

IVIVC in Transdermal Drug Delivery: Streamlining the Drug Approval Process

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F6 Pharma

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Overview

IVIVC (In Vitro/In Vivo Correlation) TDS (Patches)

Influence of Heat on TDS *in vitro* (IVPT)

In Vitro Permeation Tests

Influence of Heat on TDS *in vivo* (*humans*)

Evaluate BA (Bioavailability) for Transdermal Semisolids

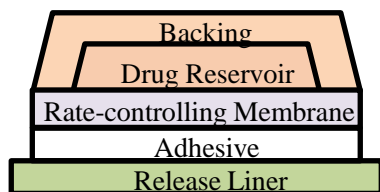
Tape-stripping (not discussing today)

(Bunge, Guy, Delgado-Charro)

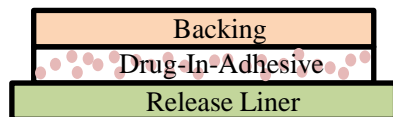
IVPT (In Vitro Permeation Tests)

Dose, Application and Heat Effect

Transdermal Delivery Systems (TDS)



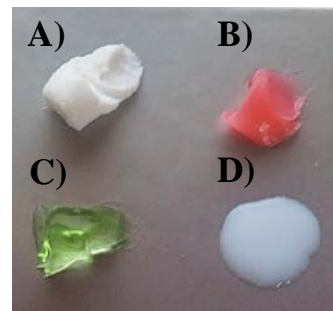
Reservoir Type



Matrix Type

- Therapy can be interrupted
- Low drug delivery efficiency
- Systemic absorption is intended
- Blood levels \approx Efficacy
- Occluded applications
- Highly reproducible application techniques
- Sustained and constant delivery
- BA: based on PK endpoint (C_{max} , t_{max} , AUC, etc)

Topical Drug Products (locally-acting)



- A) Cream
- B) Ointment
- C) Gel
- D) Lotion

- Low drug delivery efficiency
- Systemic Absorption is NOT desirable
- Local tissue levels \approx Efficacy
- Open applications
- Highly individualized application techniques
- Short-acting
some applied 5 x daily
- No straightforward BA evaluation method

Flynn G.L. (2002). Cutaneous and Transdermal Delivery – Processes and Systems of Delivery. In *Modern Pharmaceutics* (pp. 187-235). New York, NY: Marcel Dekker, Inc.

Overall Objectives

- Identify surrogate method(s) which closely simulate the complex mechanism of drug permeation through skin layers and drug retention within skin layers *in vivo* for selected transdermal and topical drug products

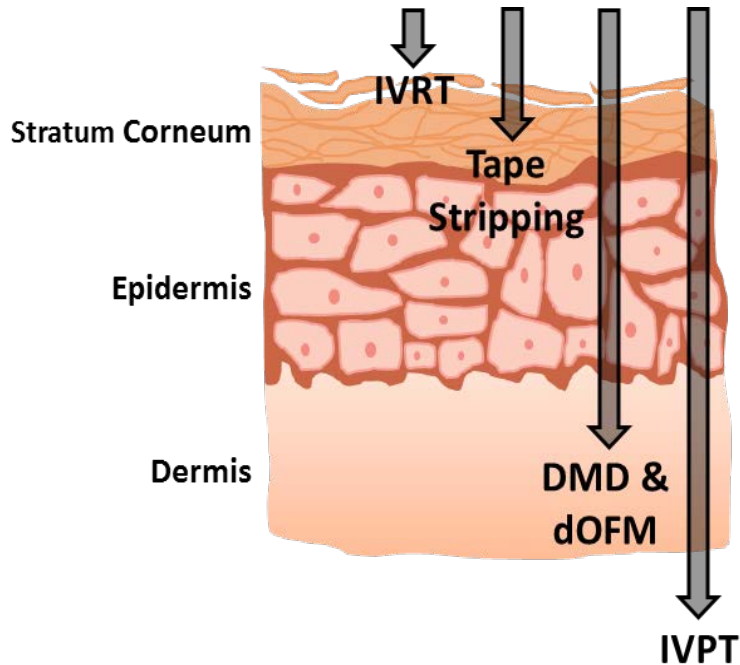
Hypothesis

- IVPT and/or other surrogate methods can predict the performance of transdermal and topical drug products *in vivo*

Positive Outcomes

- Examine IVPT and other surrogate methods for their relevance in developing IVIVC
- Develop IVIVC models which can predict the *in vivo* performance of transdermal and topical drug products

Methods to Determine Bioavailability (BA)



- IVRT (in vitro release test)
- Tape-stripping
- DMD (dermal microdialysis) & dOFM (dermal open flow microperfusion)
- IVPT (in vitro permeation test)
- + VCA (Vasoconstriction Assay)
- + Clinical Studies (PK &/or efficacy)

Why is Heat effect on TDS of Interest?

NDC 50458-091-05

Five (25mcg/h) Systems

DURAGESIC[®] 25 mcg/h 
(FENTANYL TRANSDERMAL SYSTEM)

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

© Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2009

Revised May 2009 0017965-2

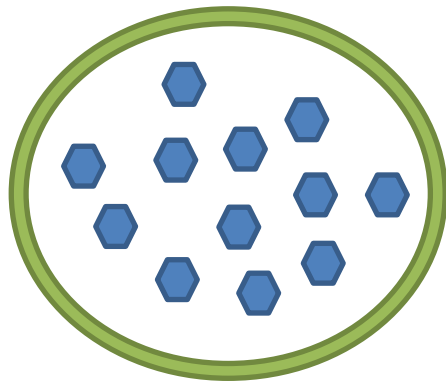
PriCara.

Division of Ortho-McNeil-Janssen
Pharmaceuticals, Inc.

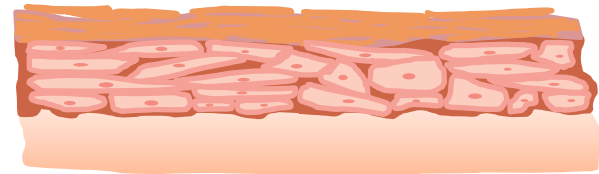
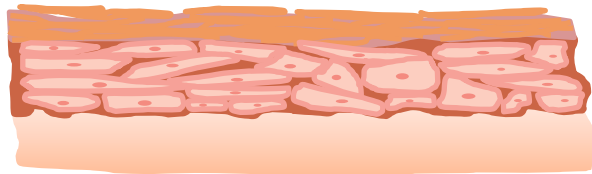
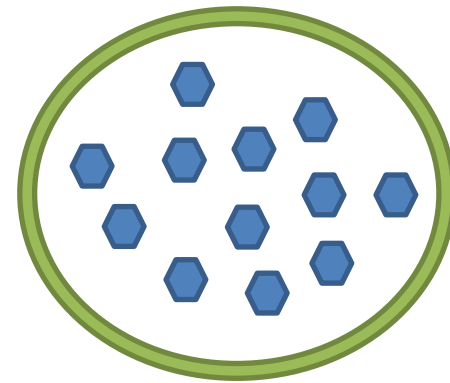
**ONLY for pain requiring
opioid medicine
around-the-
clock**

Influence of Heat on Percutaneous Absorption

1) ↑ Diffusivity of Drug from its Vehicle

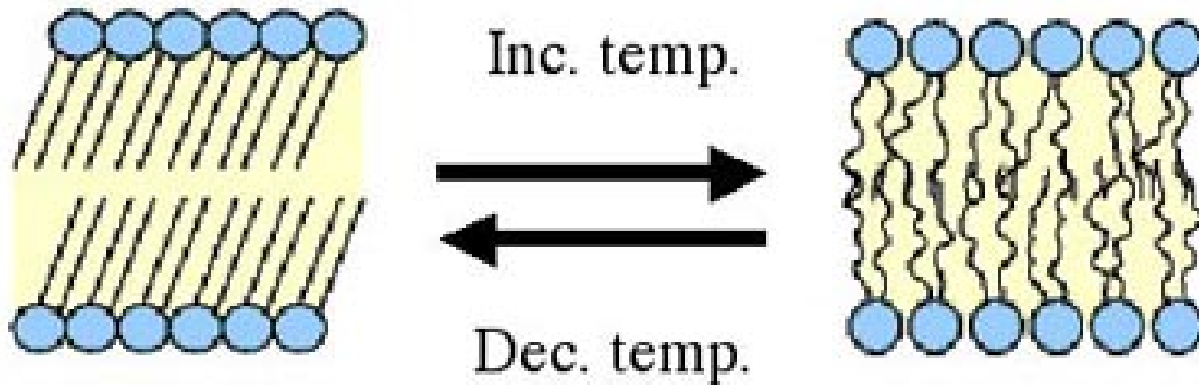


+ Heat
→



Influence of Heat on Percutaneous Absorption

2) ↑ Fluidity of Stratum Corneum Lipids



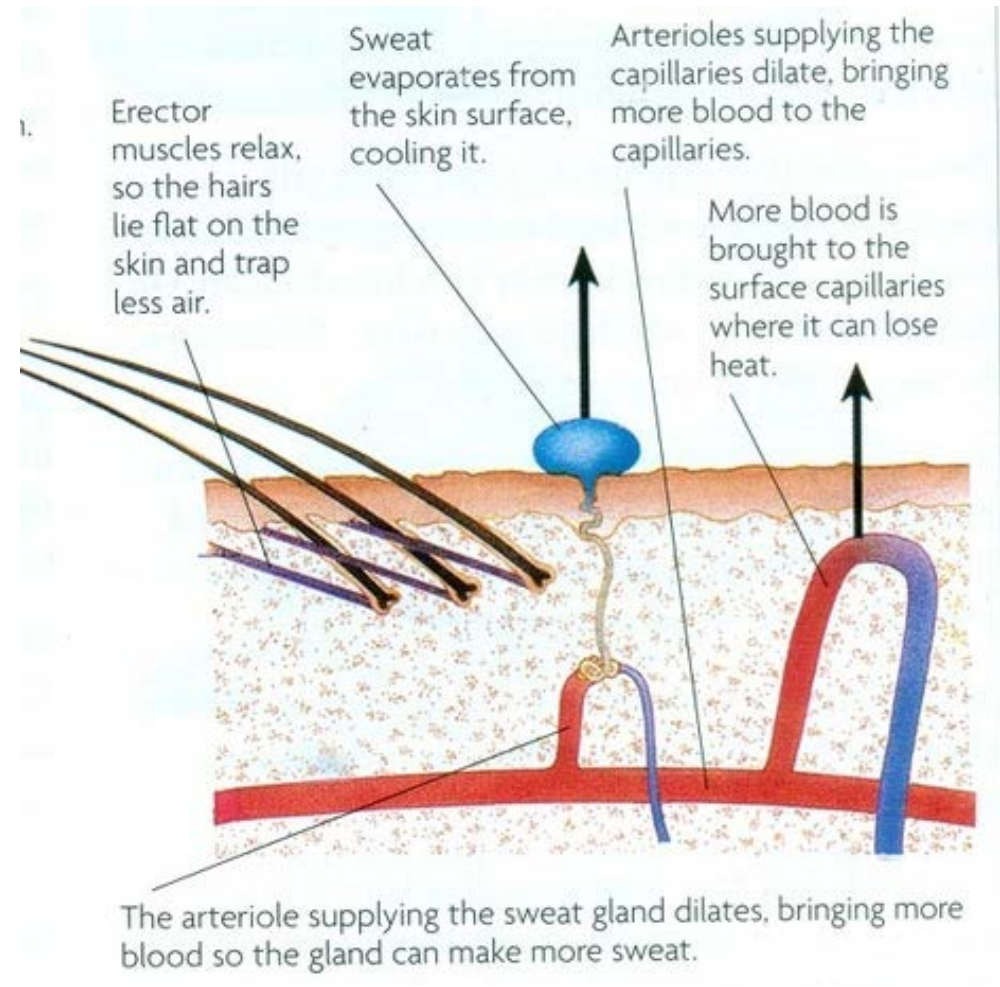
Very regular,
Ordered structure

Less tightly packed,
Hydrocarbon tails
Disordered.

Influence of Heat on Percutaneous Absorption

3) ↑ Cutaneous Vasodilation

Body temperature regulation
When the body is too hot



Selected TDS

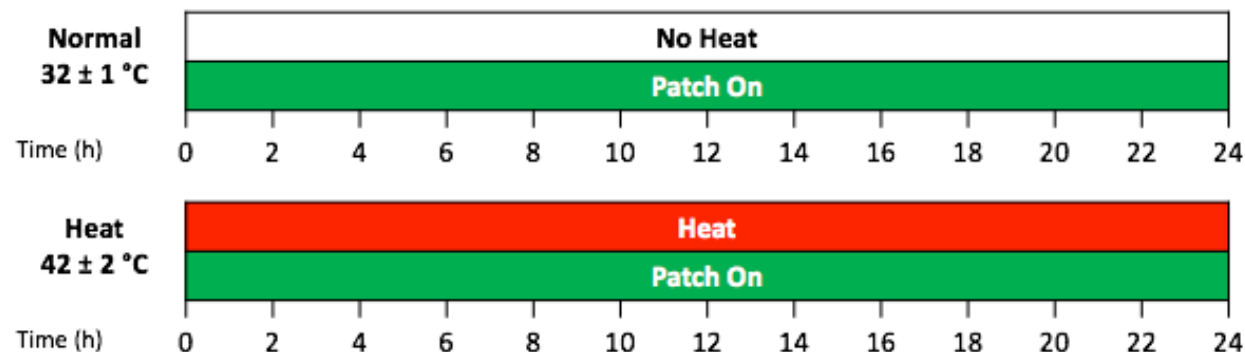
Nicotine TDS

Fentanyl TDS

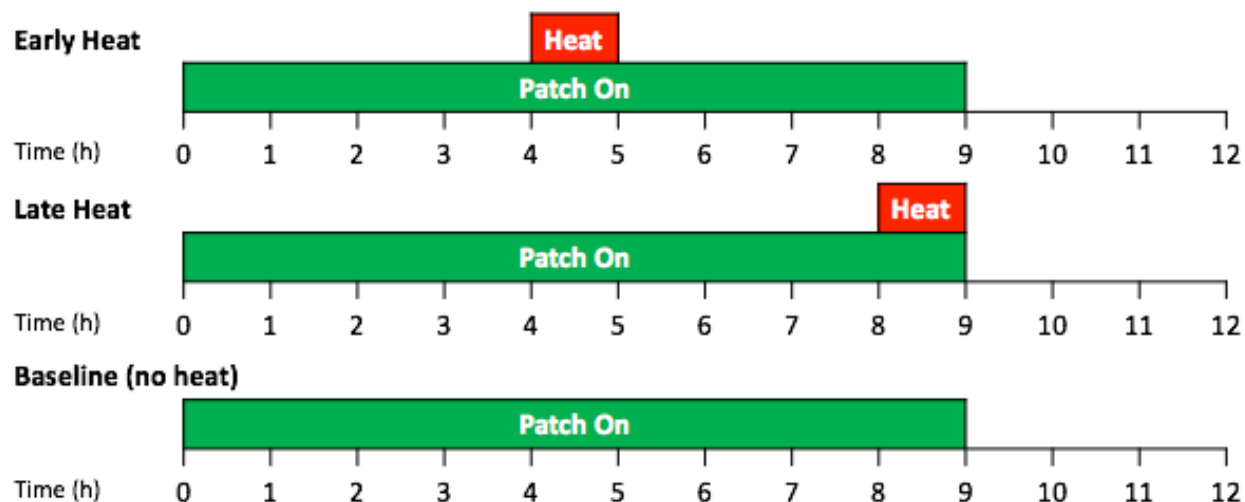
	NicoDerm CQ®	Aveva	Duragesic®	Mylan	Apotex
Patch size (cm ²)	15.75	20.12	10.5	6.25	10.7
Drug content (mg)	Not available	Not available	4.2	2.55	2.76
Rate/Area (µg/h/cm ²)	37	29	2.4	4.0	2.3
Inactive ingredients	Ethylene vinyl acetate-copolymer, polyisobutylene and high density polyethylene between clear polyester backing	Acrylate adhesive, polyester, silicone adhesive	Polyester/ethyl vinyl acetate backing film, polyacrylate adhesive	Dimethicone NF, silicone adhesive, polyolefin film backing	Isopropoyl myristate, octyldodecanol, polybutene, polyisobutylene adhesive

IVPT Study Designs: Nicotine With and Without Heat

24h Study Designs

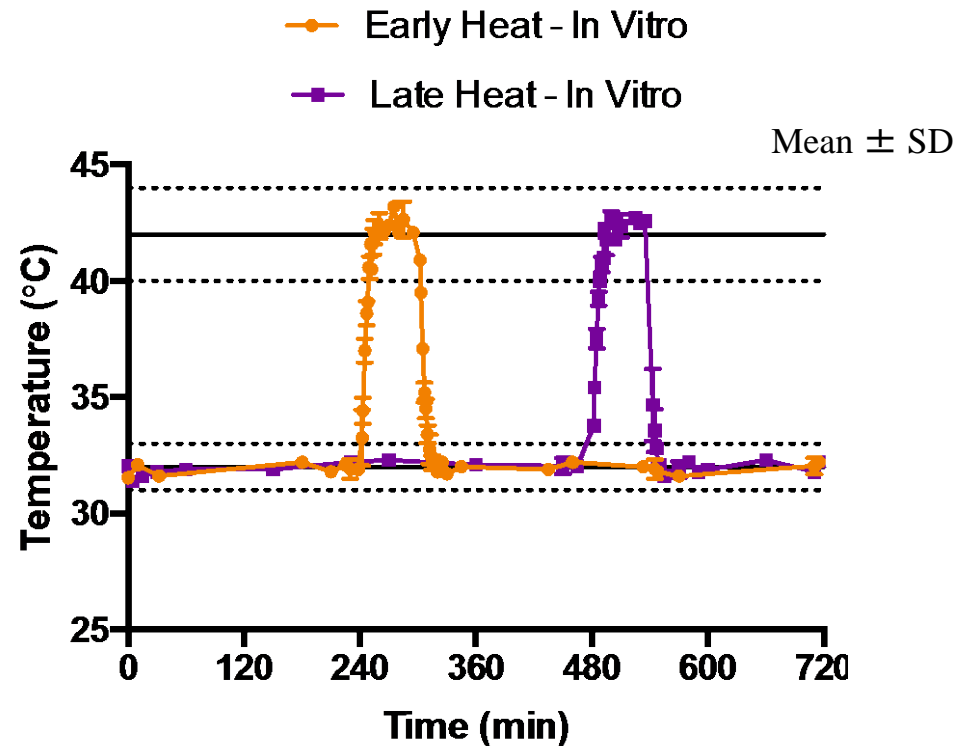
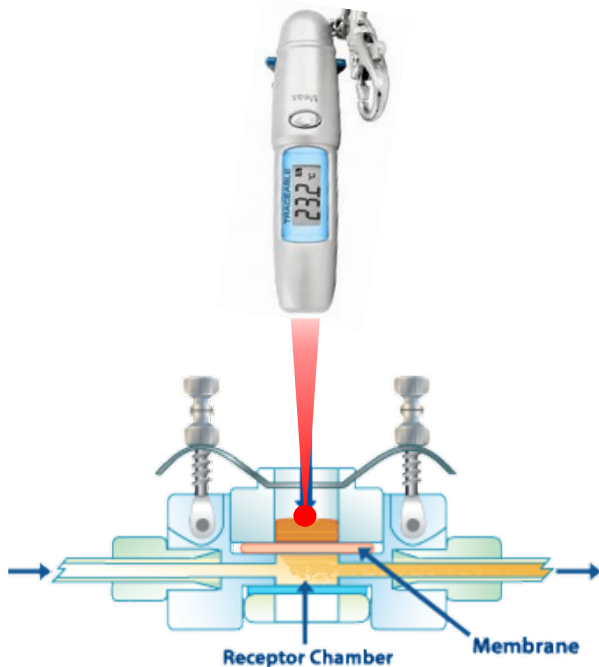


12h Study Designs



Temperature Monitoring

- Infrared Thermometer

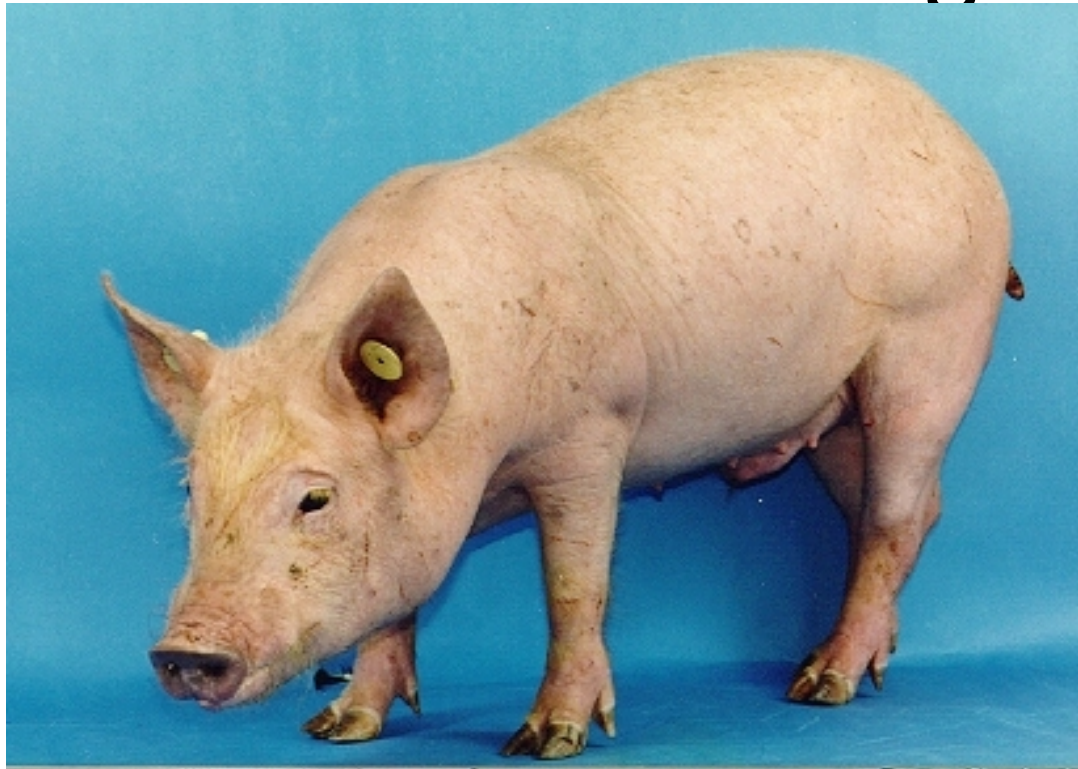


Images from <https://traceable.com/products/thermometers/4480.html> and www.permegear.com

Residual Patch Analysis

- Objective: to investigate whether residual patch analysis can be a potential surrogate method for predicting the extent of drug absorption from TDS
- Extraction solvent, volume of extraction solvent, and the duration of extraction needs to be tested and optimized for each TDS

Yucatan Miniature Swine: Pre-human skin screening in vitro



Skin Preparation

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

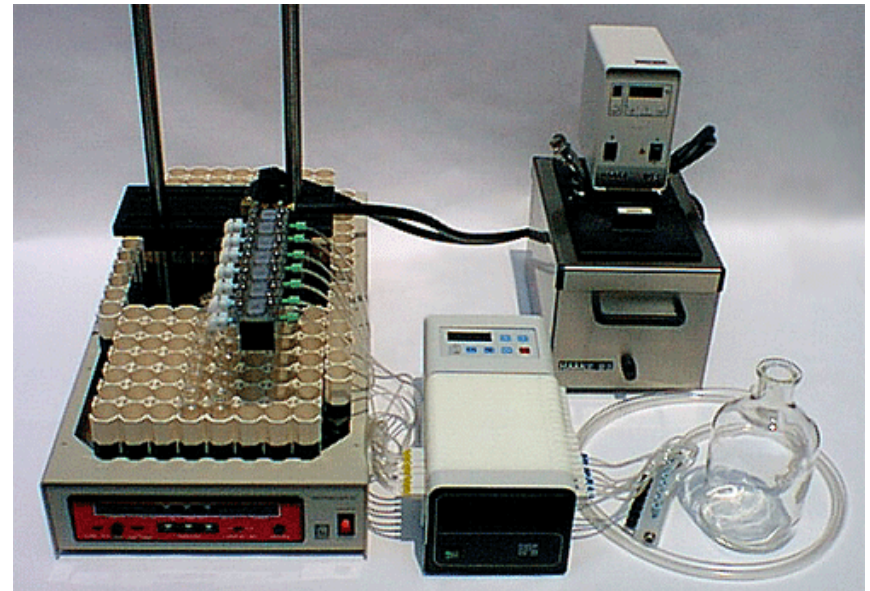
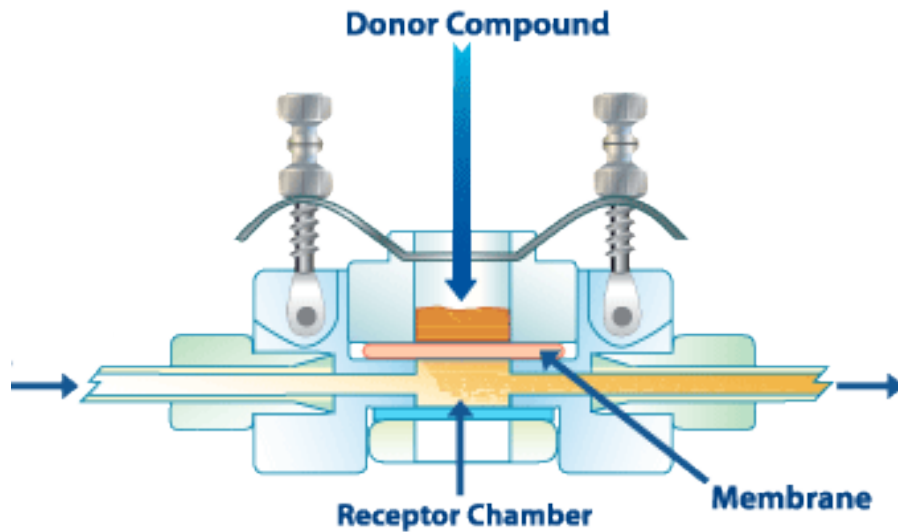


Image obtained from the Stinchcomb Lab's SOP

IVPT Setup

In Vitro Permeation Test

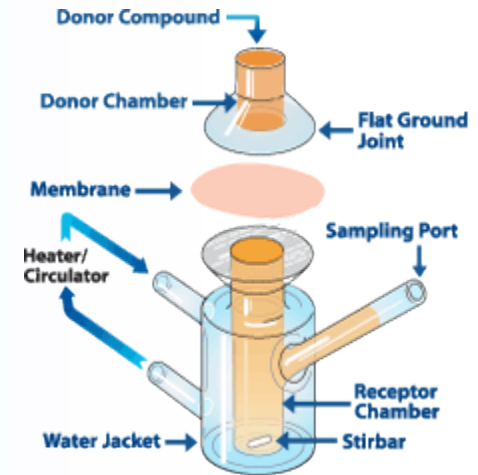
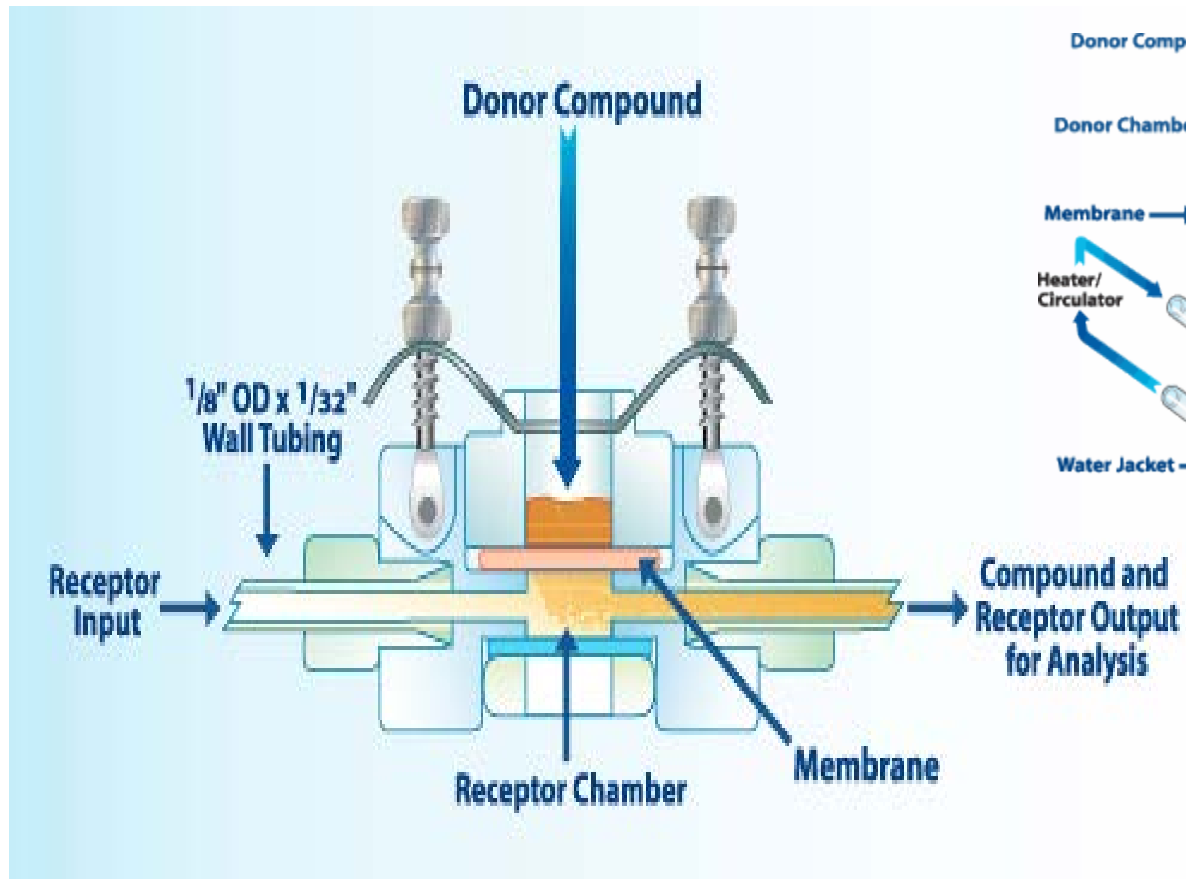
- In-line flow-through diffusion system
- Permeation area of 0.95 cm^2



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

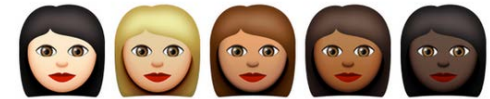
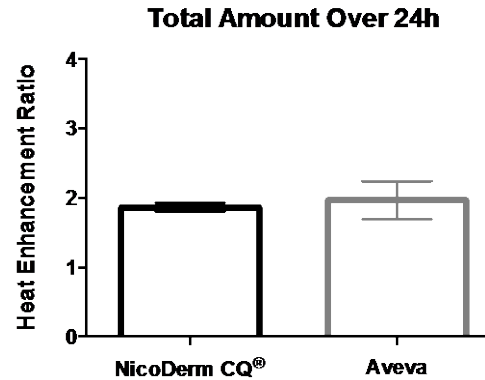
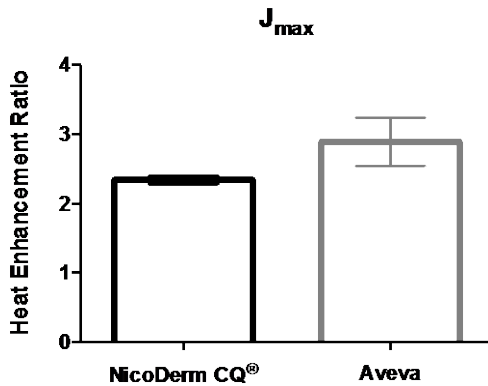
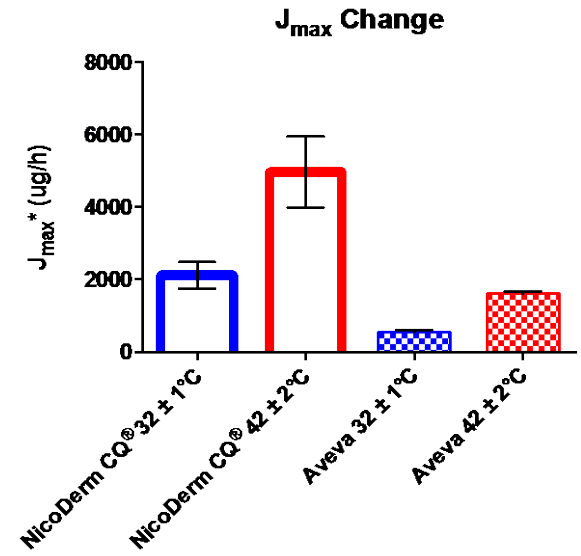
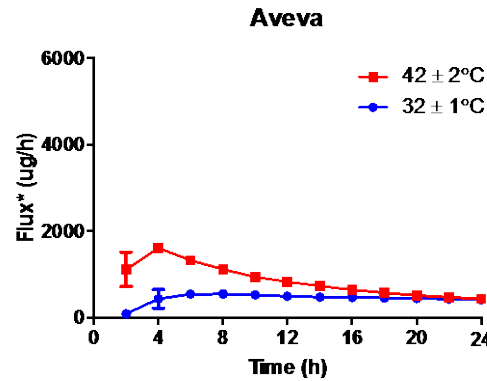
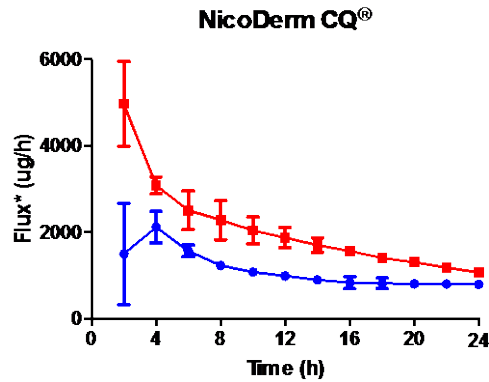
In Vitro Skin Permeation Study (IVPT)

Automated
In-Line
Flow Through
System



Standard
Franz cell

IVPT Continuous Heat Effect

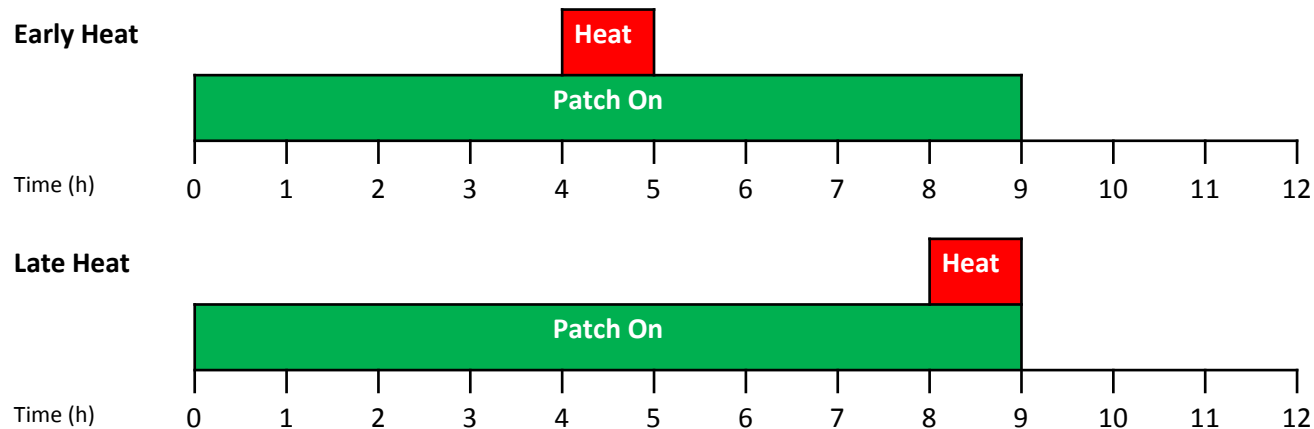


Human Skin Data

Mean ± SD from 2 donors with
n=4 per each donor

Clinical Study Designs – Nicotine

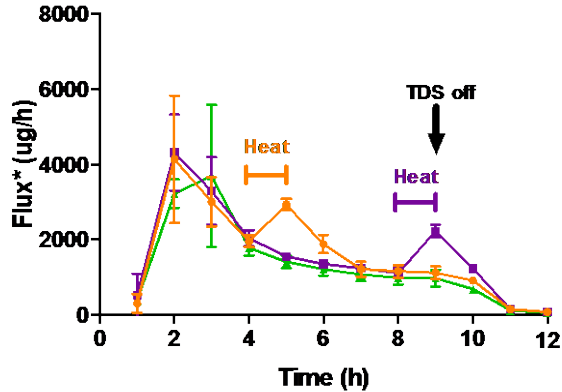
- A four-way crossover PK study in 10 adult smokers (two nicotine TDS)



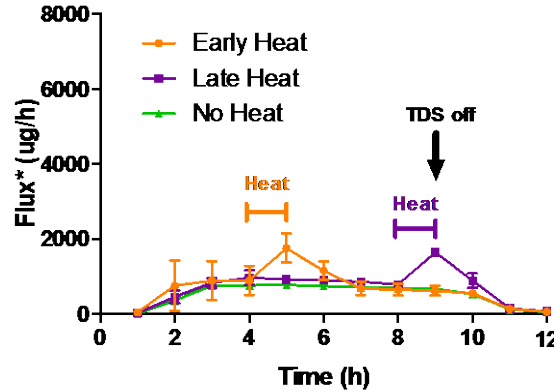
- Residual amount of nicotine in TDS was analyzed
- Temperature of skin surface was monitored throughout the study

Preliminary: IVPT Temporary (1h) Heat Effect

NicoDerm CQ[®]



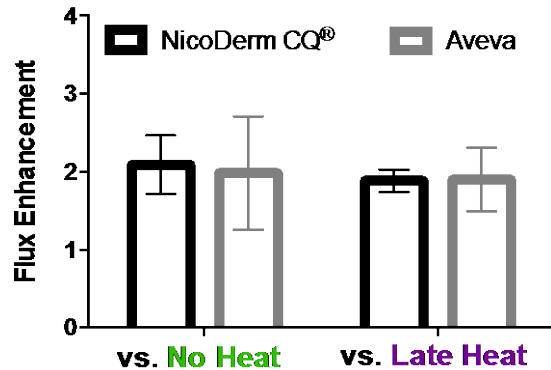
Aveva



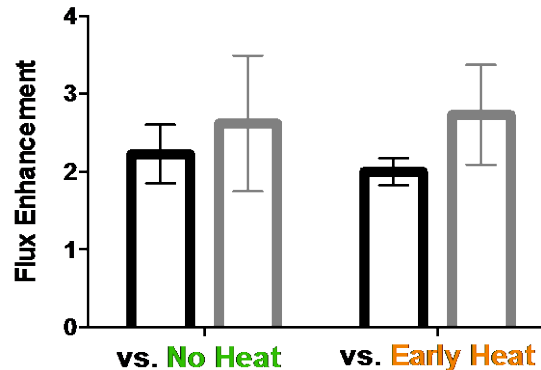
Human Skin Data

Mean \pm SD from 4 donors for Heat and 2 donors for No Heat with n=4 per each donor

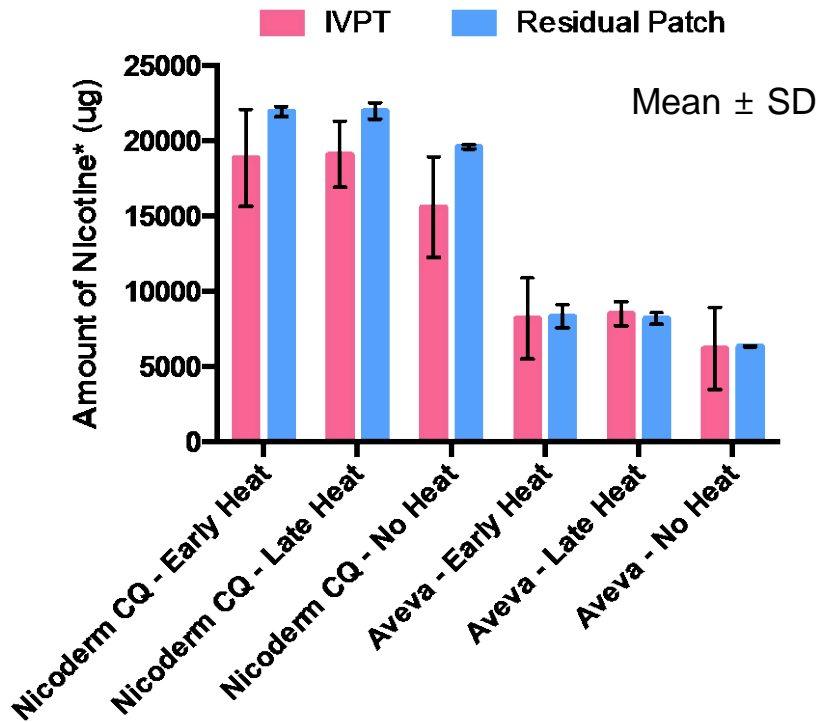
Early Heat Effect



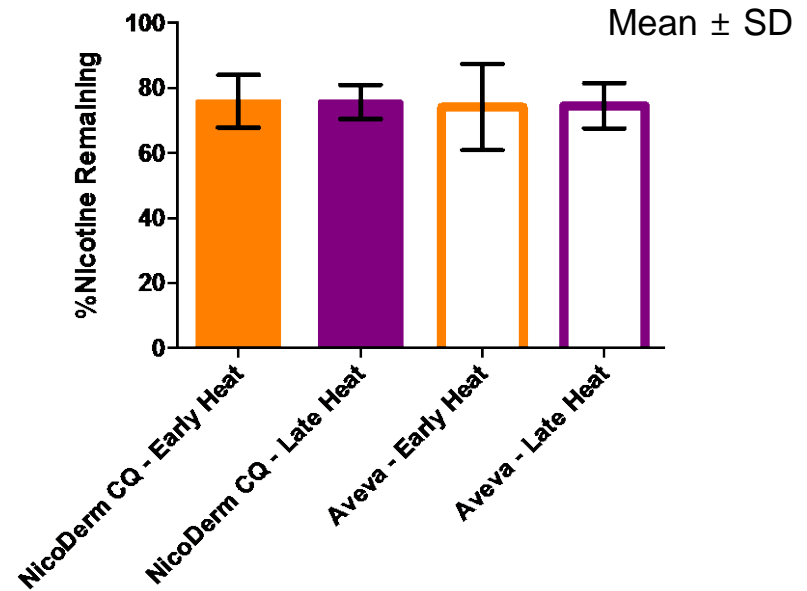
Late Heat Effect



Preliminary: Nicotine Residual TDS Extraction

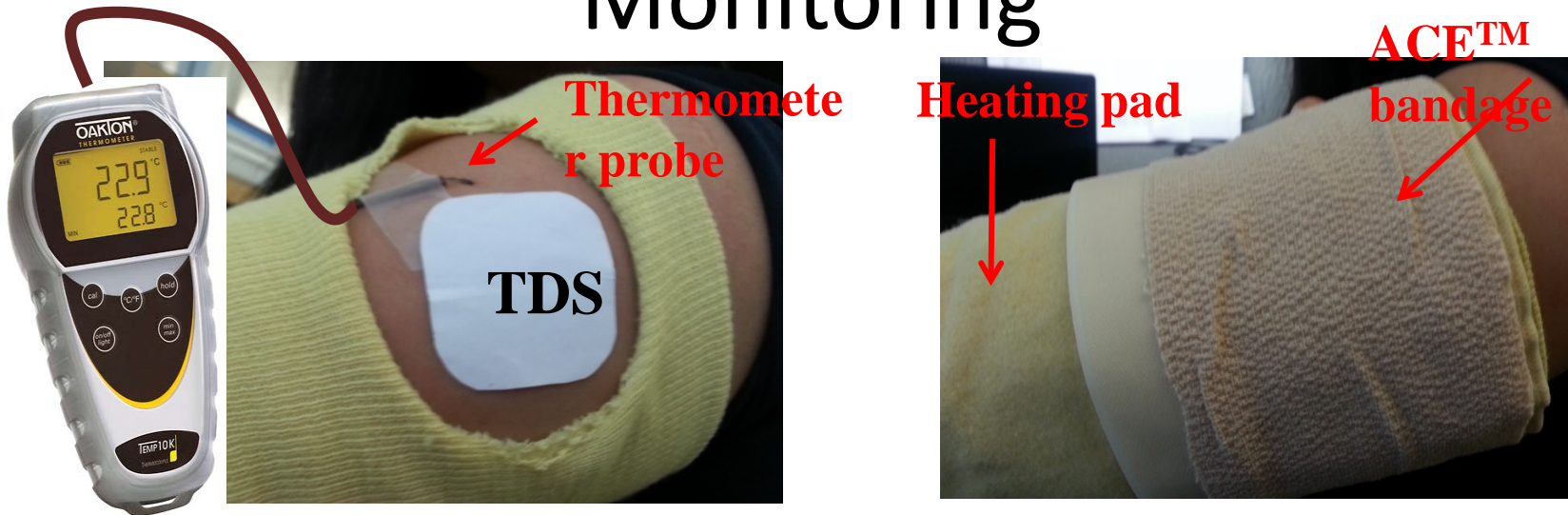


$p > 0.05$ for all treatment groups between IVPT and Residual Patch Analysis Data



$p > 0.05$ between early vs. late heat
 \Rightarrow paralleled the results from IVPT

Heat application and Temperature Monitoring

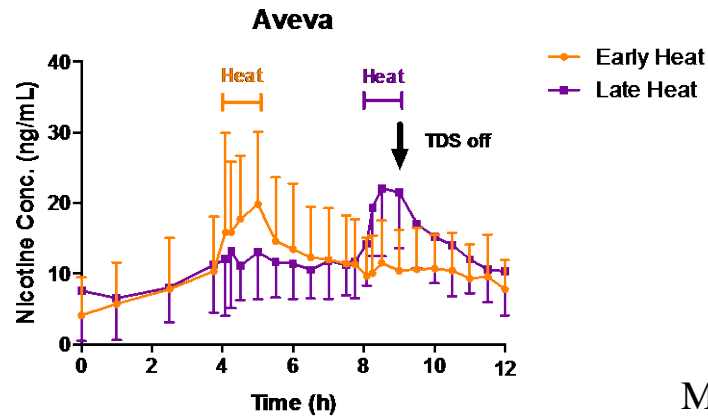
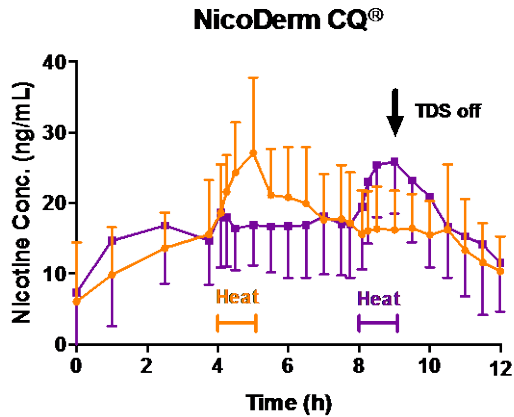


- Kevlar sleeve with an opening to expose TDS, while protecting skin from other areas
- Thermometer probe adjacent to TDS

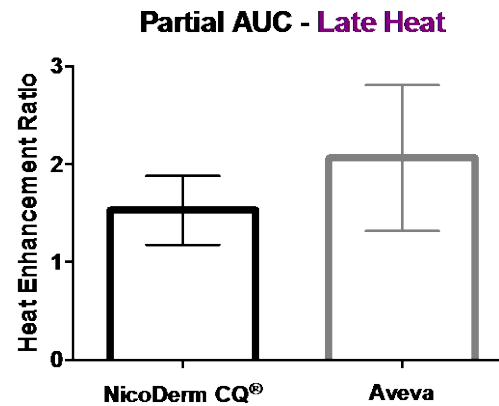
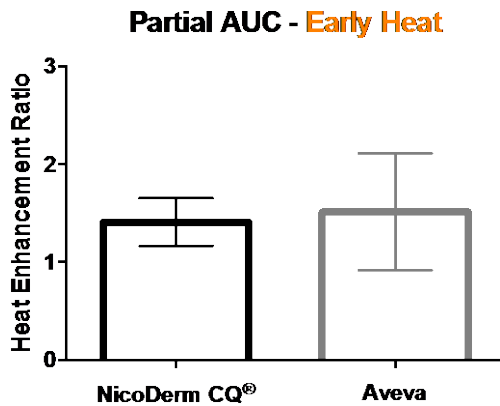
- Pre-heated heating pad
- ACE™ Bandage to ensure good contact between TDS and heating pad

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

Nicotine PK profiles

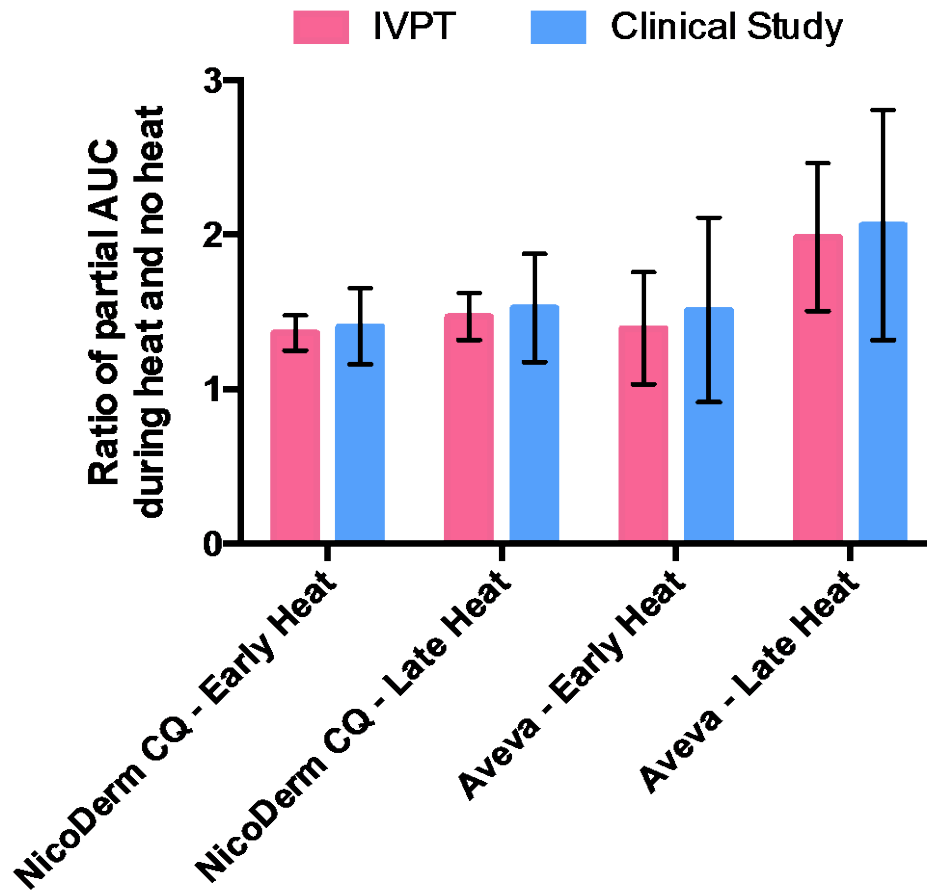


Mean \pm SD from 10
Subjects



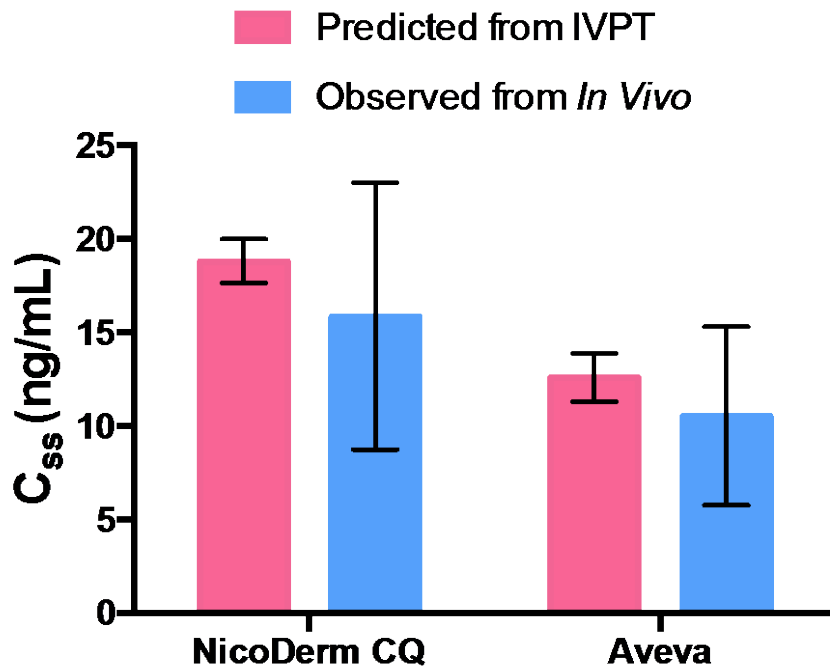
- Serum samples analyzed by S. Thomas
- LC-MS/MS method developed by I.
Abdallah

IVIVC – Heat Effect on Nicotine TDS



- $p > 0.05$ between IVPT and clinical study results
- IVPT can predict heat effect on TDS *in vivo*

Nicotine IVIVC – Absence of Heat



- At steady-state, $R_{in} = R_{out}$
- $R_{in} \text{ (ng/hr)} = J \text{ (ng/cm}^2\text{/hr)} \times \text{Area (cm}^2\text{)}$
- $R_{in} = CL \times C_{ss}$
- $CL = 72000 \text{ mL/h}$

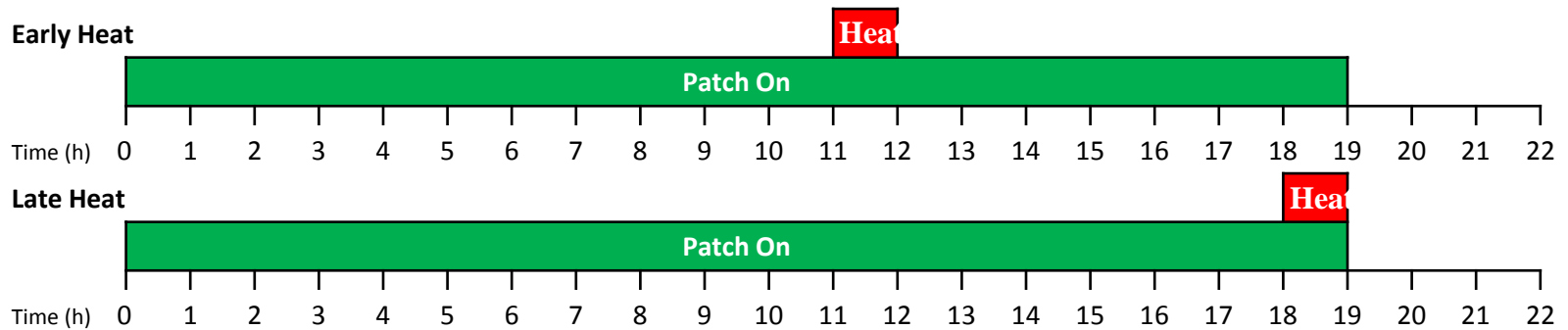
- $p > 0.05$ between predicted and observed C_{ss}
- IVPT can predict the performance of TDS *in vivo*



Fentanyl

Heat with Fentanyl TDS

- A six-way, crossover PK study in 10 healthy adults

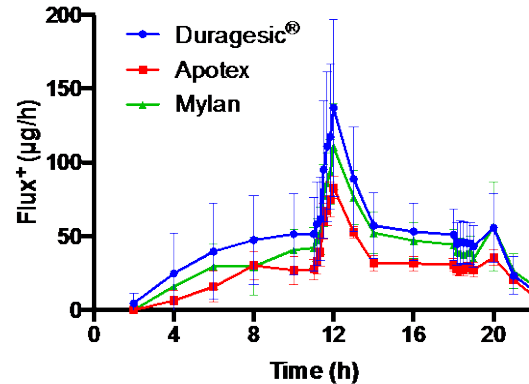


- 3 Fentanyl Patches
- Duragesic, Apotex generic, Mylan generic
- 1 hr heat

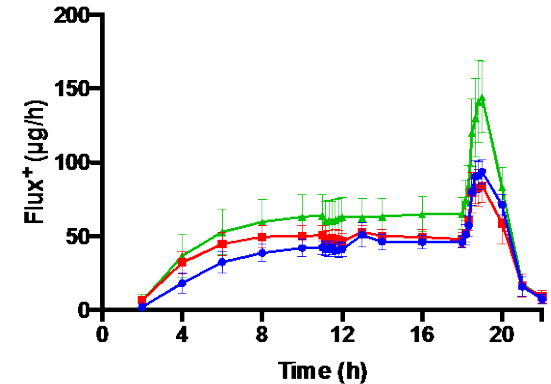
Fentanyl Heat-IVPT

6 samples during 1 h
of heat application
(same number of
samples as in vivo)

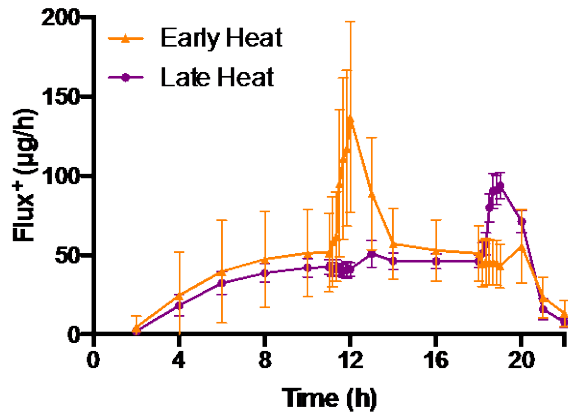
Donor A: Early Heat



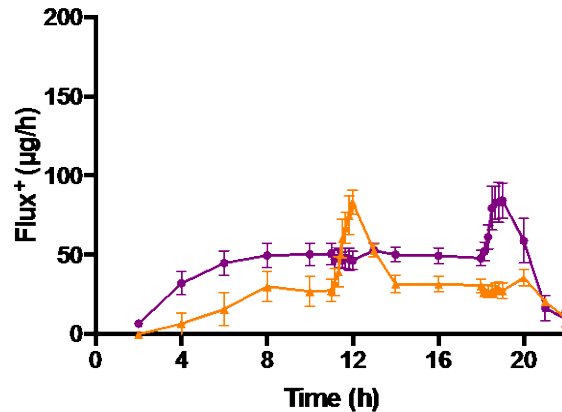
Donor A: Late Heat



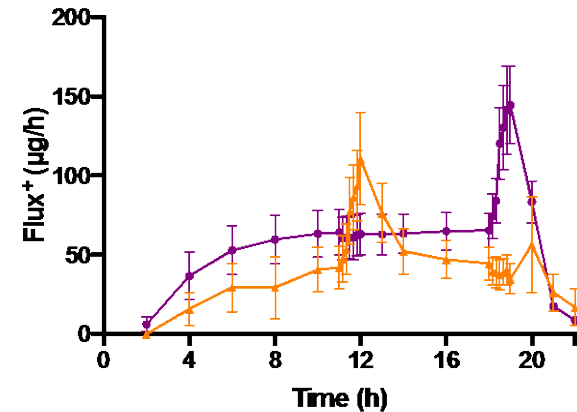
Duragesic®



Apotex



Mylan



Mean +/- S.D. n=4

Fentanyl Heat: Ratio IVPT amt & partial AUC

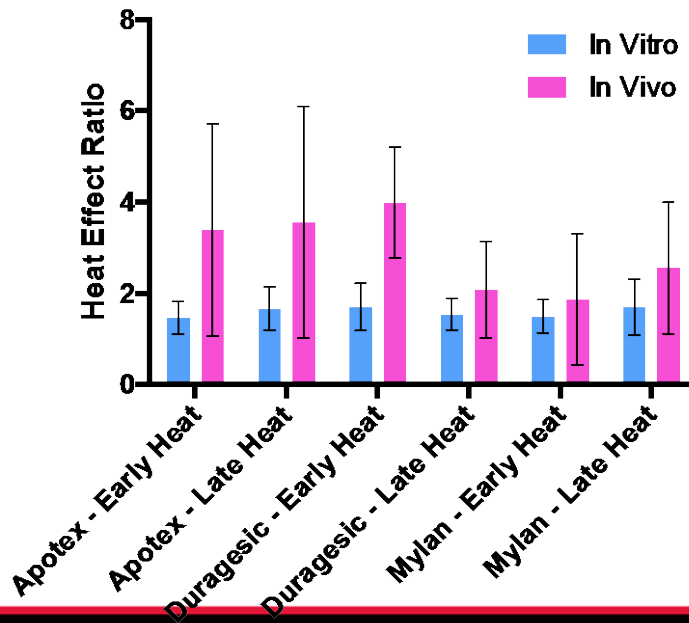
Mean Enhancement Ratio, determined by the ratio of the permeation amounts (in vitro) or partial AUC (in vivo) over 3 h from the two designs

- Early Heat: from 11 h until 14 h post-TDS application
- Late Heat: from 18 h until 21 h post-TDS application

Early Heat Effect	In Vitro			In Vivo
	Donor A	Donor 1	Donor 2	
Duragesic®	2.0	1.1	2.0	4.0 ± 1.2
Apotex	1.1	1.5	1.8	3.4 ± 2.3
Mylan	1.1	1.6	1.8	1.9 ± 1.4

Late Heat Effect	In Vitro			In Vivo
	Donor A	Donor 1	Donor 2	
Duragesic®	1.5	1.9	1.2	2.1 ± 1.1
Apotex	2.2	1.3	1.5	3.6 ± 2.5
Mylan	2.4	1.4	1.3	2.6 ± 1.4

In Vitro vs. In Vivo



No statistically significant ($p > 0.05$) difference between in vitro and in vivo values for all 6 arms

(Two-way ANOVA followed by Bonferroni's post-hoc analysis)

In vivo data from six subjects

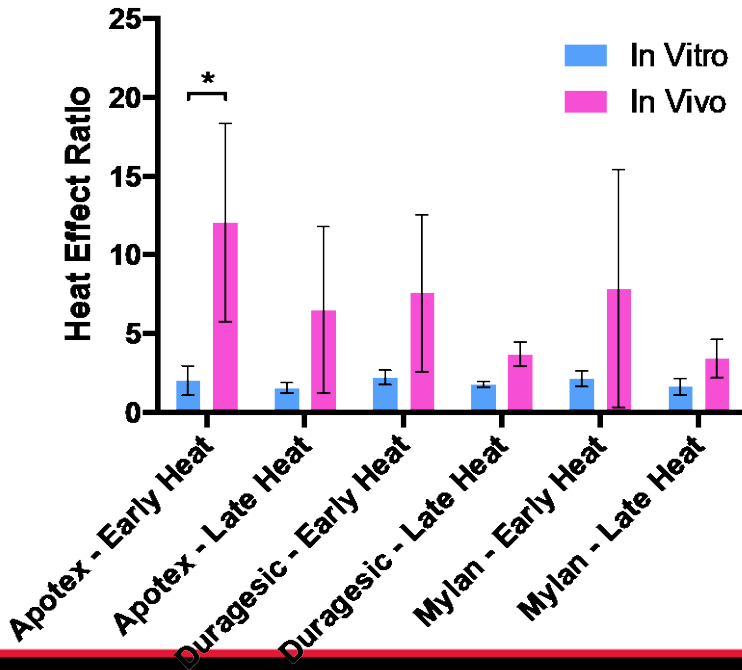
Fentanyl Heat: Ratio IVPT Jmax & Cmax

Mean Enhancement Ratio, determined by the ratio of the highest value during the 3 h window and the value immediately before heat application

Early Heat Effect	In Vitro: J _{max}			In Vivo: C _{max}
	Donor A	Donor 1	Donor 2	
Duragesic®	2.7	2.2	1.8	7.6 ± 5.0
Apotex	3.1	1.5	1.5	12.1 ± 6.3
Mylan	2.7	1.9	1.8	7.8 ± 7.5

Late Heat Effect	In Vitro: J _{max}			In Vivo: C _{max}
	Donor A	Donor 1	Donor 2	
Duragesic®	2.0	1.6	1.8	3.7 ± 0.8
Apotex	1.7	1.2	1.8	6.5 ± 5.3
Mylan	2.2	1.4	1.3	3.4 ± 1.2

In Vitro vs. In Vivo



	p-value
Apotex – Early Heat	0.01 (*)
Apotex – Late Heat	0.64 (ns)
Duragesic – Early Heat	0.49 (ns)
Duragesic – Late Heat	> 0.99 (ns)
Mylan – Early Heat	0.38 (ns)
Mylan – Late Heat	> 0.99 (ns)

(Two-way ANOVA followed by Bonferroni's post-hoc analysis)

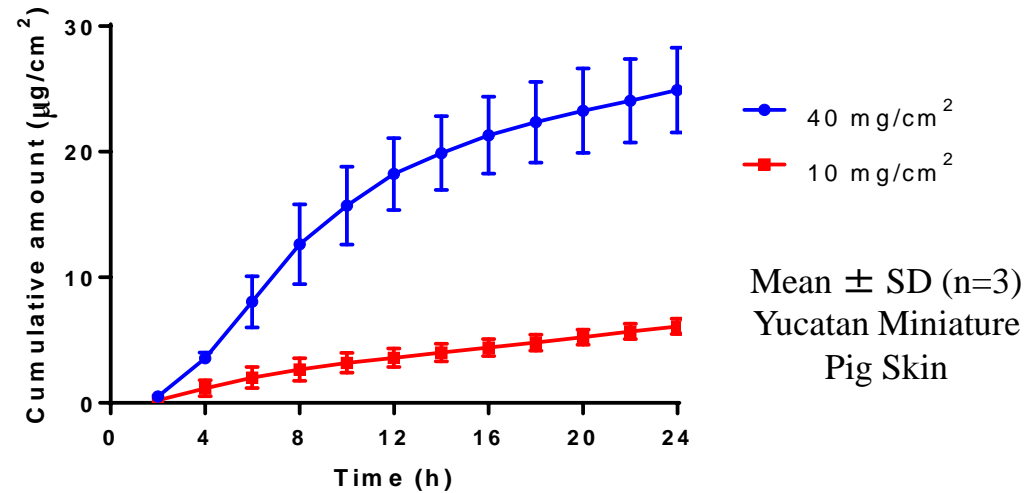
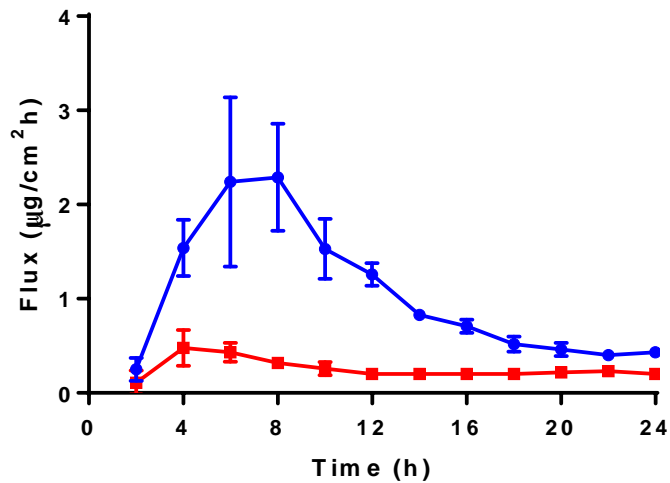
In vivo data from six subjects

IVPT

in vitro permeation testing

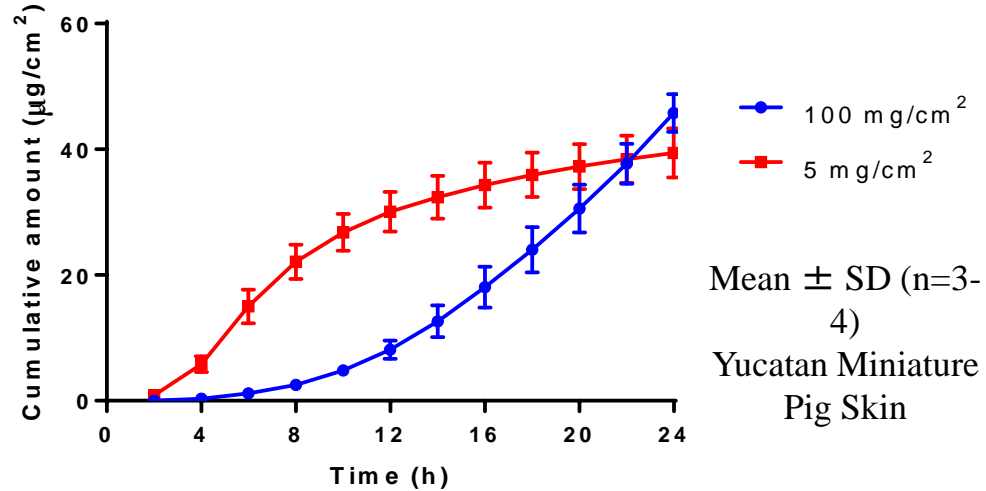
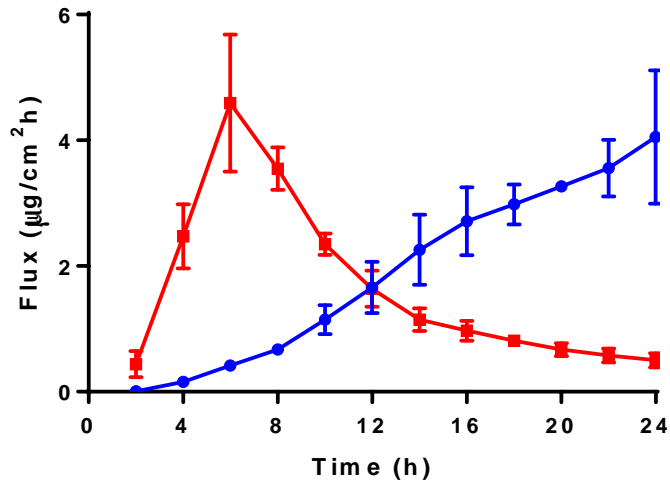
Dose Selection and Application
Methods for Transdermal Semisolids

Importance of Dose – Voltaren® gel



	$J_{\max} \pm \text{SD} (\mu\text{g}/\text{cm}^2/\text{h})$	$T_{\max} (\text{h})$	Cumulative Amount $\pm \text{SD} (\mu\text{g}/\text{cm}^2)$
40 mg/cm ²	2.29 \pm 0.57	8	24.91 \pm 3.38
10 mg/cm ²	0.48 \pm 0.19	2	6.10 \pm 0.61

Importance of Dose – Pennsaid® 2%



	$J_{\text{max}} \pm \text{SD}$ ($\mu\text{g}/\text{cm}^2/\text{h}$)	T_{max} (h)	Cumulative Amount \pm SD ($\mu\text{g}/\text{cm}^2$)
100 mg/cm ²	4.05 \pm 1.06	24	45.79 \pm 3.00
5 mg/cm ²	4.59 \pm 1.09	6	39.43 \pm 3.90

Dose Administration Techniques

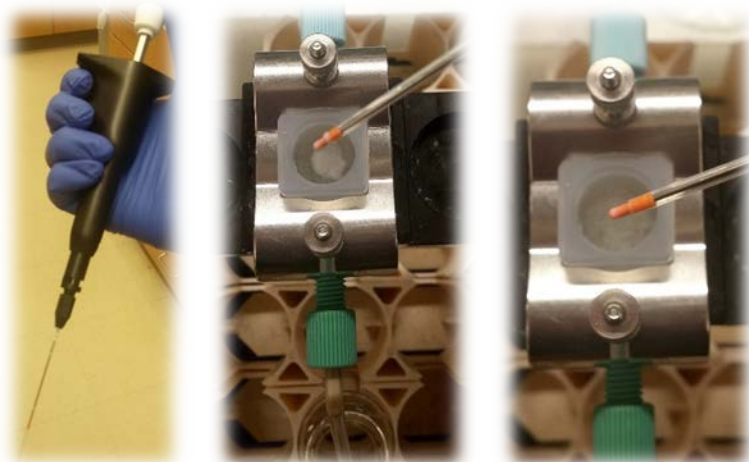
- Highly variable among labs, researchers, and patients
 - Methods of dispensing formulation
 - Duration of rubbing
 - Force used for rubbing
 - Loss of formulation during rubbing
- Need a reproducible and clinically-relevant technique



Image from <http://www.telegraph.co.uk/expat/expatlife/10441983/Pale-and-interesting.html>

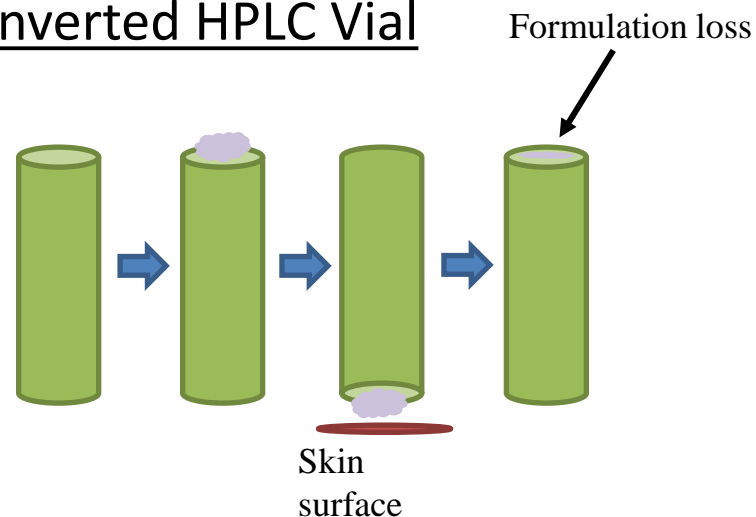
Dose Administration Techniques

Positive Displacement Pipette



- Quick, convenient, low variability
- Minimal formulation loss
- Lack of rubbing effect

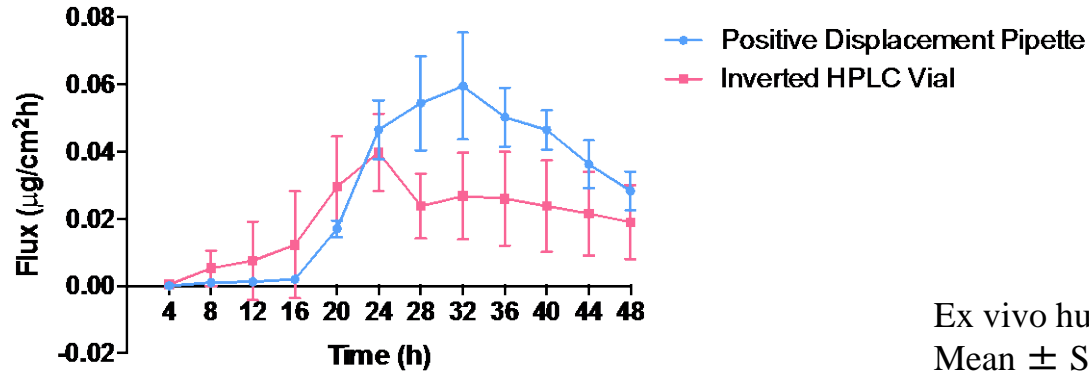
Inverted HPLC Vial



- Time-consuming, more variability
- Some formulation loss
- Simulates clinically-relevant rubbing effect

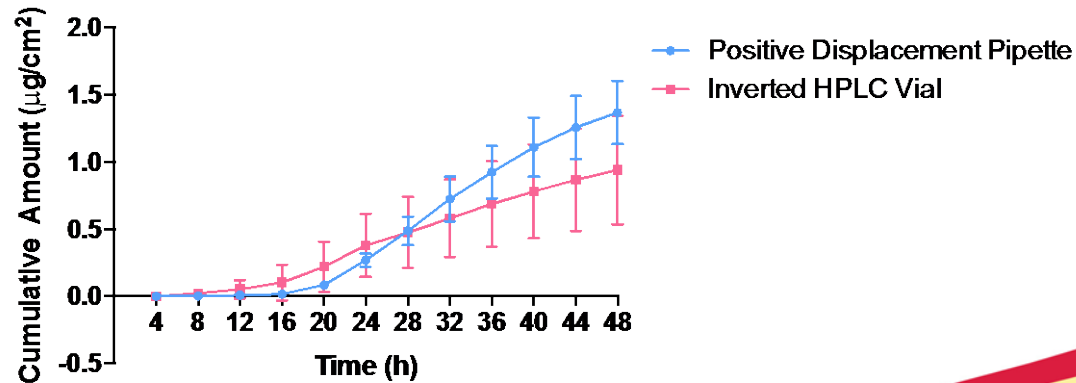
Dose Administration Techniques

U.S. Zovirax Cream



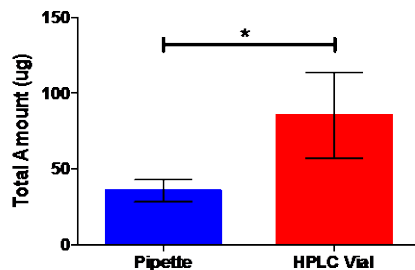
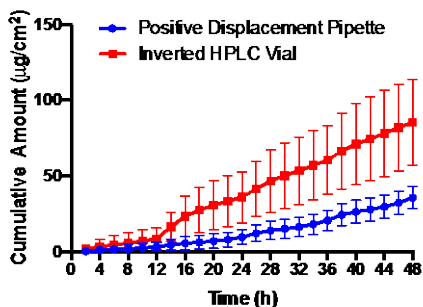
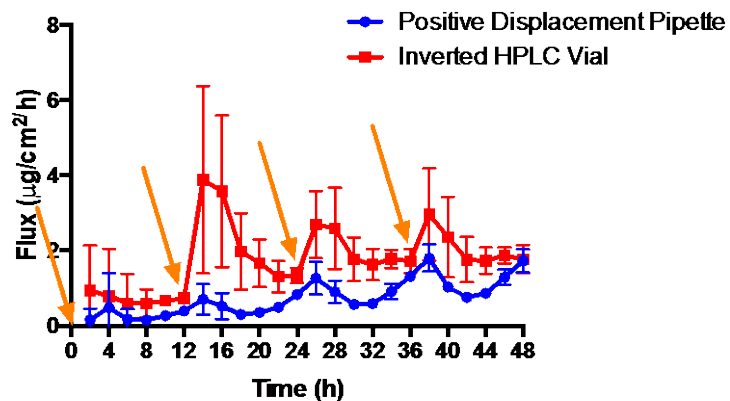
Ex vivo human skin
Mean \pm SD (n=4 for each technique)

U.S. Zovirax Cream

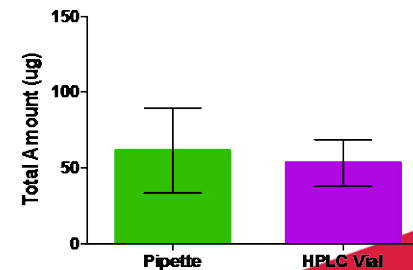
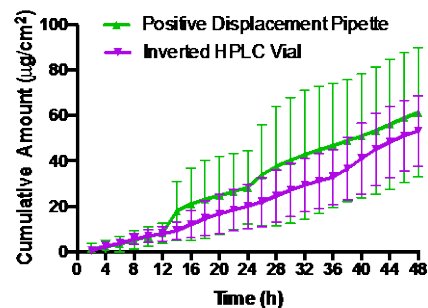
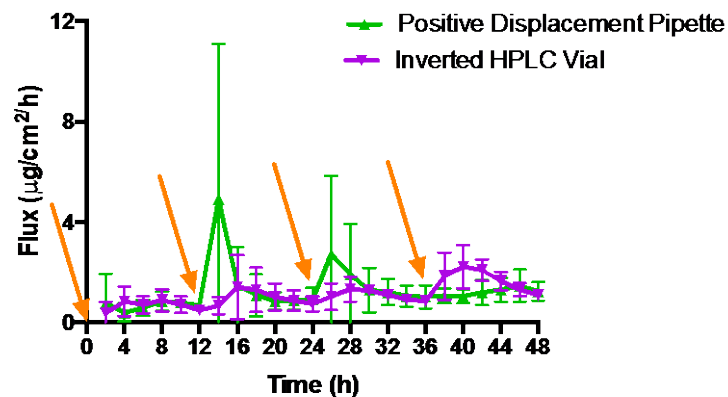


Preliminary: Dose Administration Techniques

Pennsaid® 2% (more viscous)



Pennsaid® 1.5%



Orange Arrow: dosing ($\sim 5 \text{ mg}/\text{cm}^2$ of formulation)

Mean \pm SD (n=3-4)
Yucatan Miniature Pig Skin

Conclusions

- Expense and time of clinical PK studies for transdermal and dermal products highlight the needs for developing surrogate methods to evaluate BA
- The IVPT method is a sensitive test that can be used to help predict clinical performance in some cases, if the methods are carefully designed
- In order for surrogate methods to be recognized by regulatory agencies, they need to be able to produce data that is reliable, low in variability and relevant to clinical settings
- Each method will have its own challenges to overcome
 - Needs to be addressed in order to evaluate IVIVC

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Thank you for your attention!

Questions?