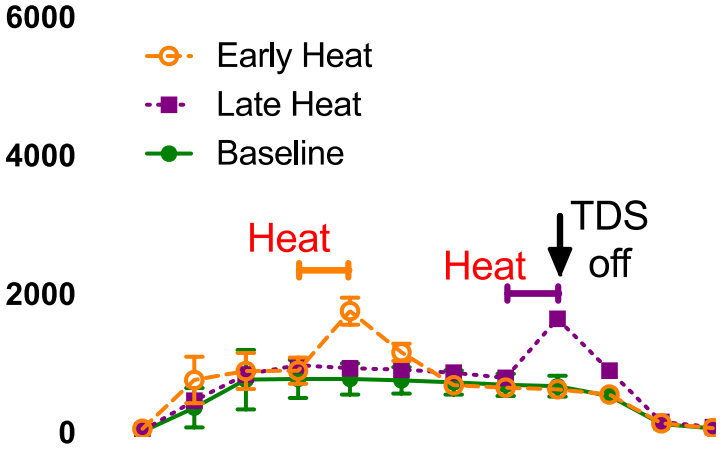


In Vitro Only

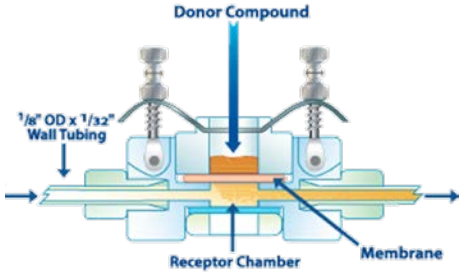


IVPT Results

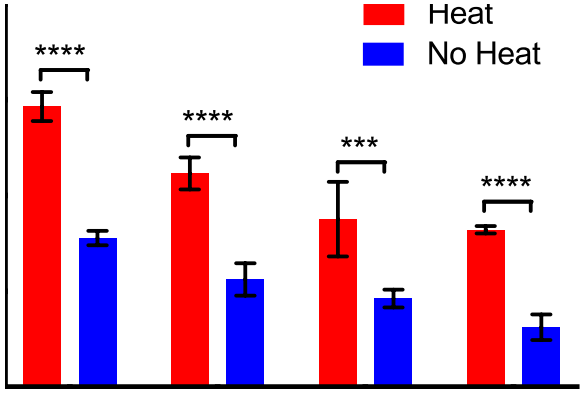


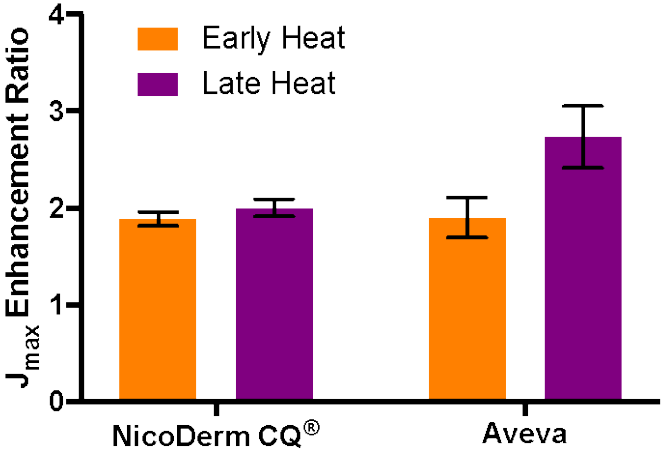


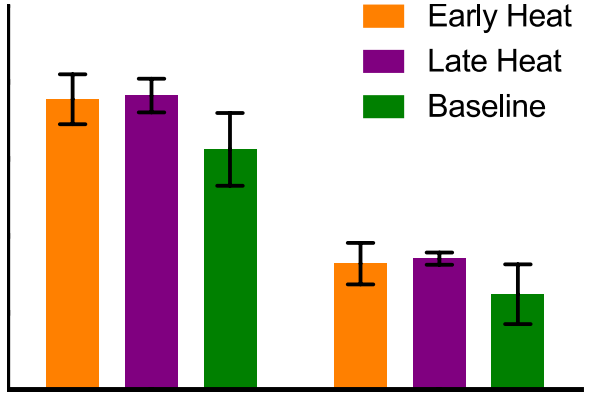
Human Skin Data



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

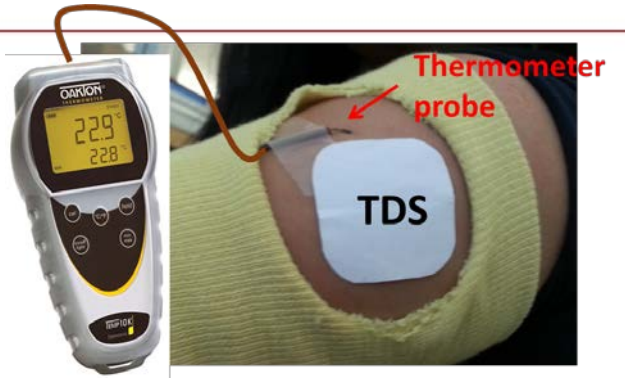




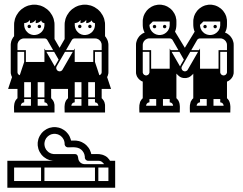


Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

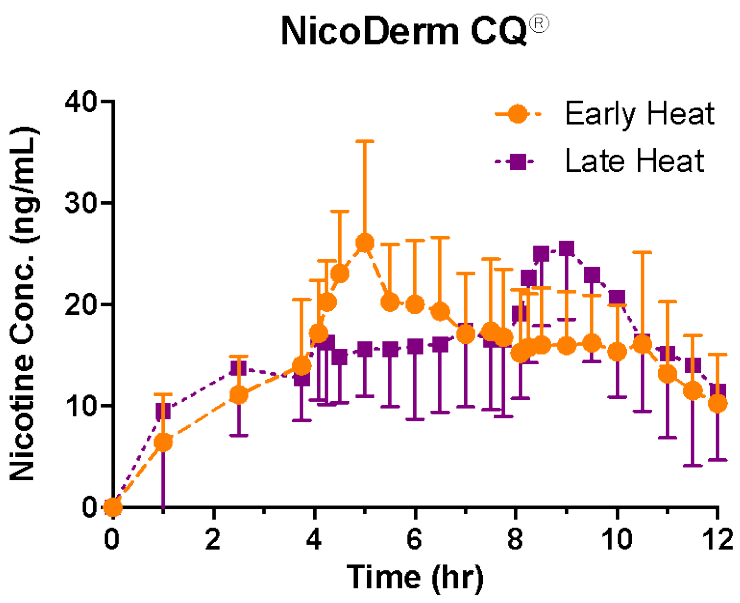
In Vivo Results

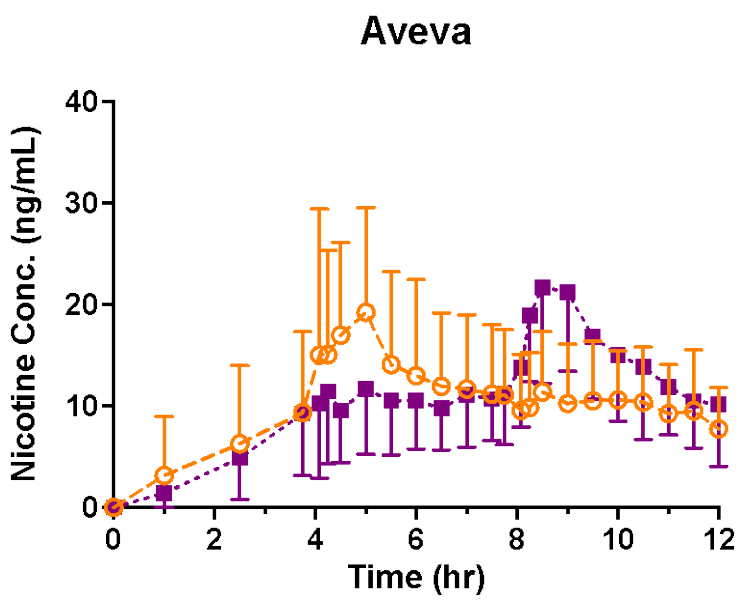


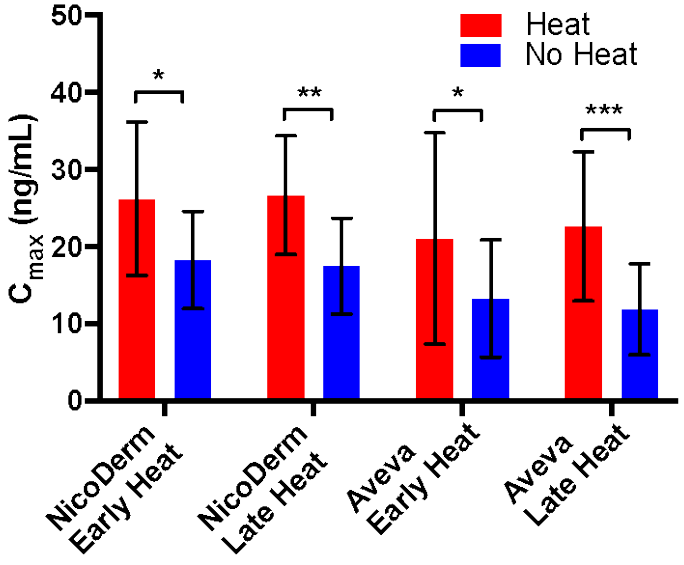
Mean ± SD
from 10 human subjects

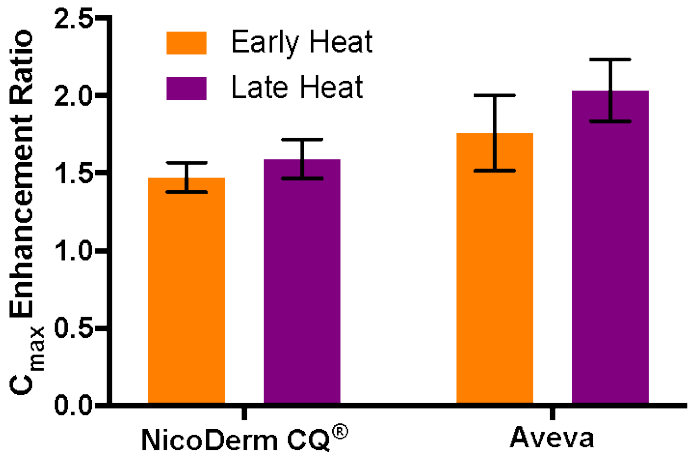


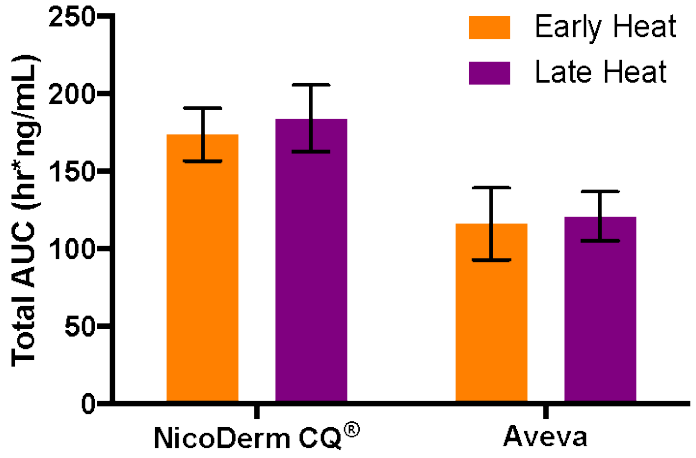
Patch off 9h





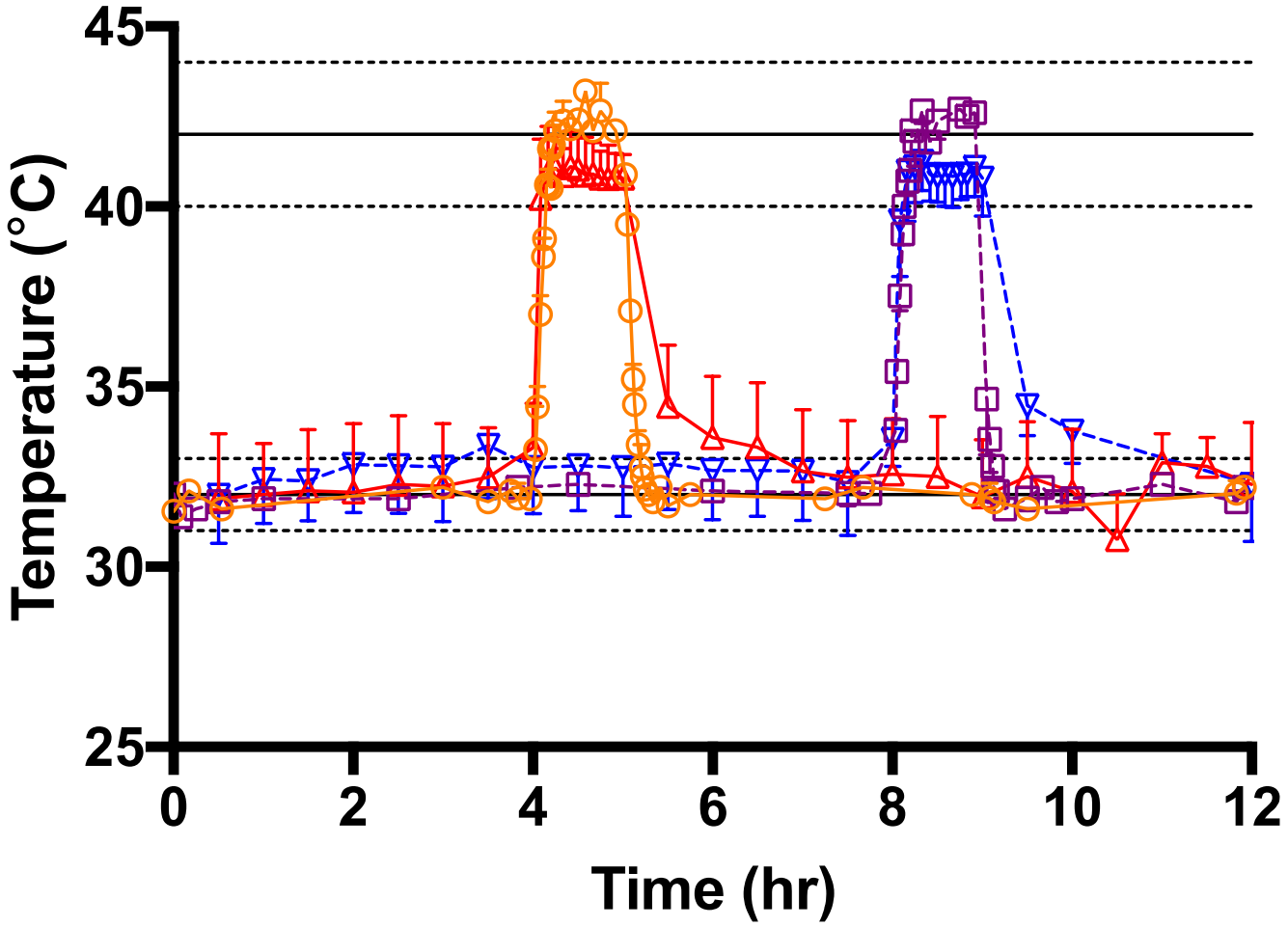






Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

Temperature: *In Vitro* & *In Vivo*



Early Heat - In Vitro

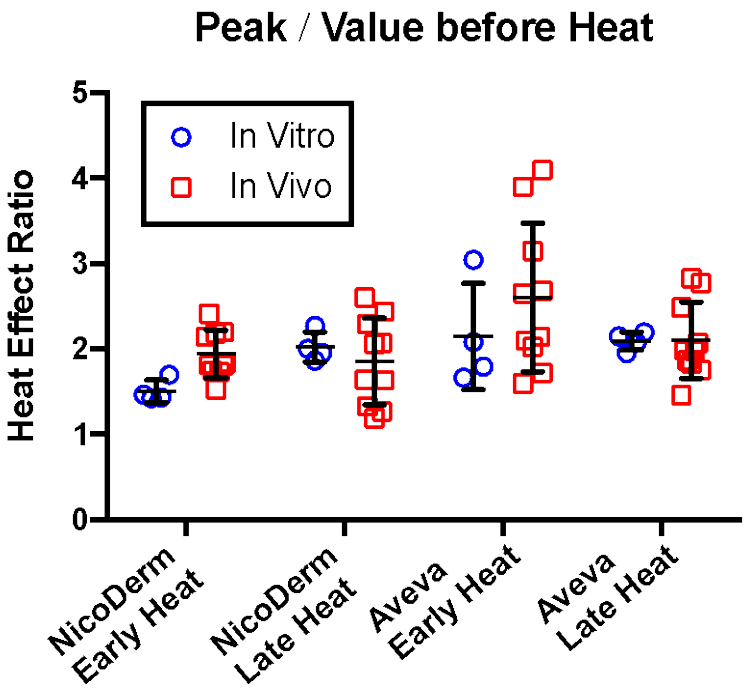
Late Heat - In Vitro

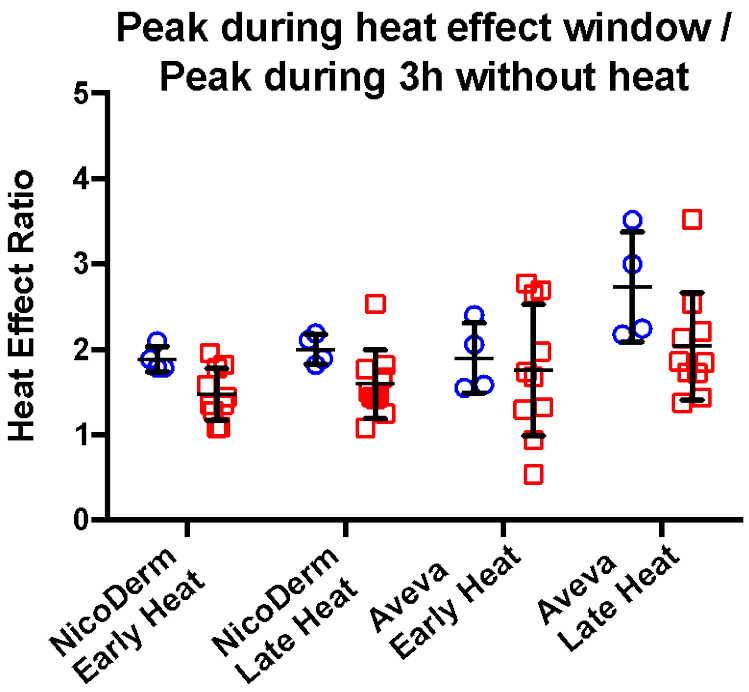
Early Heat - In Vivo

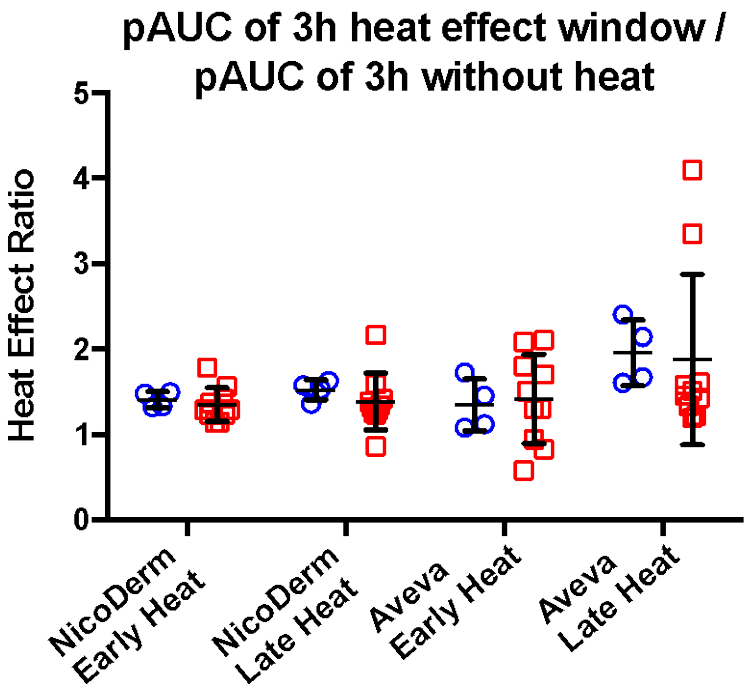
Late Heat - In Vivo

(42 ± 2°C)

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

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

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

Approach I
Level A

Eq. 1 for prediction while TDS was worn:

$$C_s = \frac{F \times R_{in} \times H_i}{CL_{IV}} \times \left(1 - e^{-k_1 t}\right)$$

Eq. 2 for prediction after TDS removal:

$$C_s = C_0 \times e^{-k_2 t}$$

C_s: Predicted in vivo serum concentration

F: Absolute bioavailability for TDS $\quad F = \frac{AUC_{0-\infty,TDS} \times Dose_{IV}}{AUC_{0-\infty,IV} \times Dose_{TDS}}$

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 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

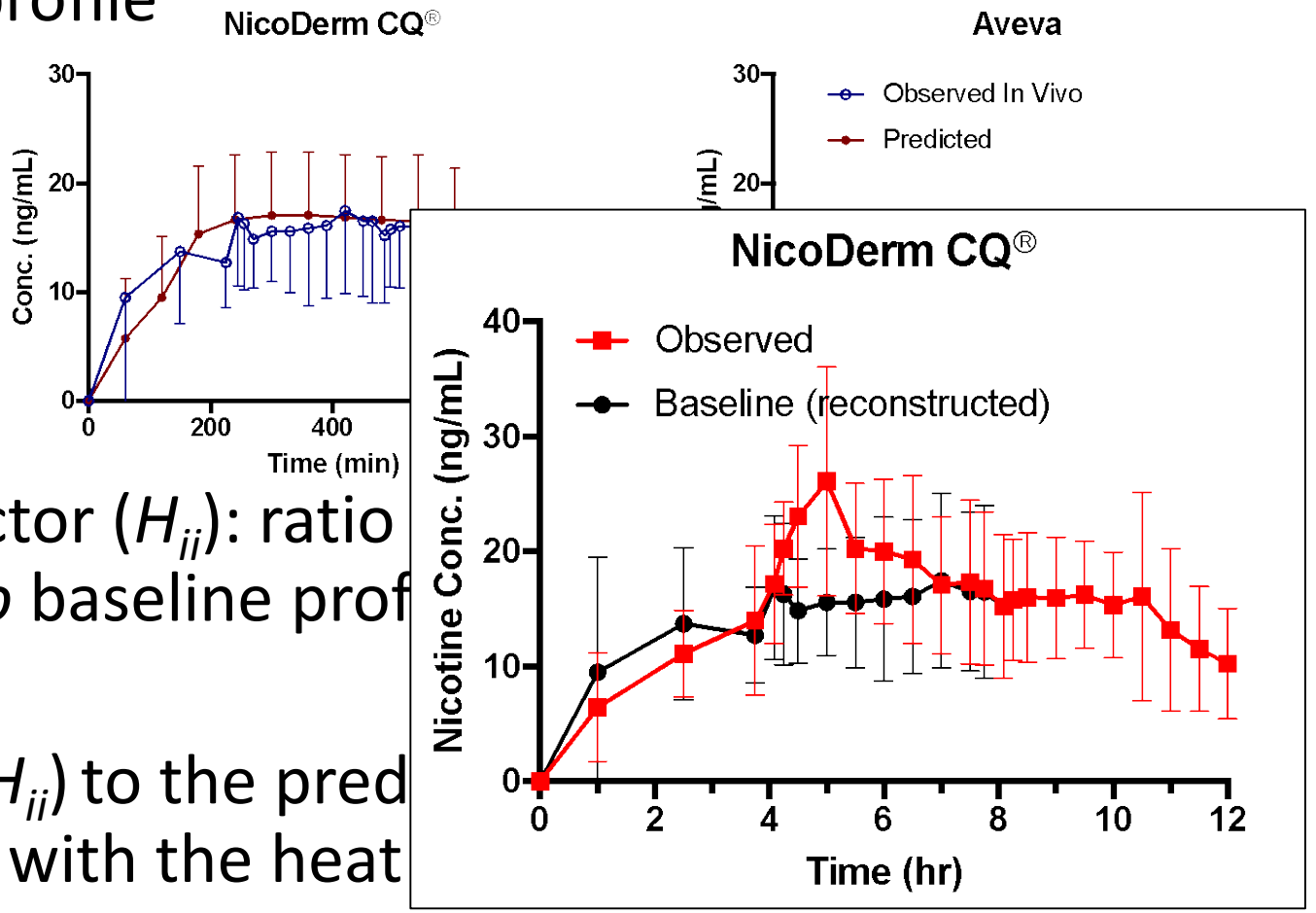
(k_1: after IV dose; k_2: after TDS dose)

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

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

Approach II and III

1. Reconstruct baseline (without heat) profile by combining non-heat portion from two study designs

2. Deconvolute in vivo baseline conc. vs time profile using Phoenix®

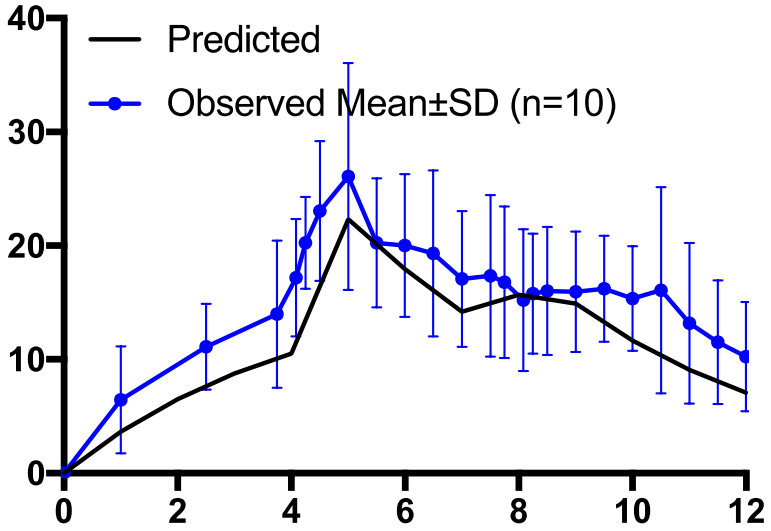
3. Construct IVIVC model by plotting fraction permeated in vitro vs. fraction absorbed in vivo

4. Predict in vivo fraction absorbed using the IVIVC model and IVPT data

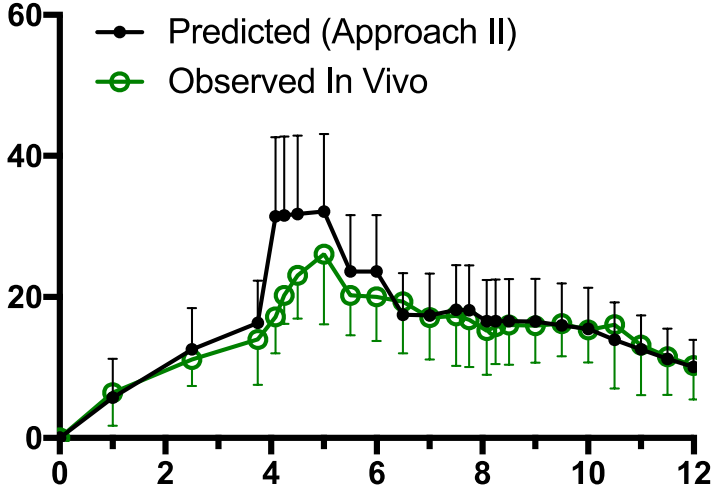
5. Convolute the predicted in vivo fraction absorbed data using Phoenix® to obtain conc. vs. time profile

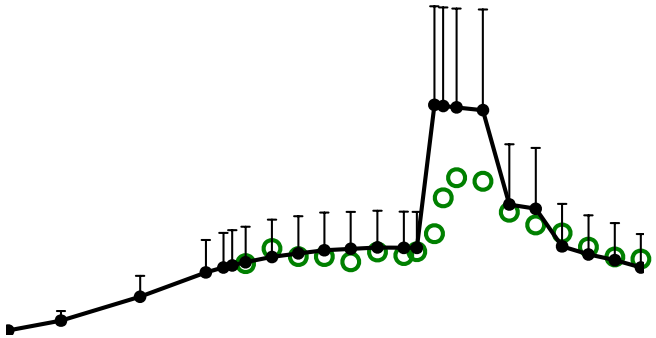
6. Apply in vitro heat effect coefficient, H_i (Approach II) or in vivo heat effect coefficient, H_{ii} (Approach III) to the predicted in vivo profile

Approach I

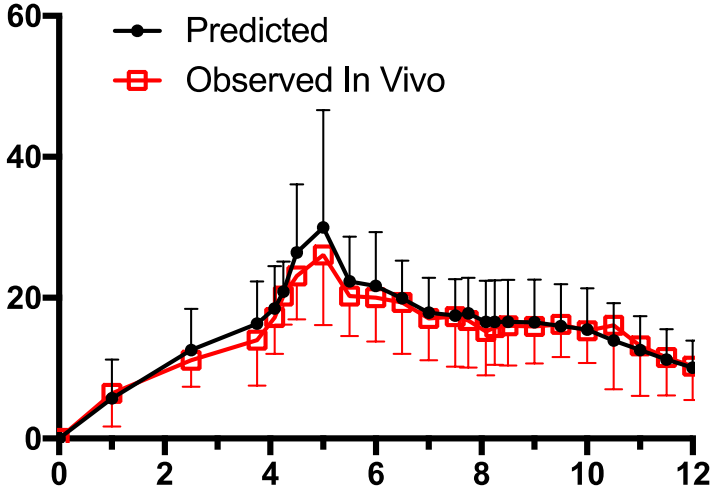


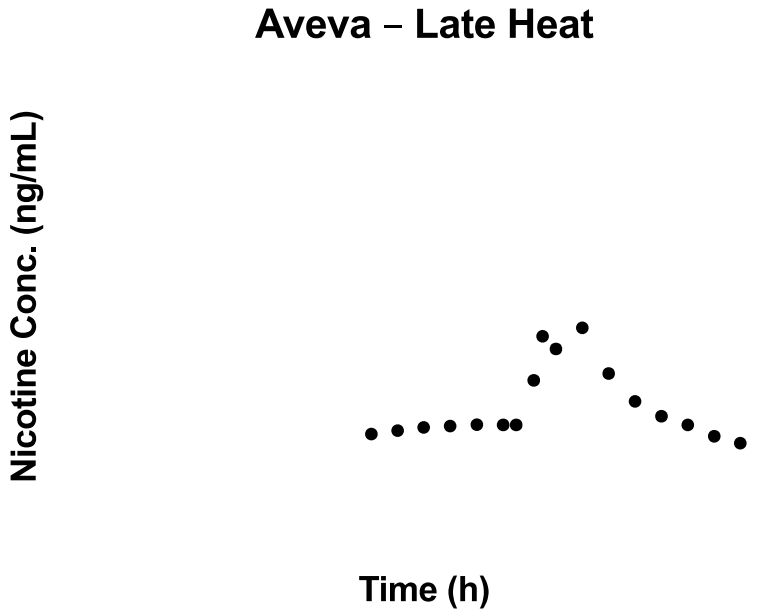
Approach II





Approach III

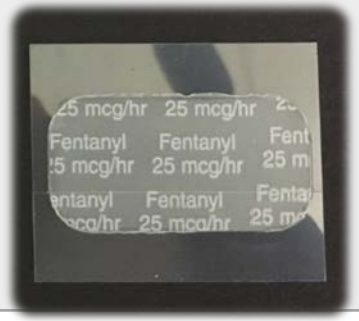




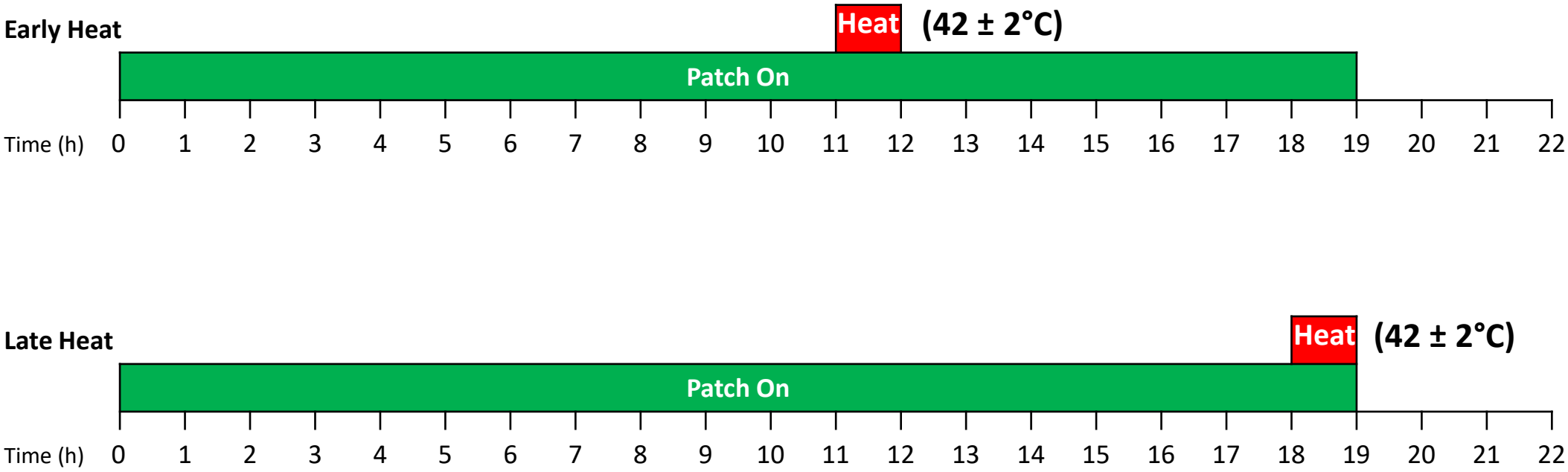
% Prediction Error

Nicotine TDS	NicoDerm CQ®		Aveva	
	Early Heat	Late Heat	Early Heat	Late Heat
Approach I				
Total AUC	20.3	12.9	7.5	5.0
C_{max}	14.4	16.6	9.8	13.5
Approach II				
Total AUC	10.3	5.0	1.5	13.3
C_{max}	23.3	30.2	3.5	47.5
Approach III				
Total AUC	5.1	1.2	1.1	4.5
C_{max}	15.0	5.8	8.9	17.7

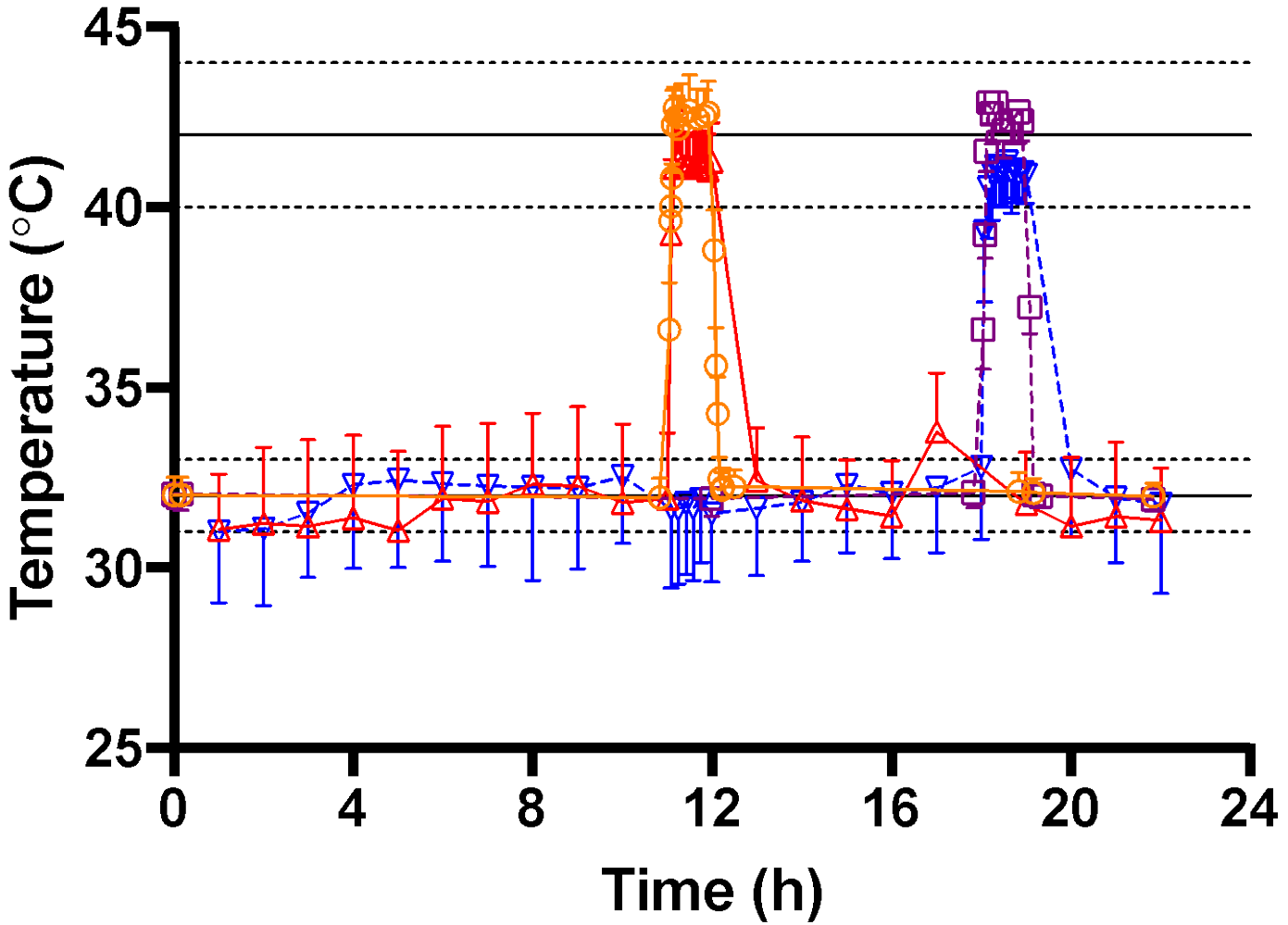
Fentanyl TDS, 25 µg/hr

	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



Temperature: In Vitro & In Vivo



Early Heat - In Vitro

Late Heat - In Vitro

Early Heat - In Vivo

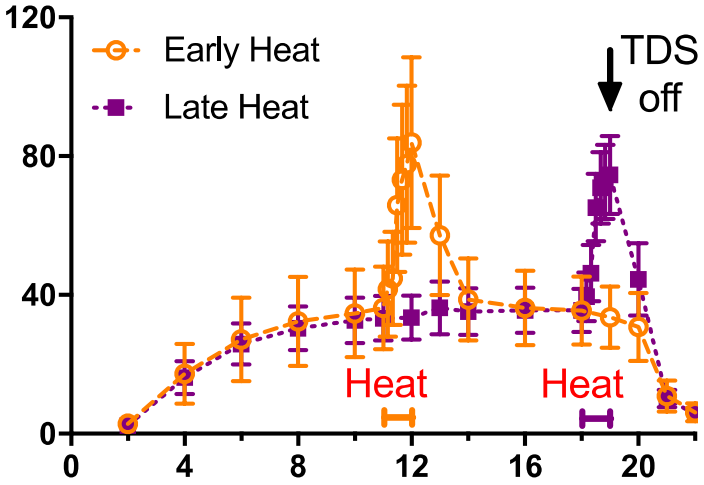
Late Heat - In Vivo

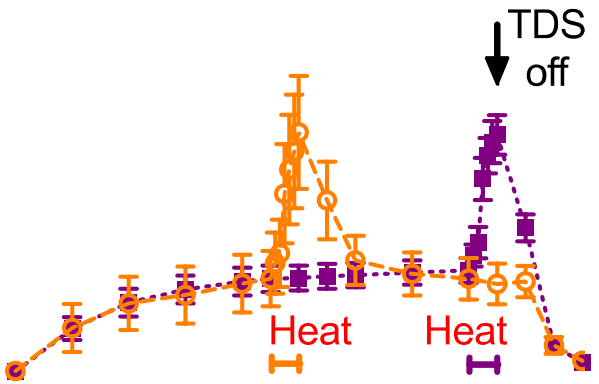
(42 ± 2°C)

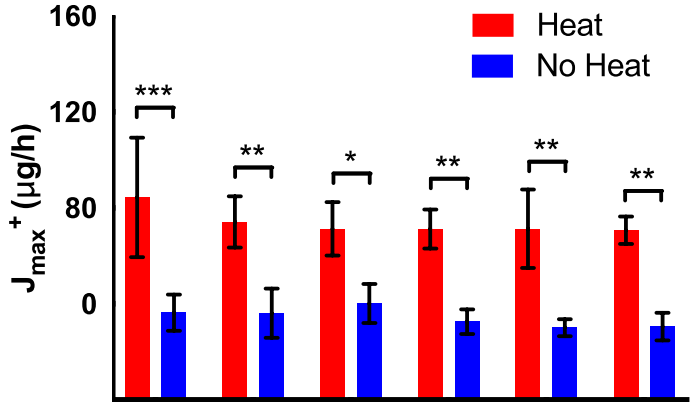
Human Skin Data

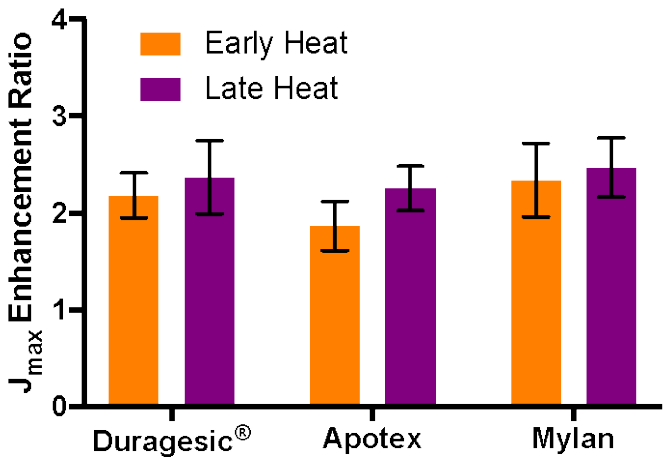
IVPT Results

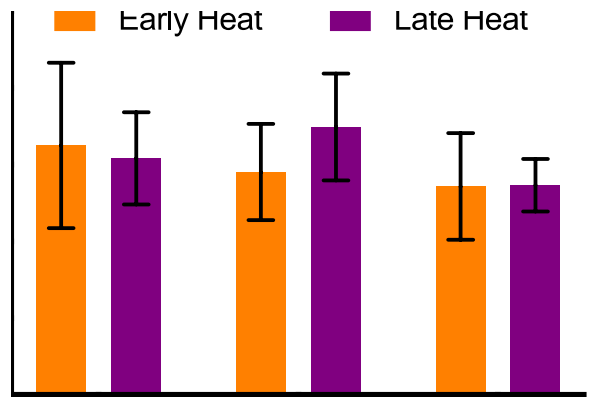
Mean ± SEM from 4 donors
with n=4 per each donor









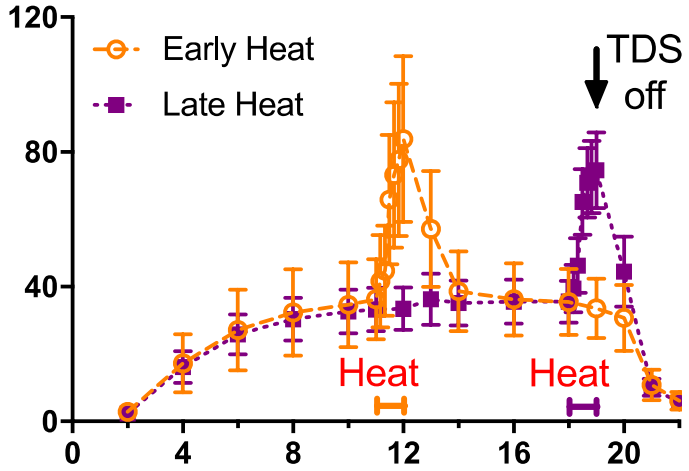


Two-way ANOVA followed by Bonferroni's post-hoc multiple comparisons

Results

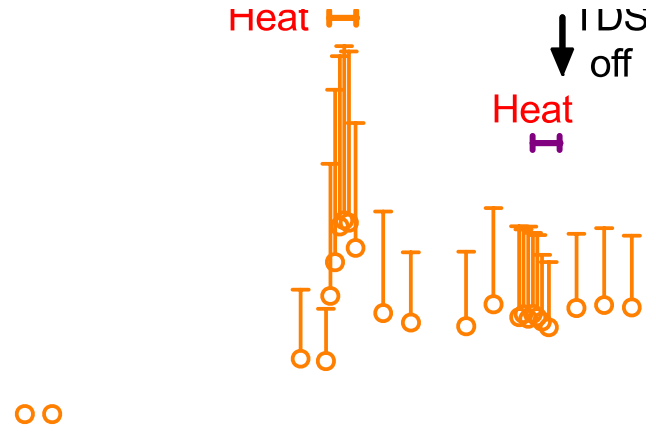
In Vitro

Mean ± SEM from 4 donors
with n=4 per donor (Human Skin)

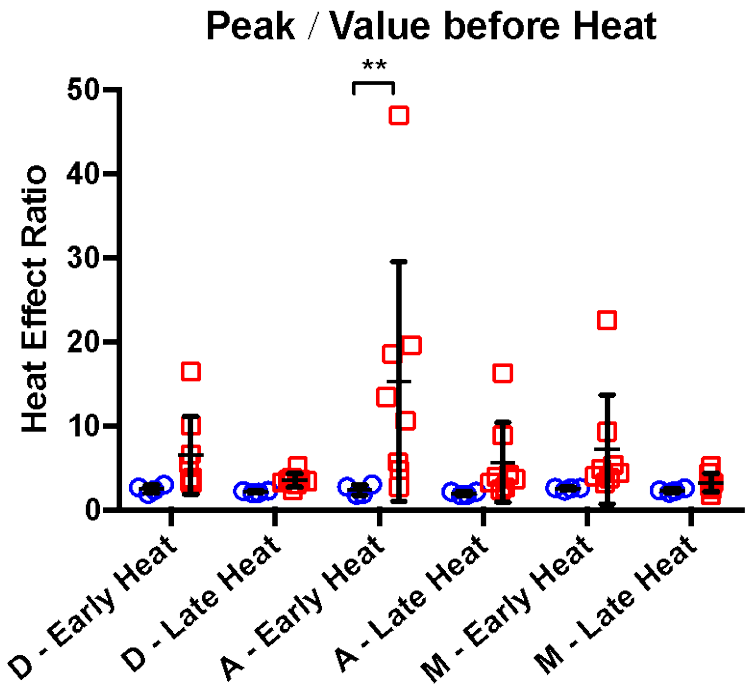


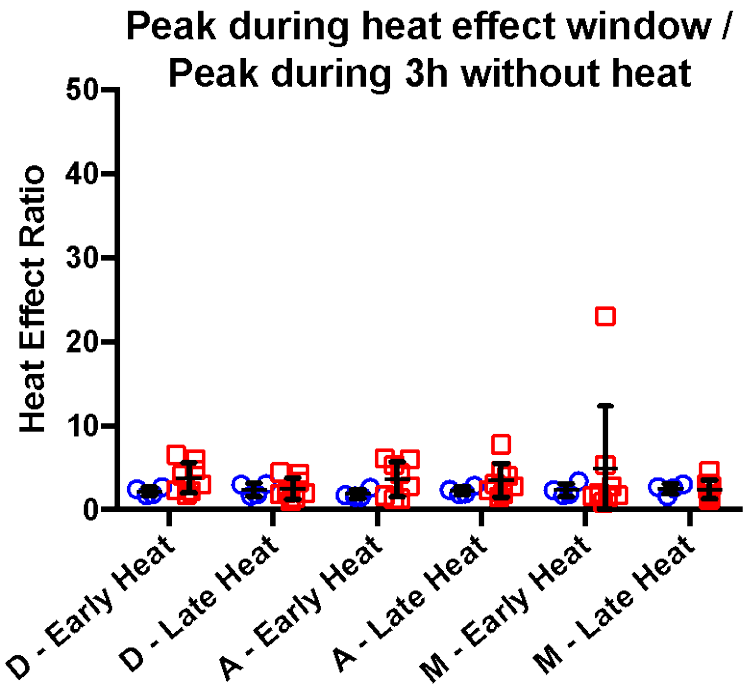
In Vivo

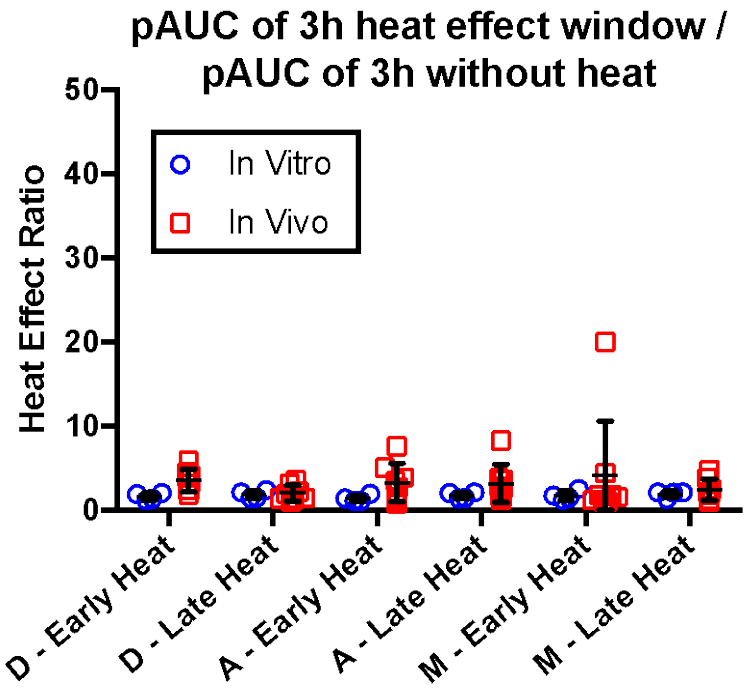
Mean ± SD from 10 Healthy Adults



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 10 subjects

Clearance Value of Fentanyl

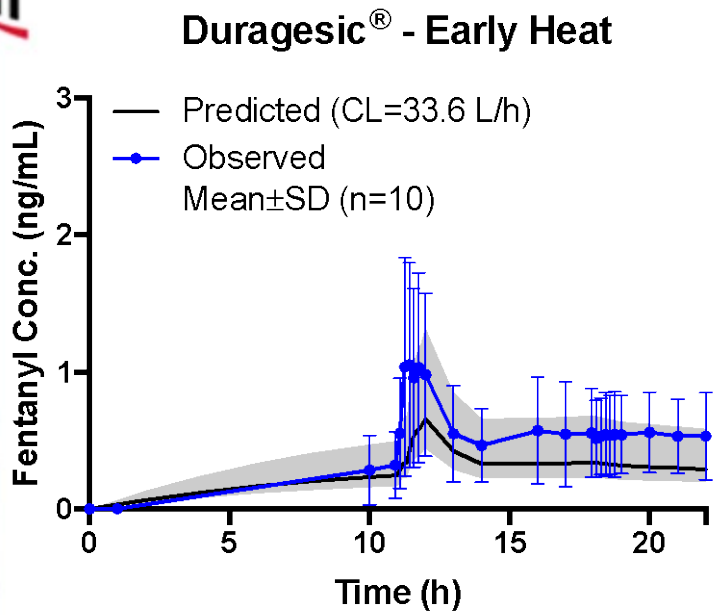
Reference	Subject #	Condition	CL_{IV} (L/h)	# of comp for PK Analysis
Ariano et al. J Clin Pharmacol 2001	18	Healthy	128	1
Bower et al. Br J Anaesth 1982	7	Healthy	92	2
Bentley et al. Anesth Analg 1982	5	Surgical	59	3
McClain et al. Clin Pharmacol Ther 1980	5	Healthy	57	3
Varvel et al. Anesthesiology 1989[1]	8	Surgical	46	3
Shibutani et al. Anesthesiology 2004	16	Surgical	43	3
Haberer et al. Br J Anaesth 1982	13	Surgical	42	2
Scott et al. J Pharmaol Exp Ther 1986	15	Healthy	34	2
Hengstmann et al. Br J Anaesth 1980	5	Surgical	26	2
Schleimer et al. Clin Pharmacol Ther 1978	6	Surgical	12	3
Fung et al. J Clin Pharmacol 1980	9	Healthy	10	3
Univ. of Maryland, Baltimore (ongoing)	14	Healthy	11	2

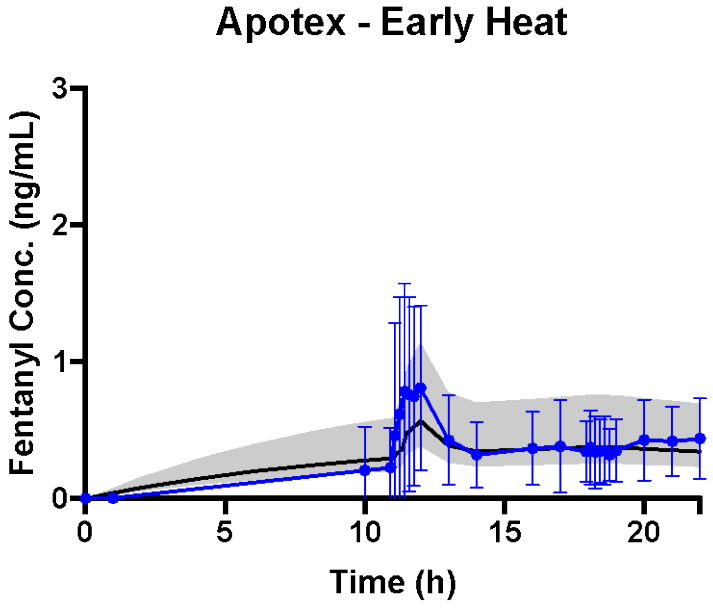
Weighted Mean CL_{IV} from Healthy subjects with PK value obtained from 2 or 3 compartmental analysis = **33.6 L/h**

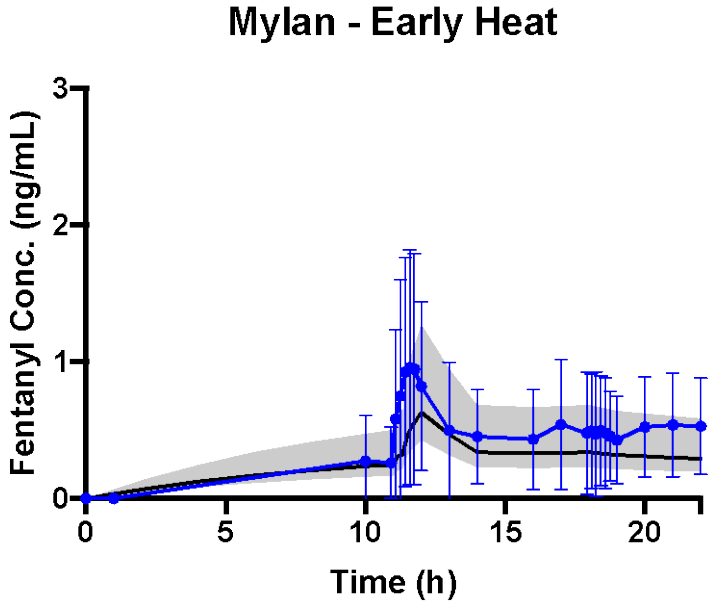
[1] Source of IV PK parameters reported in Duragesic® Package Insert

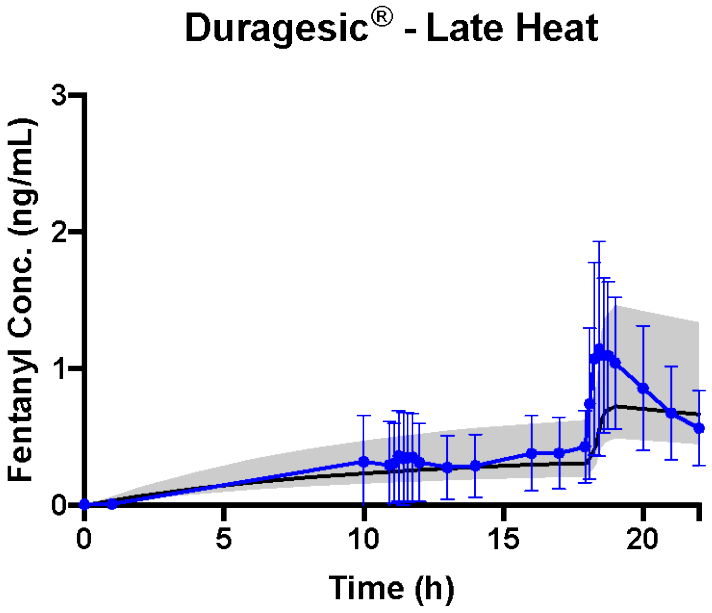
Approach I

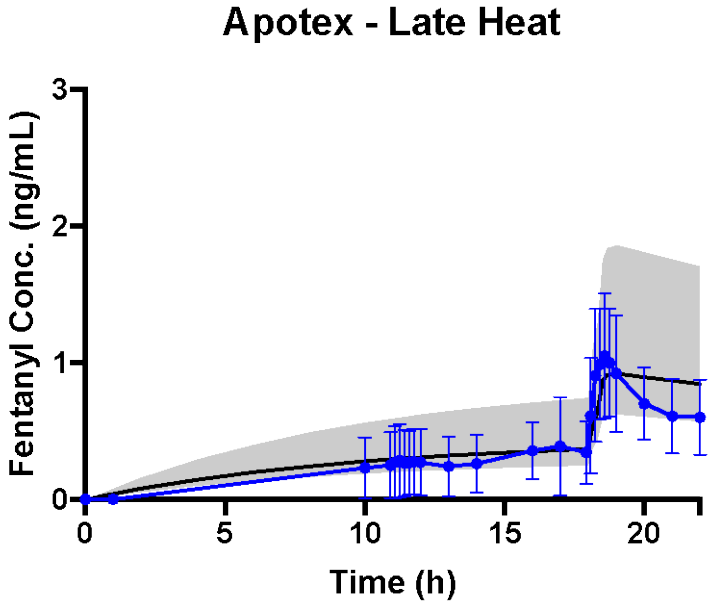
Grey shade represents prediction range when inter-subject variability of CL = 50%

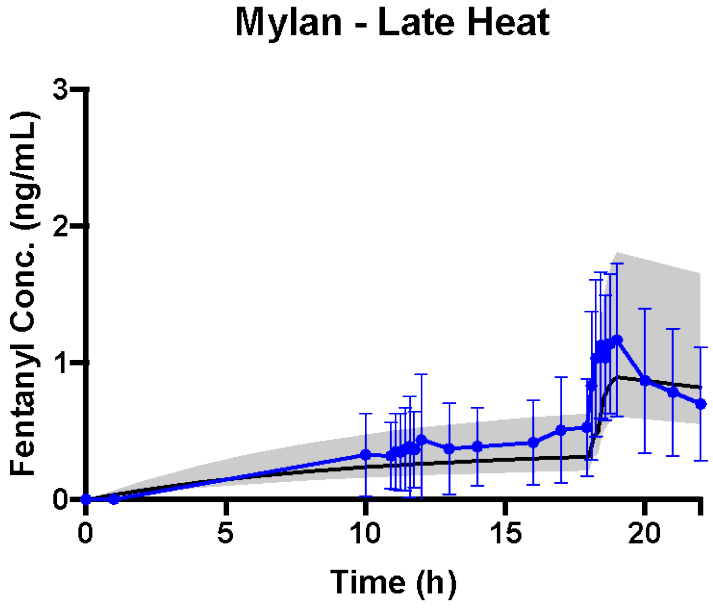






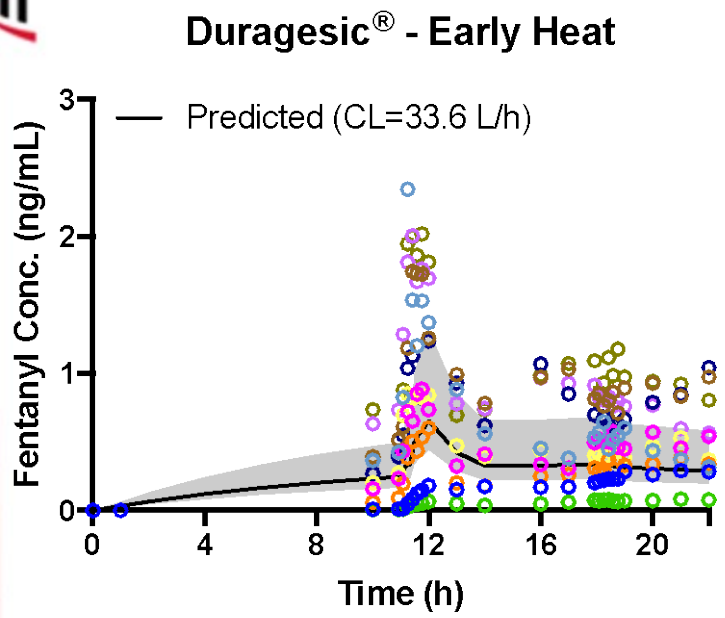


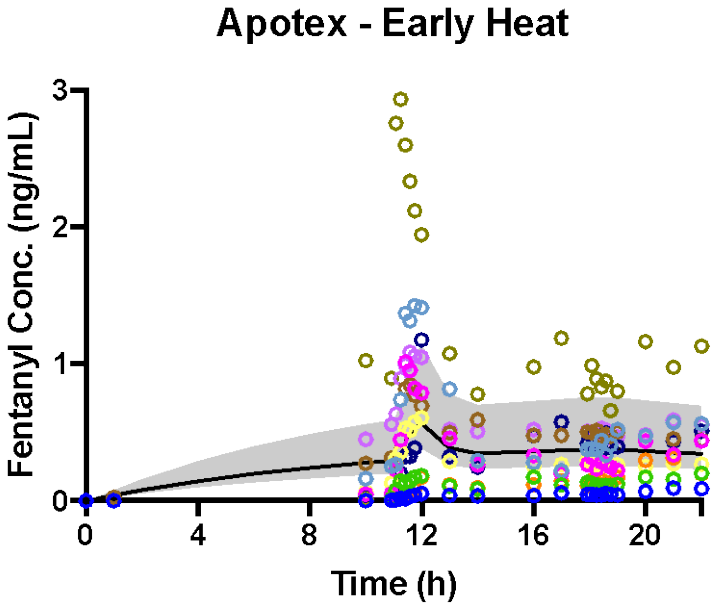


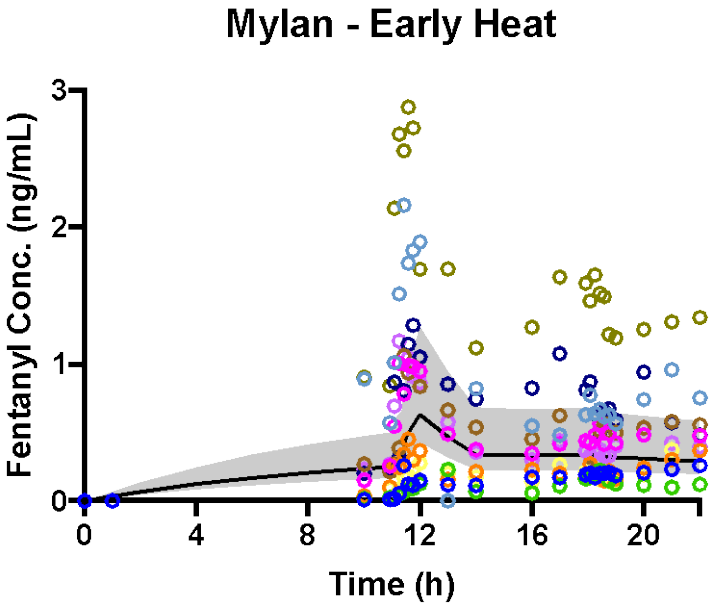


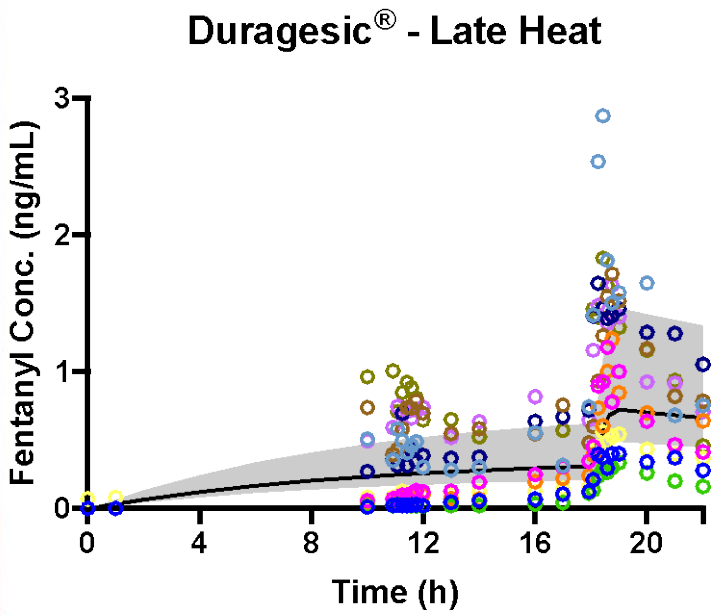
Approach I

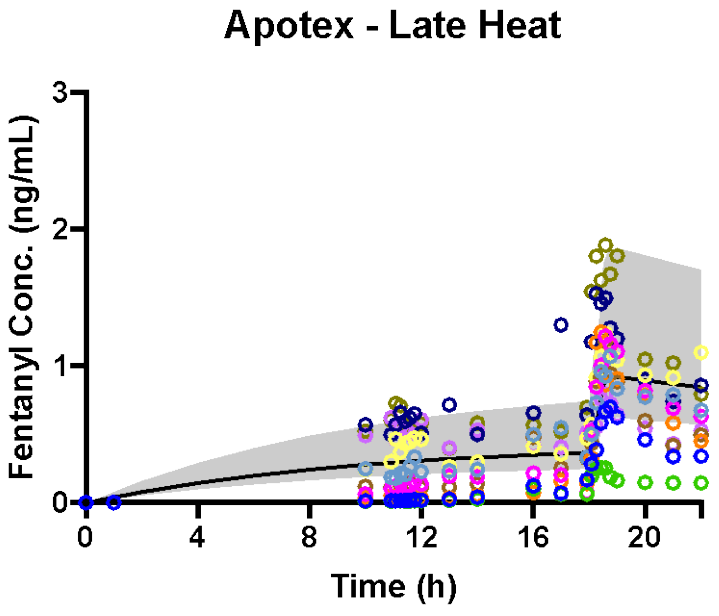
Grey shade represents prediction range when inter-subject variability of CL = 50%

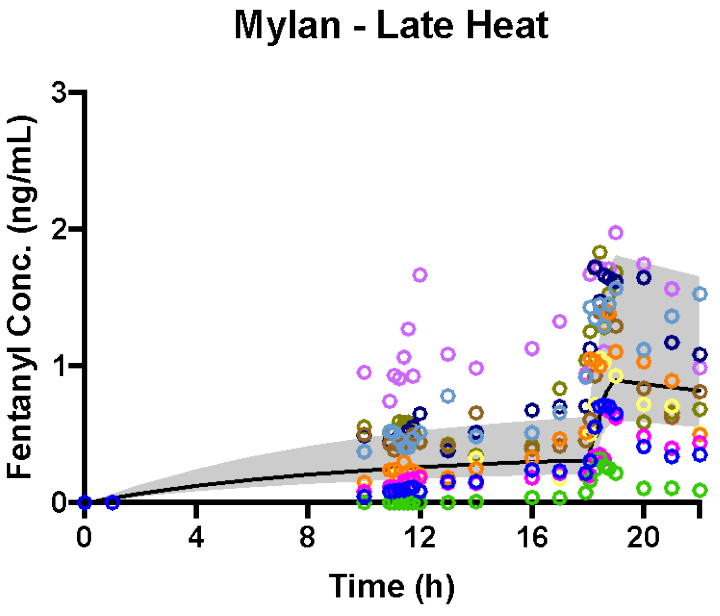






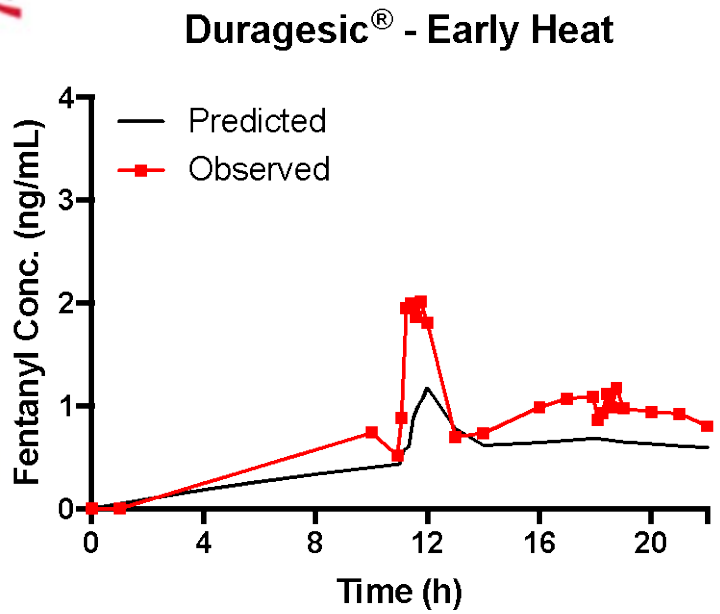


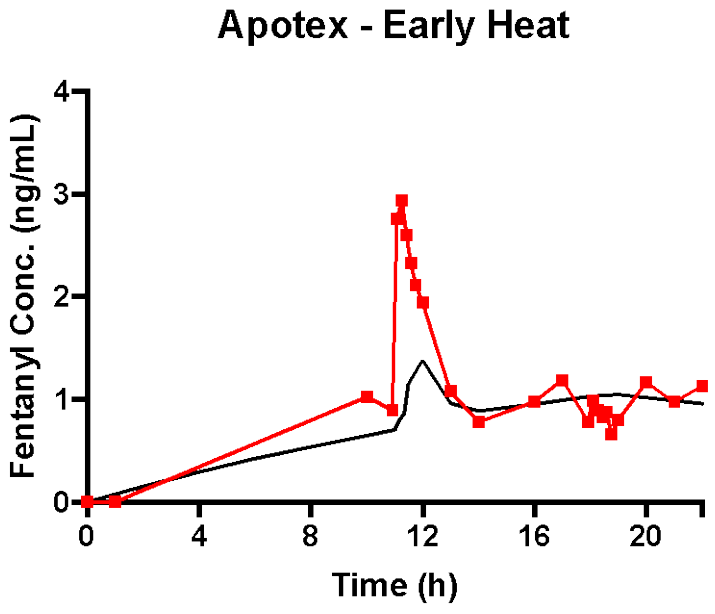


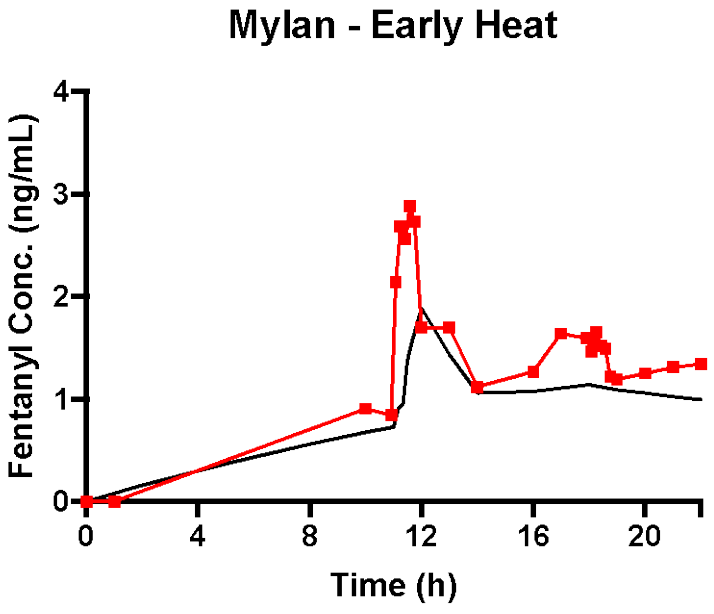


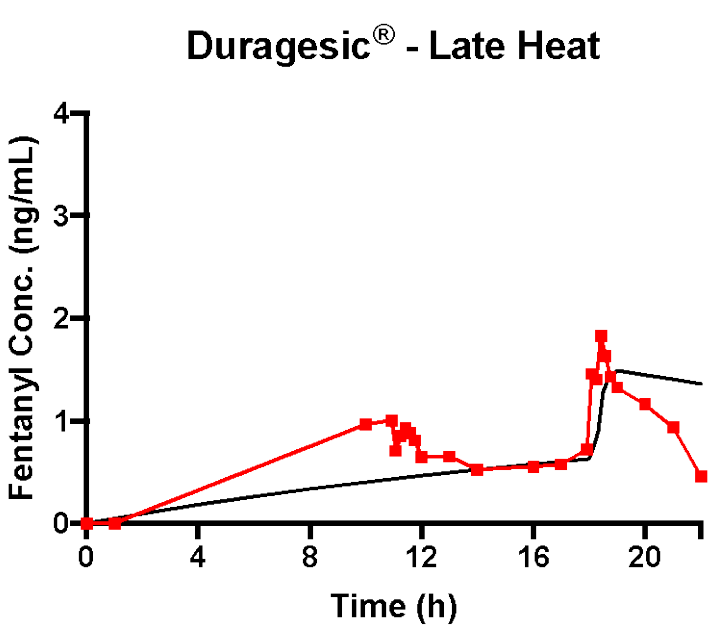
Approach I

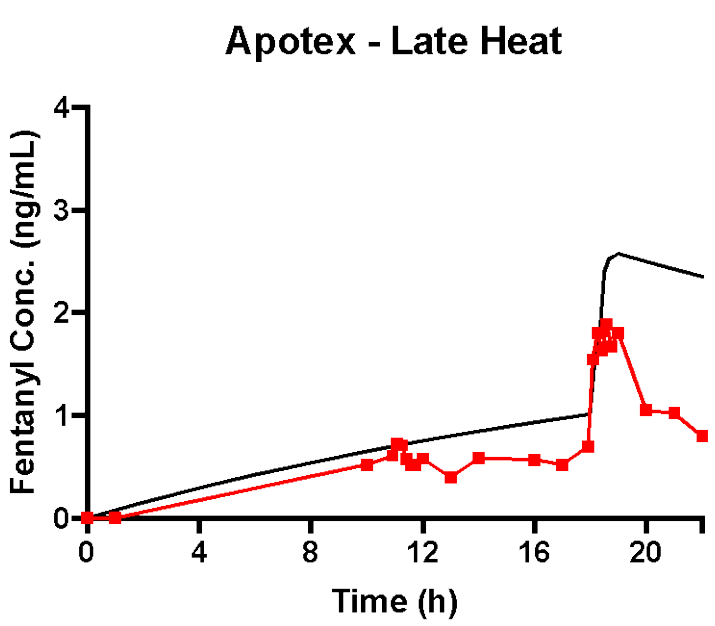
Subject TDF 024: Predicted using the subject's own F, CL_{IV} and k values

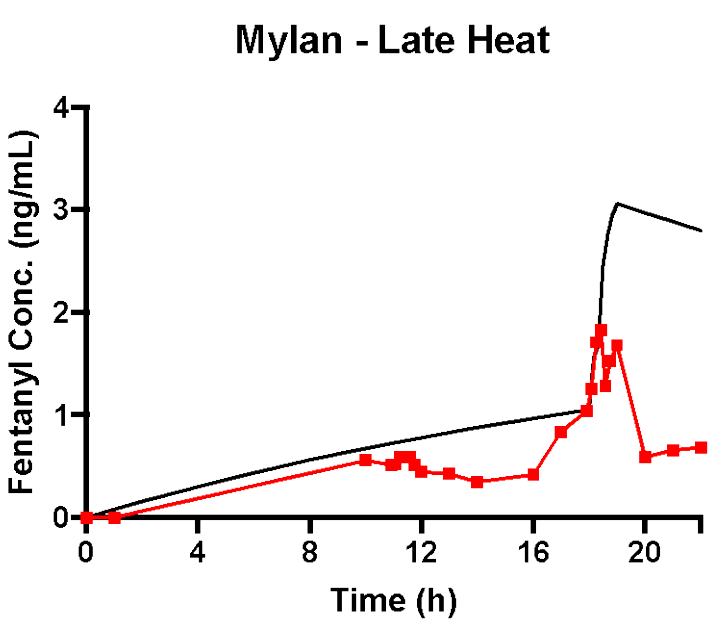




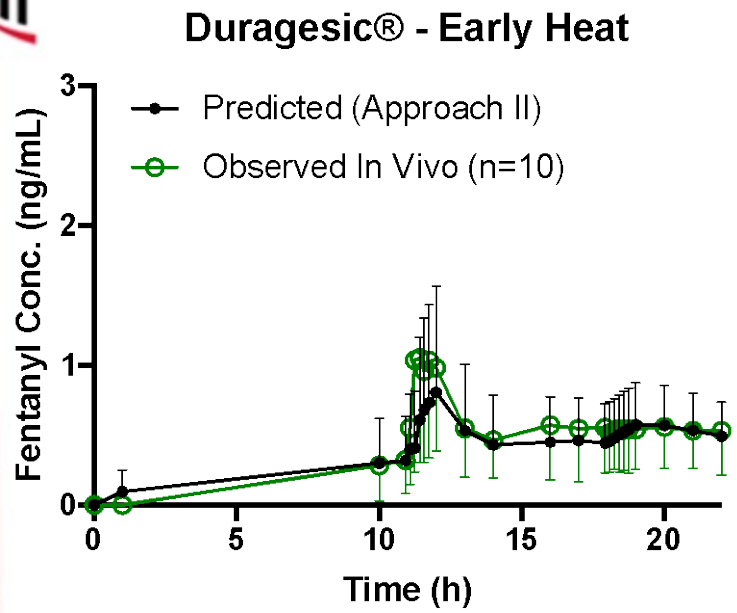


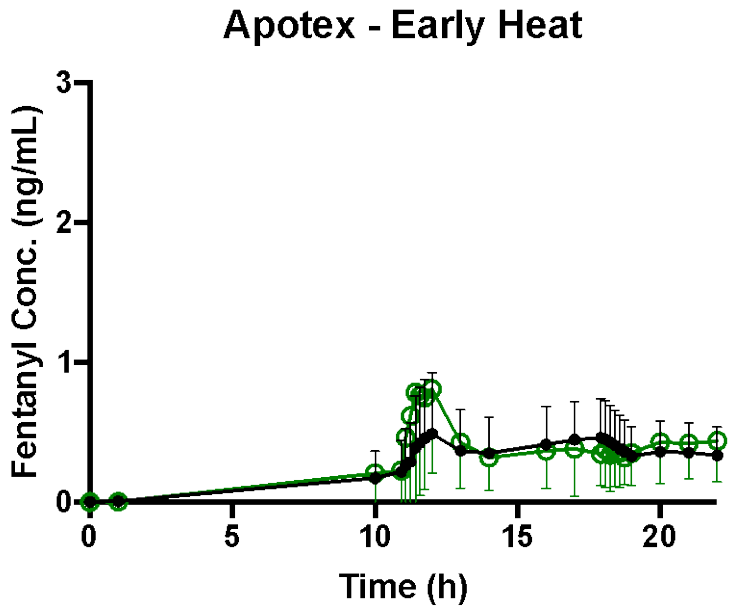


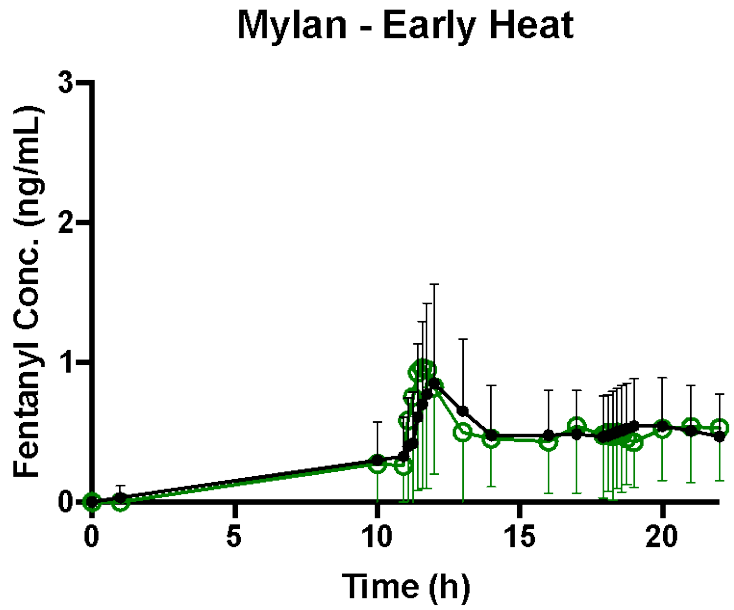


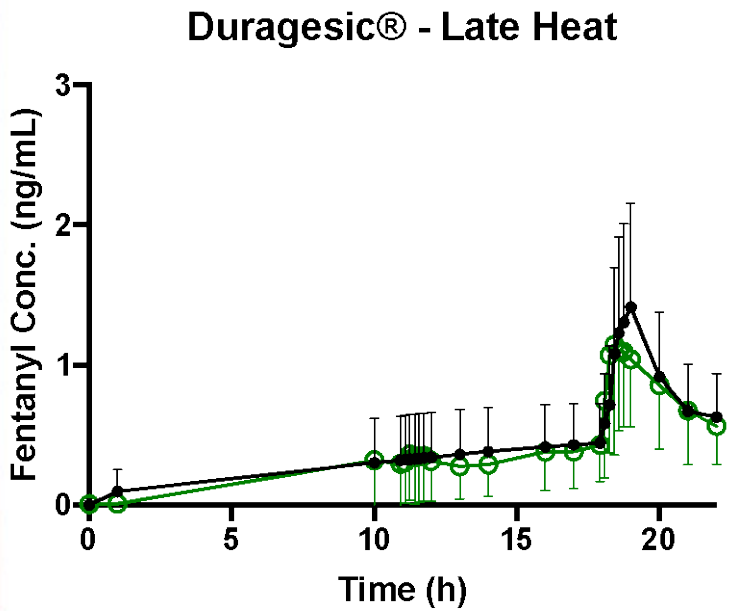


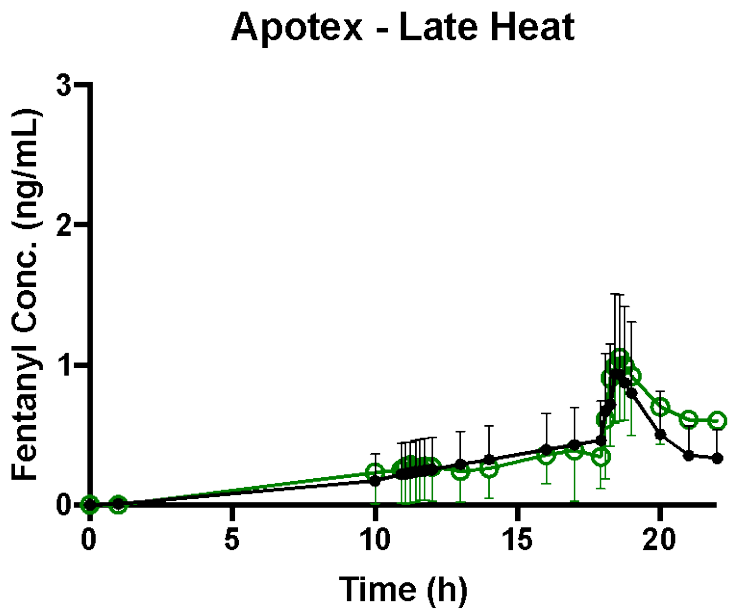
Approach II

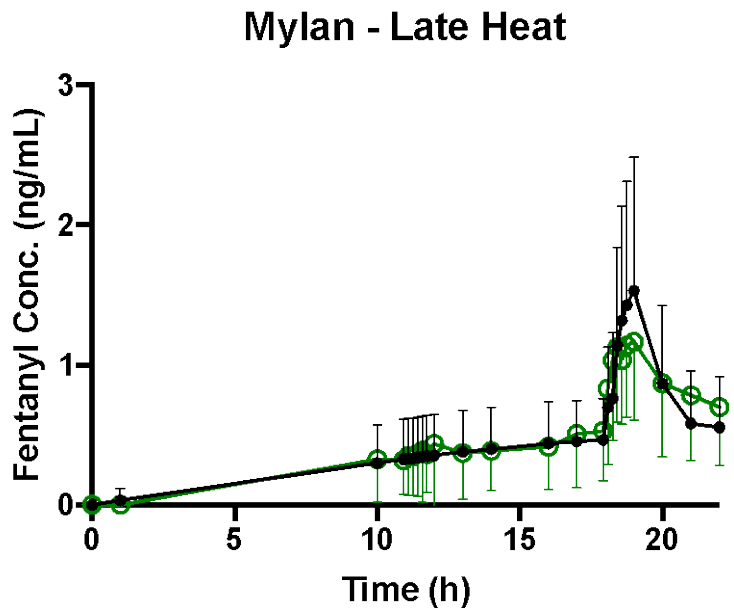

Duragesic® - Early Heat
Predicted (Approach II)
Observed In Vivo (n=10)
Fentanyl Conc. (ng/mL)
Time (h)


Apotex - Early Heat
Fentanyl Conc. (ng/mL)
Time (h)

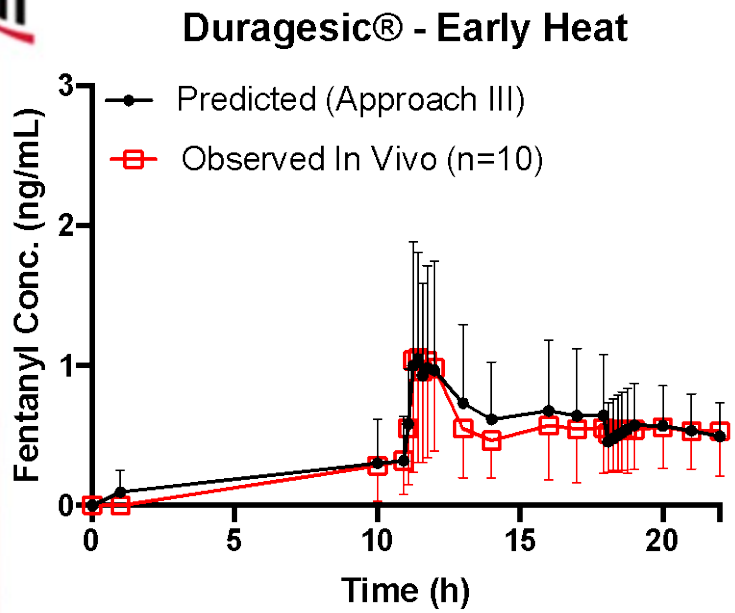

Mylan - Early Heat
Fentanyl Conc. (ng/mL)
Time (h)

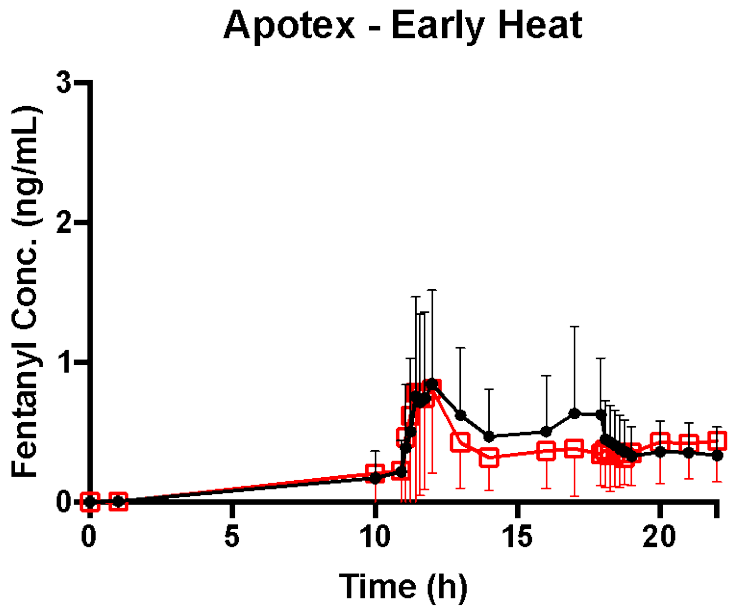

Duragesic® - Late Heat
Fentanyl Conc. (ng/mL)
Time (h)

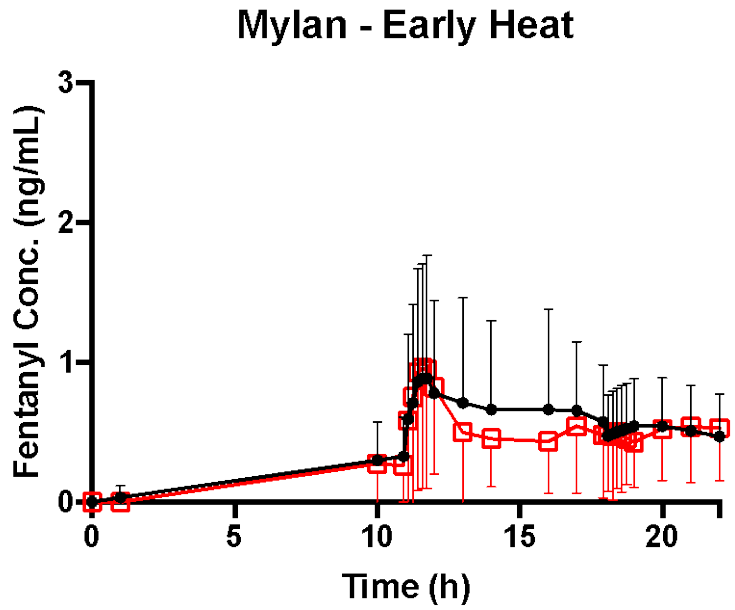

Apotex - Late Heat
Fentanyl Conc. (ng/mL)
Time (h)

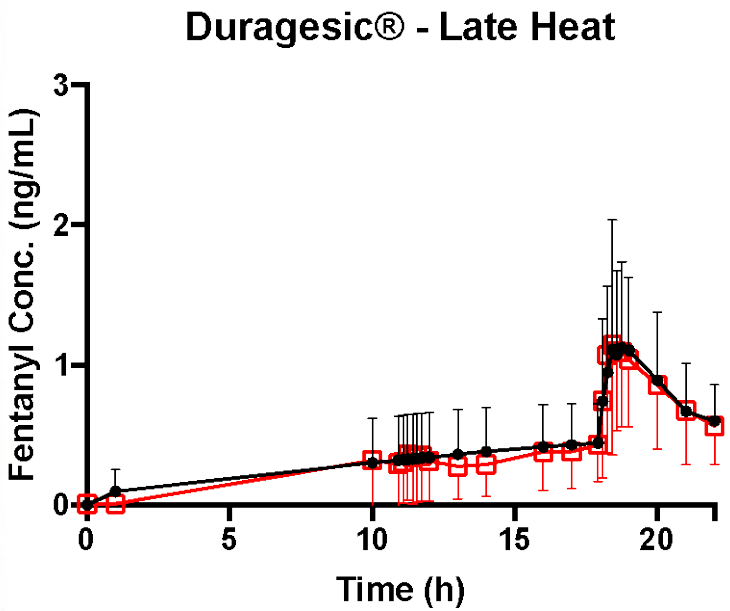

Mylan - Late Heat
Fentanyl Conc. (ng/mL)
Time (h)

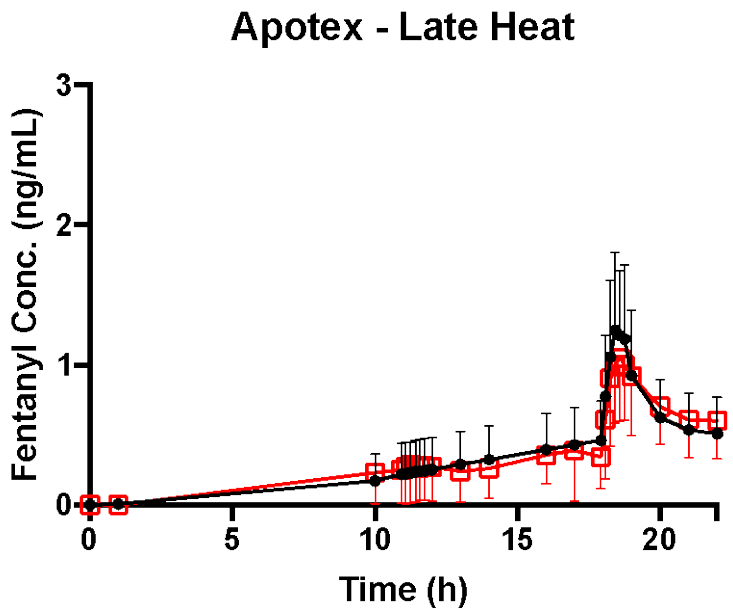
Approach III

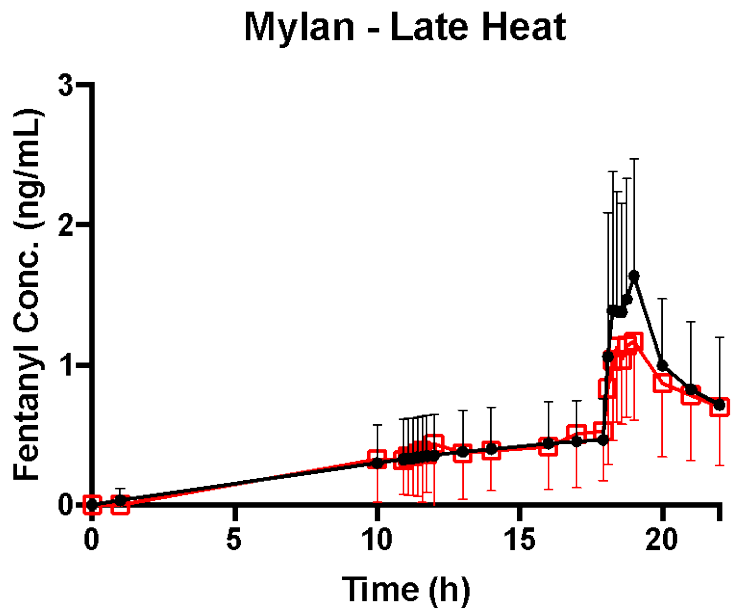












% Prediction Error

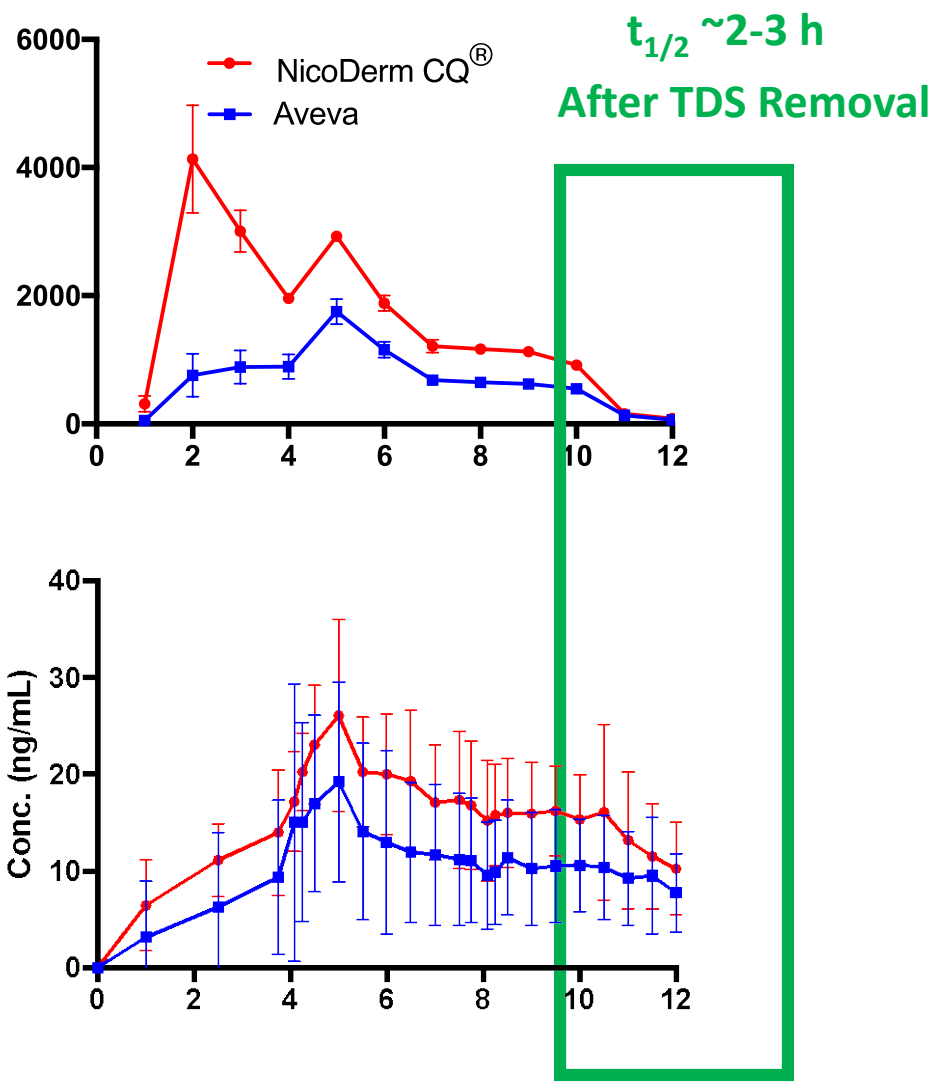
Fentanyl TDS	Duragesic®		Apotex		Mylan	
	Early Heat	Late Heat	Early Heat	Late Heat	Early Heat	Late Heat
Approach I						
Total AUC	31.7	17.5	4.0	19.3	24.3	18.4
C_{max}	37.7	36.8	29.8	12.4	34.1	23.2
Approach II						
Total AUC	3.3	13.1	10.2	11.8	5.1	0.6
C_{max}	23.4	23.6	39.6	11.2	11.4	31.5
Approach III						
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

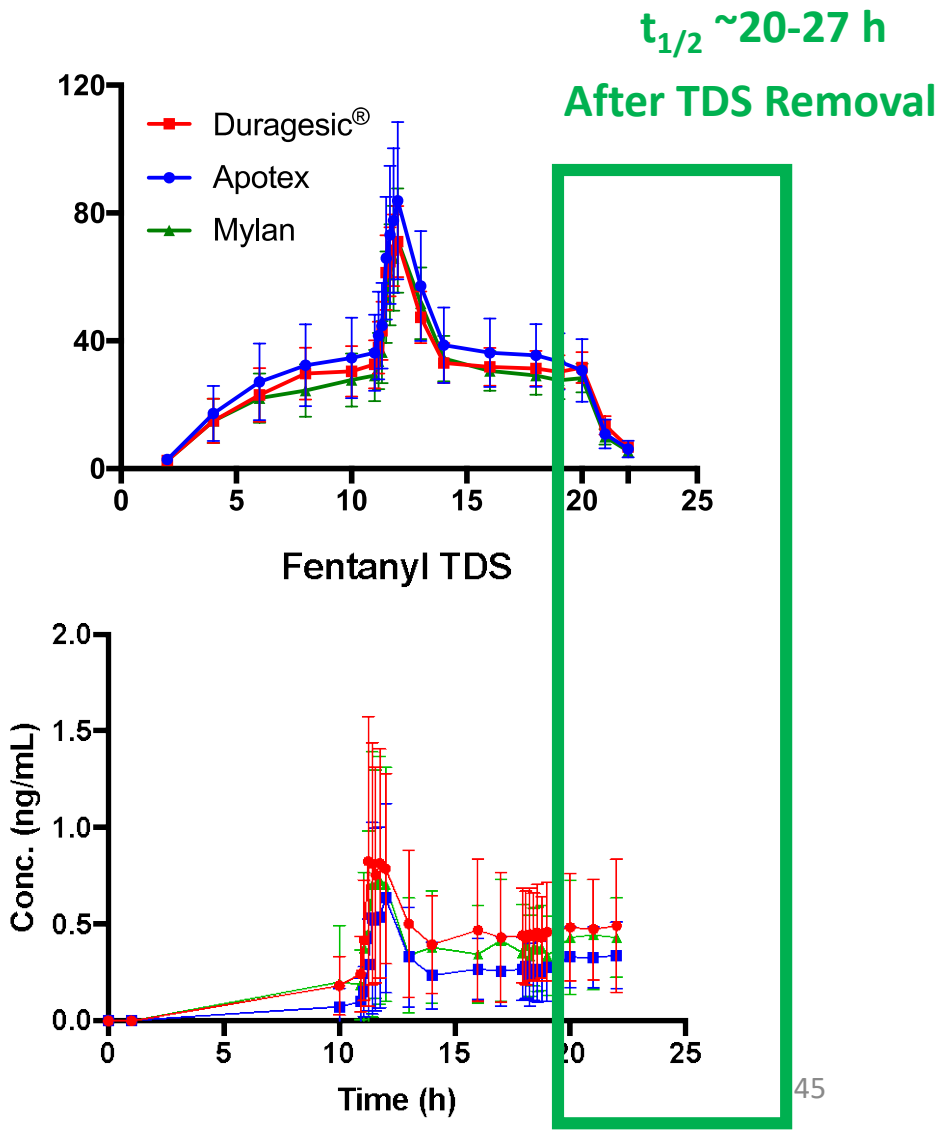
Conclusions – Fentanyl

- 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
  ⇒ Not as predictive compared to nicotine…

Why??

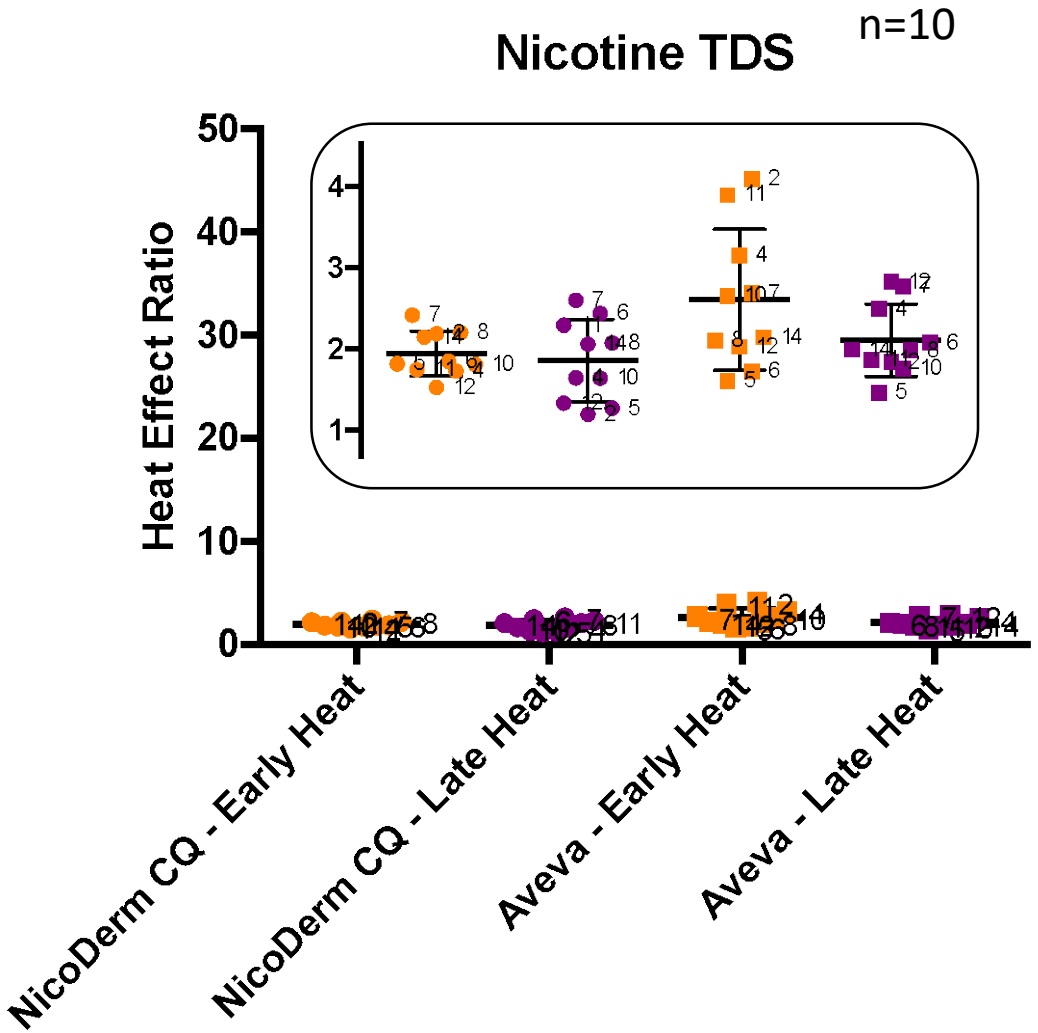
1. Lipophilicity of Fentanyl

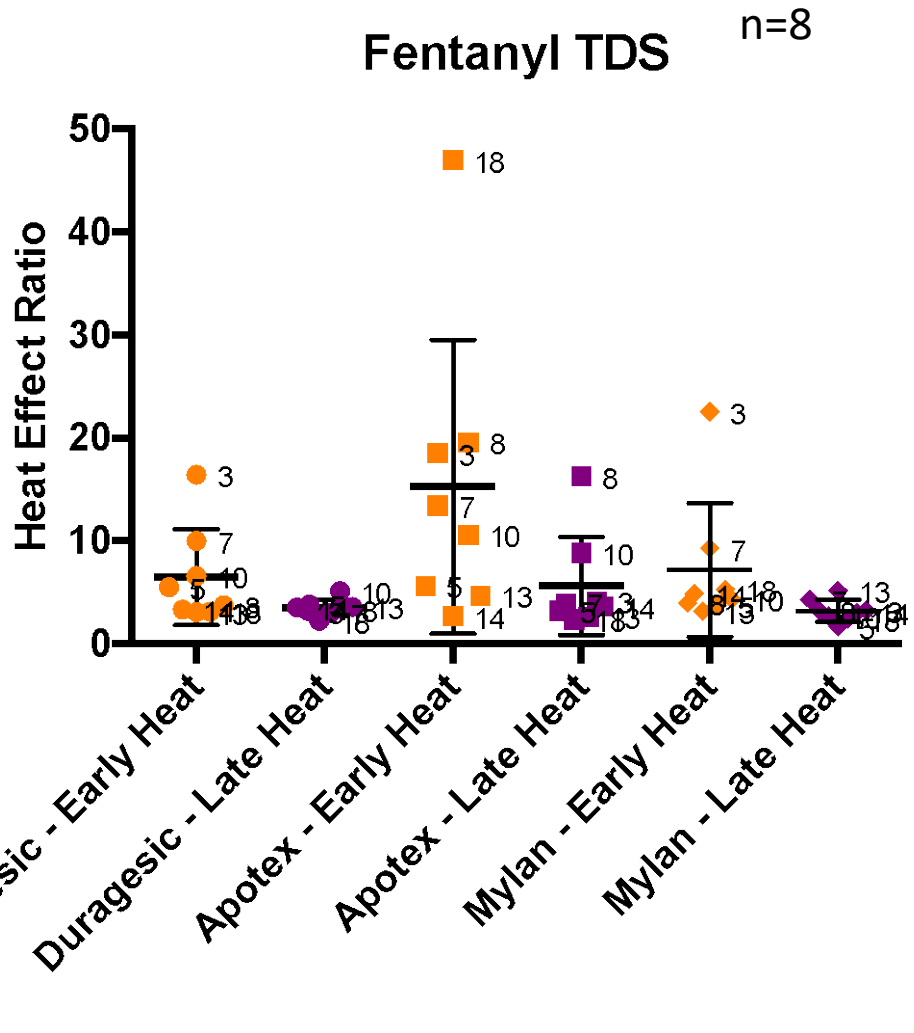




2. High Inter-subject Variability of Fentanyl

Heat Effect Ratio was determined by the ratio of the C_{max} during the 3h window and the concentration immediately before heat application





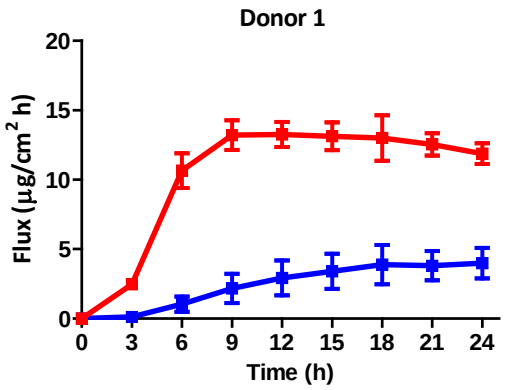
Conclusions - IVIVC

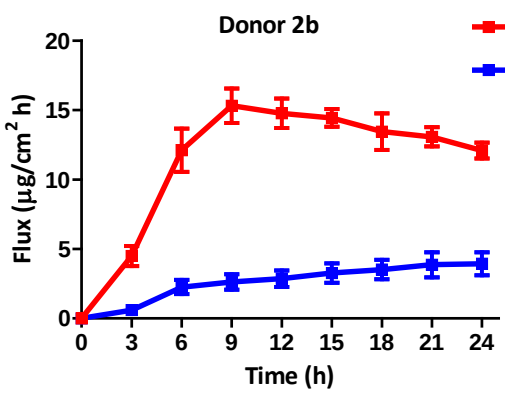
- Three approaches were evaluated to demonstrate Level A IVIVC for TDS
- Strong IVIVC demonstrated for nicotine TDS, including heat effect
- Weaker IVIVC found for fentanyl TDS
  - Limitation of mimicking drug reservoir in skin layers, microcirculation and subcutaneous tissue in vitro
  - High inter-subject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

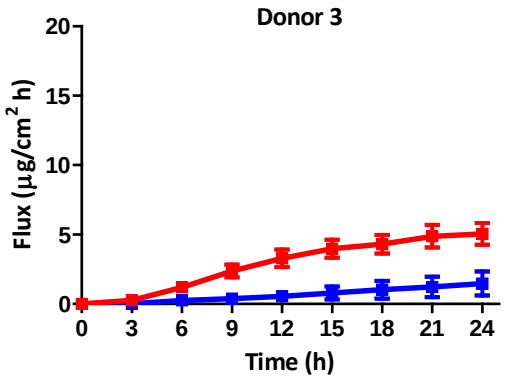
Lidocaine Patch

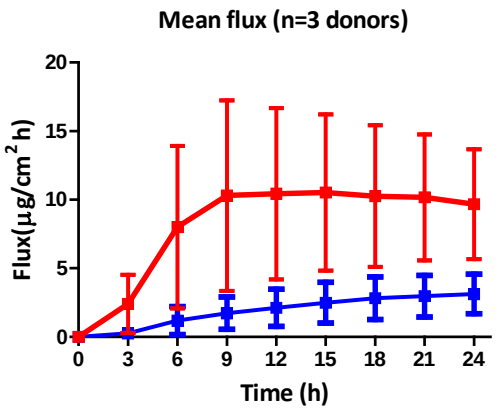
Properties	Mylan Lidocaine Patch 5%	Lidoderm® Lidocaine Patch 5%
Drug load	**Lidocaine, USP 140 mg** (50mg per gram adhesive) In a polyisobutylene adhesive matrix	**Lidocaine 700 mg** (50mg per gram adhesive) In an aqueous base Methyl paraben and propyl paraben as preservatives
Adhesive	**Non-water Based**	**Water Based**
Size	**10cm × 40cm**	**10cm × 40cm**
Weight	**3.50 g**	**15.57 g**
Thickness	**0.27 mm**	**1.59 mm**
Appearance	**Pigmented Film**	**White Felt**

Lidoderm-Human Skin
Continuous heat







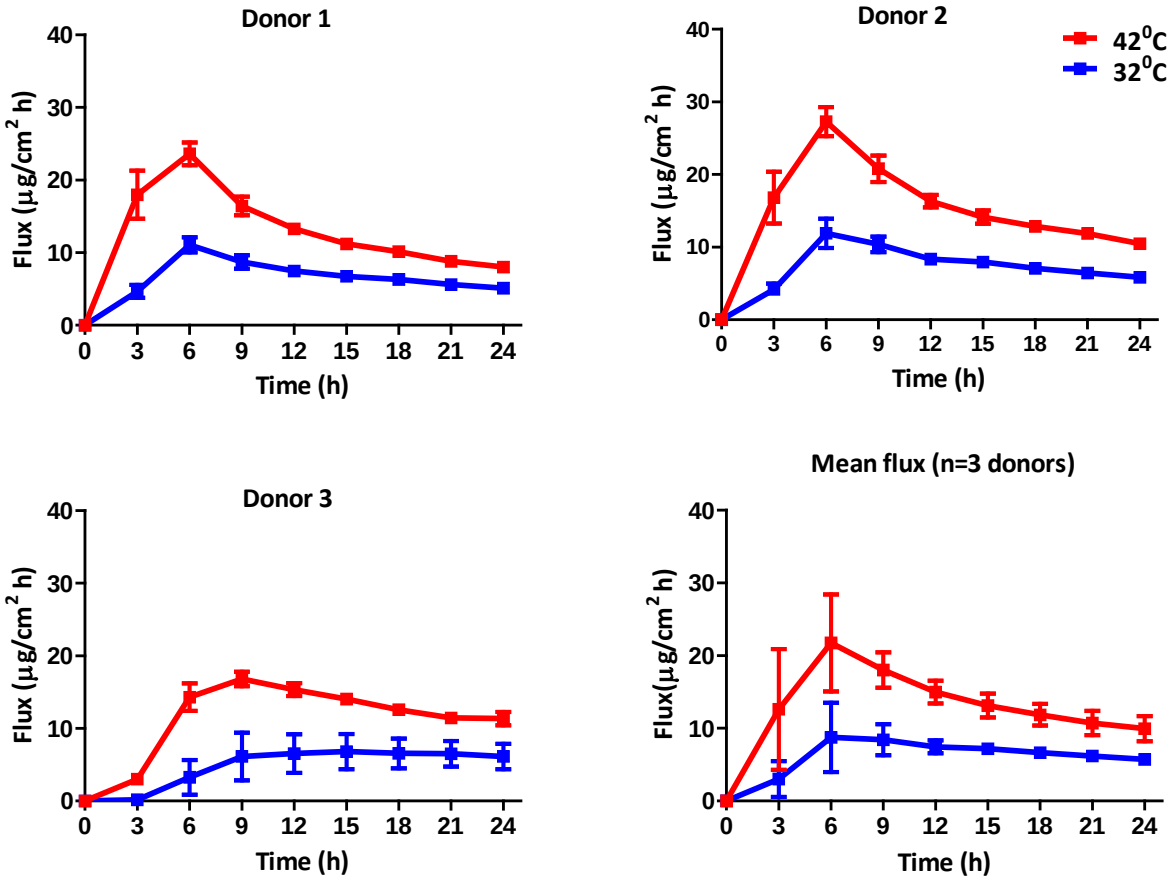


Donor (human skin)	Heat Enhancement Ratio (Heat/No Heat)		##*p* value (Heat vs No Heat)	
	J_{max}	Cum. Amt.	J_{max}	Cum. Amt.
1	3.2	4.1	< .001	< .001
2b	3.9	4.3	< .001	< .001
3	3.4	4.4	.001	< .001
Mean (n=3 donors)	3.1	4.2	.056	.083

- All 3 donors show significant increase in flux
- Shift in T_{lag}
- Flux remained elevated throughout the duration of heat application

##*p* values were obtained from unpaired t test for individual donors and paired t test for mean of three donors

5% Lidocaine Patch (Mylan)-Human Skin Continuous heat



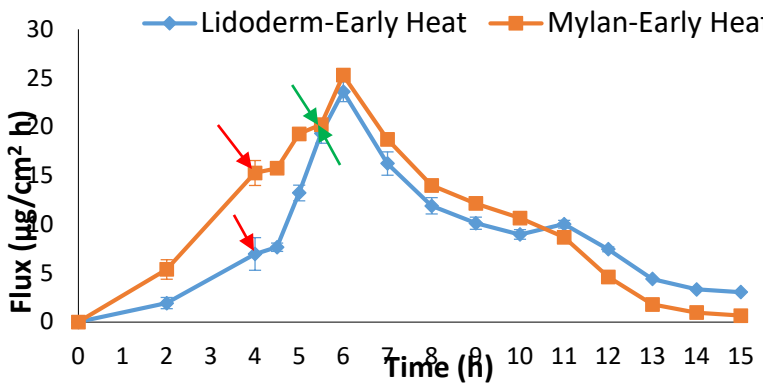
Donor (human skin)	Heat Enhancement Ratio (Heat/No Heat)		##p value (Heat vs No Heat)	
	J_{max}	Cum. Amt.	J_{max}	Cum. Amt.
1	2.6	2.1	< .001	< .001
2b	2.2	2.0	< .001	< .001
3	2.3	2.3	< .001	< .001
Mean (n=3 donors)	2.3	2.1	.021	.006

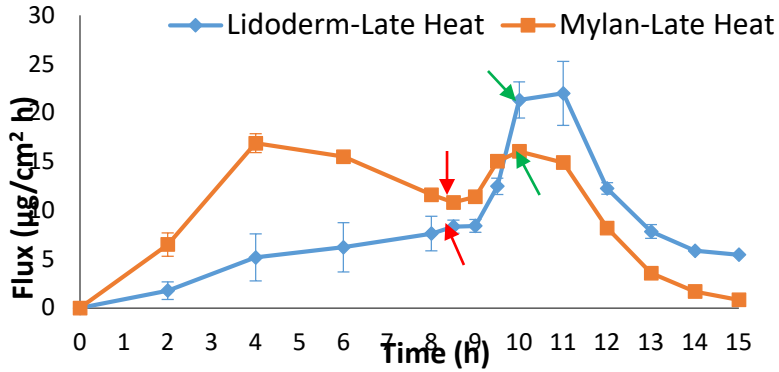
- All 3 donors show significant increase in flux
- Flux remained elevated throughout the duration of heat application

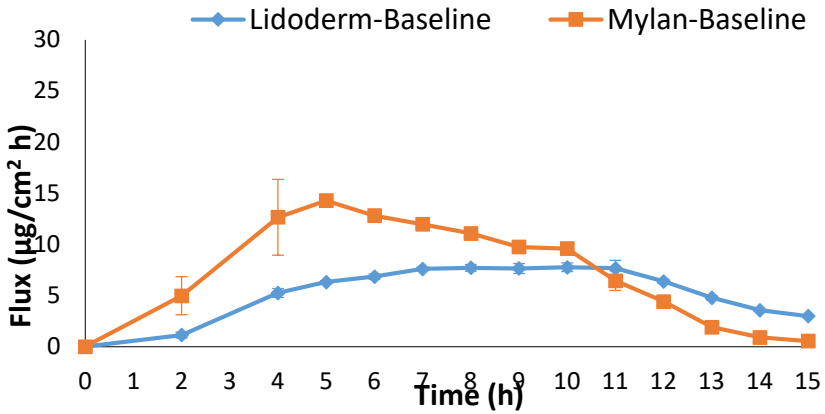
##*p* values were obtained from unpaired t test for individual donors and paired t test for mean of three donors

IVPT design parallel to clinical trial design

Human skin - donor 1 (n=4 per arm)







Red arrow: Heat on
Green arrow: Heat off
Patch off at 10h

Baseline with no heat application
Early heat application from 4-5.5h
Late heat application from 8.5-10h
Patch off at 10h

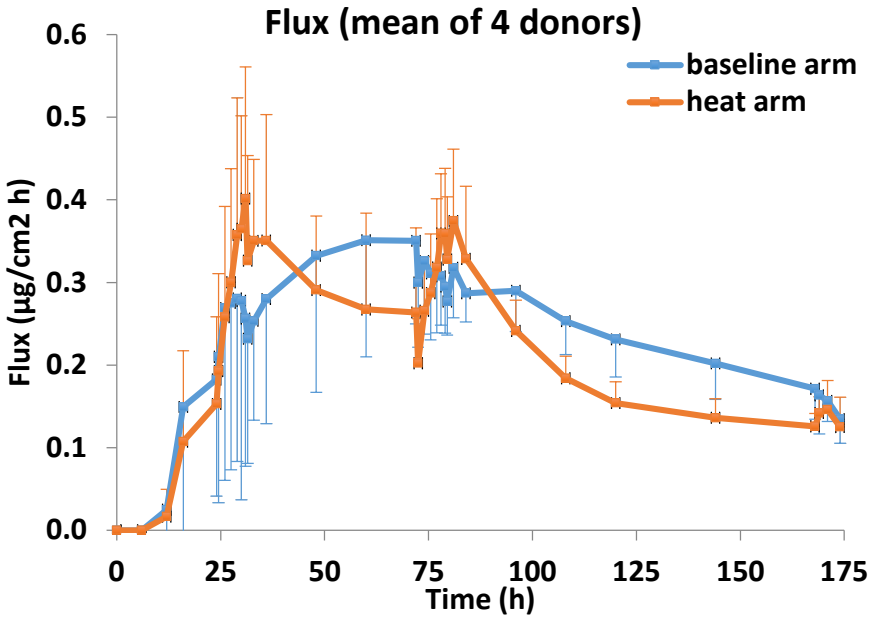
Lidocaine: IVPT & 2 human subjects
Enhancement ratio in C_{max} or J_{max}

	Early Heat		*Late Heat*	
	Lidoderm	Mylan	Lidoderm	Mylan
Donor 1	**3.4**	**1.7**	**2.6**	**1.5**
Subject 001	**6.6**	**4.2**	**3.9**	**1.8**
Subject 003	**11.9**	**3.8**	**3.4**	**3.4**

Enhancement ratio was calculated by dividing the Cmax or Jmax in the heat window by the value right before the heat application in the same arm.

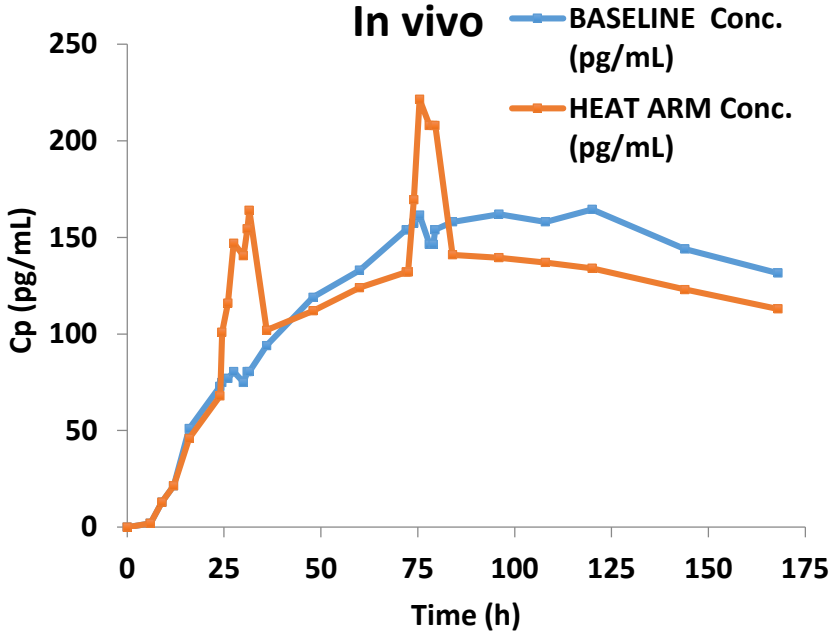
Buprenorphine Patch

Mean(±SD) In vitro flux n=4 donors



Mean In vivo concentration n=19/20 subjects

(values from graph grabbing software for graph taken from *Clinical Pharmacology and Biopharmaceutics Review* document for Butrans® available at Drugs@FDA.)



Human skin donor 4 (n=4 replicates per arm)

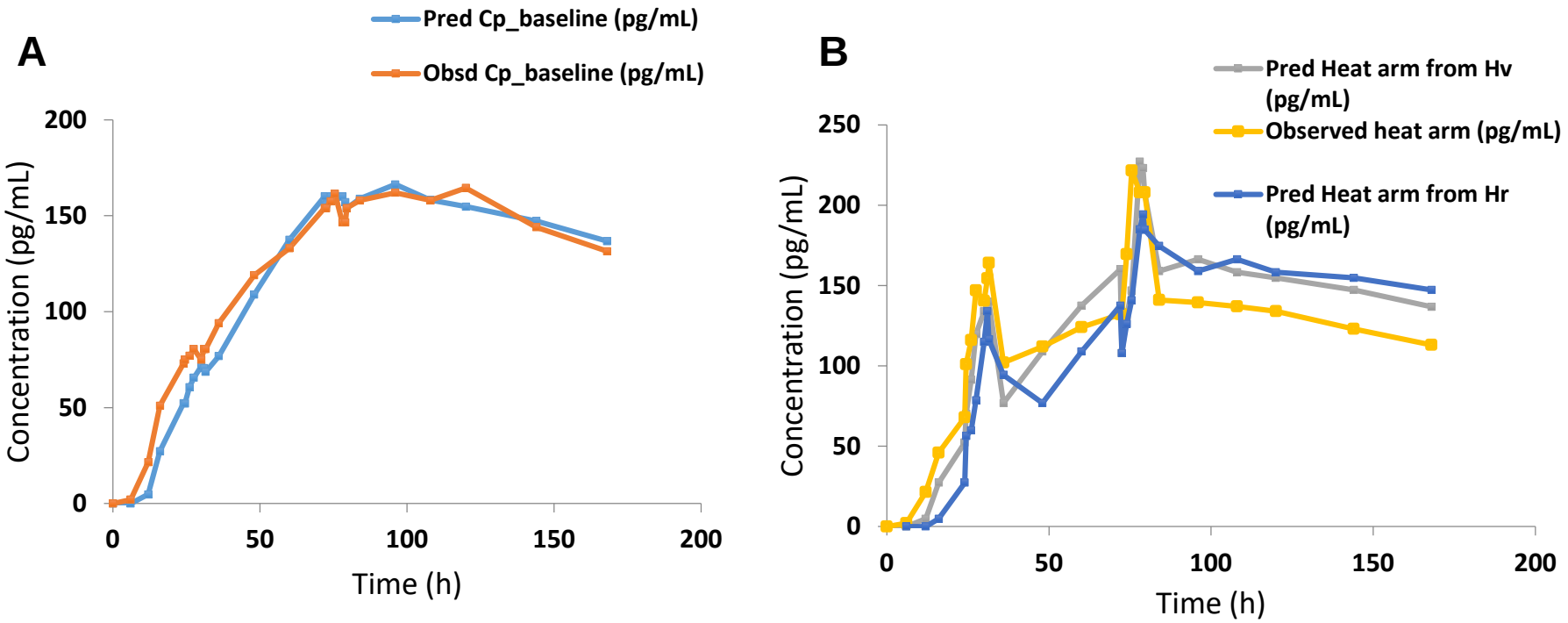
Heat Arm:

Early heat-heat applied from 24 to 31 h (every 2 h with 30 min gap)

Late heat- heat applied from 72 to 79 h (every 2 h with 30 min gap)

Patch off at 168h

Buprenorphine Patch

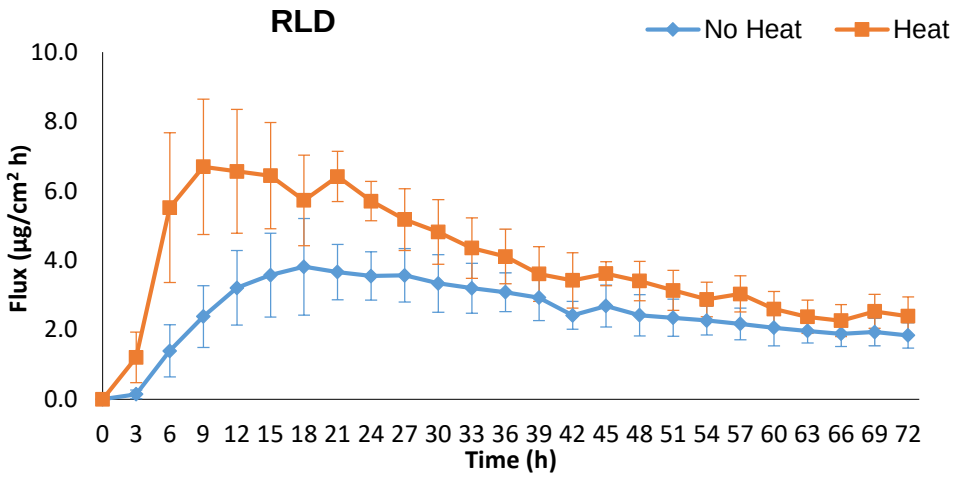


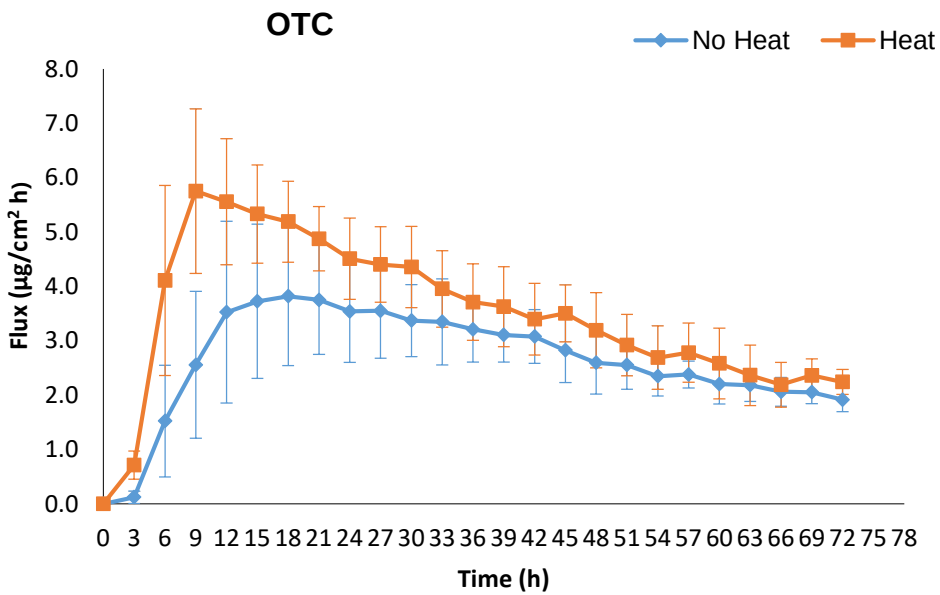
Plot for observed and predicted concentration versus time profiles for baseline arm (**A**) and heat arm (**B**)

Hv = in vivo heat factor **Hr = in vitro heat factor**

Oxybutynin patch-human skin
Continuous heat

- Human skin donor
- n=4 replicates per arm

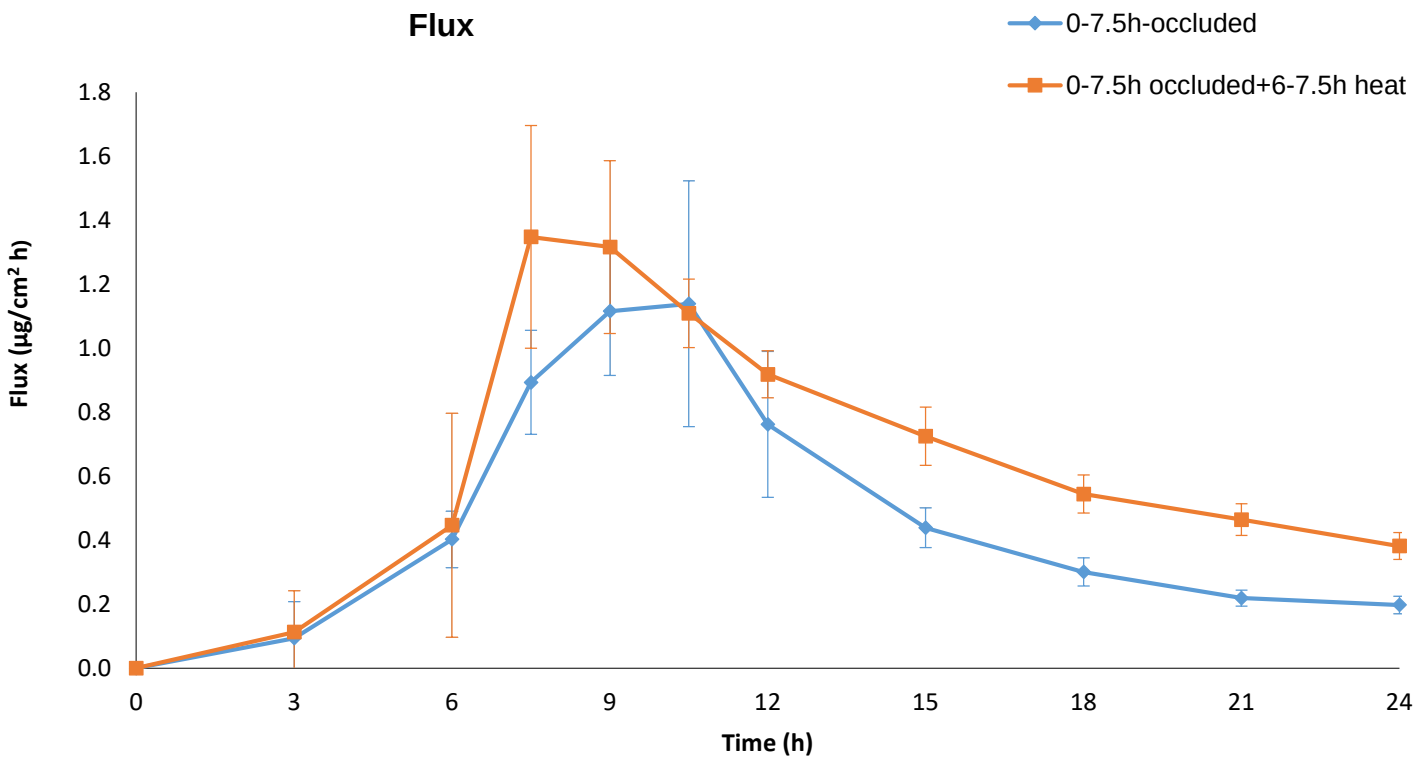




Heat enhancement Ratio	RLD	OTC
Flux at 9h	2.8 (p=0.0079)	2.2 (p=0.0222)
Cum. Amt. at 72h	1.6 (p=0.0292)	2.1 (p=0.0739)

Gelnique® Gel 10%-human skin: oxybutynin

- Human skin donor
- Gelnique® 10 mg dosing application using inverted HPLC vial
- Arm-1 -- baseline with no occlusion or heat→ samples below LLOQ (n=3)
- Arm-2 -- heat applied from 6-7.5h -- not occluded throughout→ samples below LLOQ (n=3)
- Arm-3 -- baseline with occlusion from 0-7.5h→ blue line (n=2)
- Arm-4 -- heat applied from 6-7.5h -- occluded from 0-7.5h→ orange line (n=3)



Diclofenac

	Patch	Solution	1% Gel	3% Gel
Inactive ingredients	Adhesive in aqueous base containing sodium polyacrylate, sodium carboxymethylcellulose	DMSO, ethanol, purified water, propylene glycol, hydroxypropyl cellulose	Carbomer homopolymer Type C, cocoyl caprylcaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, strong ammonia solution	Hyaluronate sodium, benzyl alcohol, polyethylene glycol monomethyl ether, purified water
Dose applied (Equivalent amount of diclofenac)	- (878 mg/cm^2)	5 mg/cm^2 (approx. 100 µg/cm^2)	10 mg/cm^2 (approx. 100 µg/cm^2)	20 mg/cm^2 (approx. 300 µg/cm^2)

Diclofenac

Formulation	Heat Enhancement Ratio (Heat/No Heat)		##*p* value (Heat vs No Heat)	
	J_{max}	Cum. Amt.	J_{max}	Cum. Amt.
Patch	2.3	5.0	0.034	0.104
Solution	4.0	5.0	0.006	0.002
1% Gel	2.6	3.0	0.001	<0.001
3% Gel	1.0	0.87	0.961	0.883

Take Home Messages

- An in vitro heat effect study could predict the in vivo heat effect for some drugs
- For certain drugs, an in vivo heat factor may need to be determined
- Heat effects are drug molecule and formulation excipient dependent
- Patches are not the only topical products affected by heat

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