UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Bioavailability and Bioequivalence of Products Applied to the Skin

Audra L. Stinchcomb, PhD

Professor, University of Maryland School of Pharmacy

Chief Scientific Officer and Founder, F6Pharma, Inc

F6 Pharma

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

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.

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

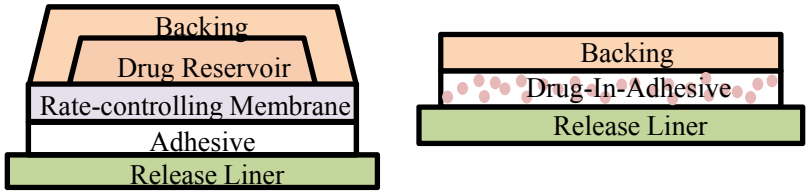
Tape-stripping (not discussing today)

(Bunge, Guy, Delgado-Charro)

IVPT (In Vitro Permeation Tests)

Dose, Application and Heat Effect

Transdermal Delivery Systems (TDS)



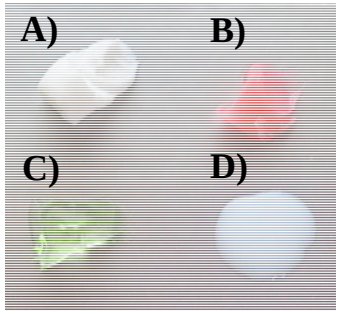
Reservoir Type **Matrix Type**

- Therapy can be interrupted
- Low drug delivery efficiency

- Systemic absorption is intended
- Blood levels ≈ 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 ≈ 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

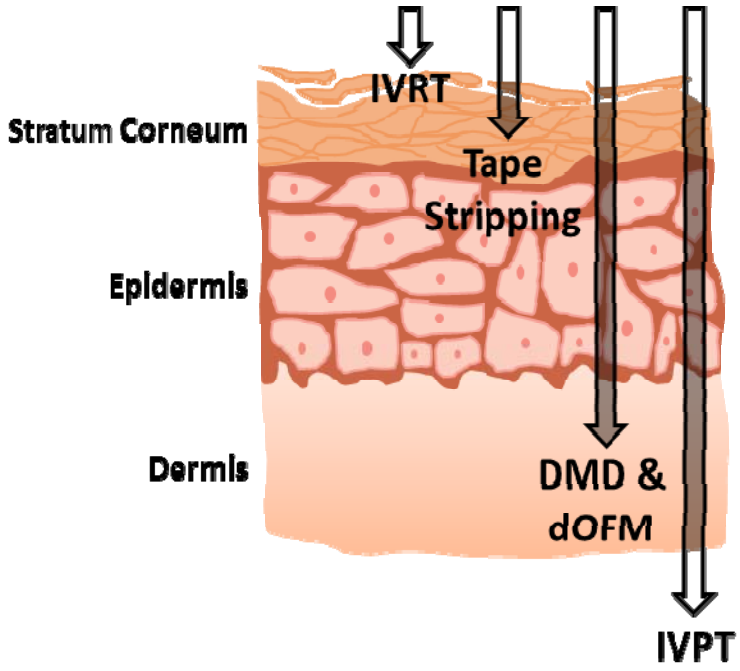
- IVPT and/or other surrogate methods can predict the performance of transdermal and topical drug products *in vivo*

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

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

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)

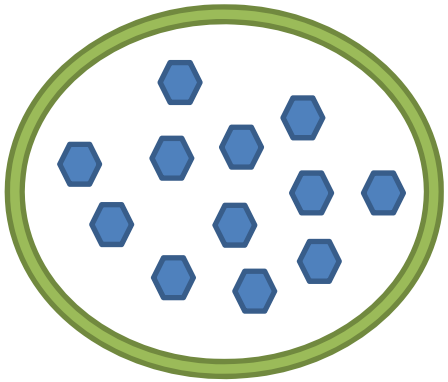
+ Clinical Studies (PK &/or efficacy)

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Why is Heat effect on TDS of Interest?

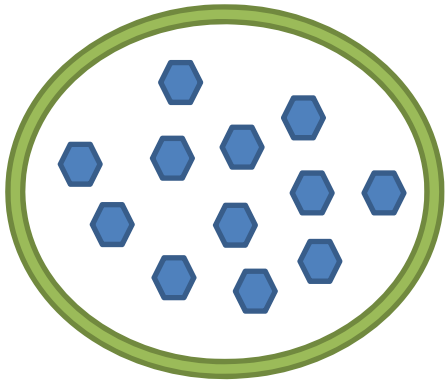
Influence of Heat on Percutaneous Absorption

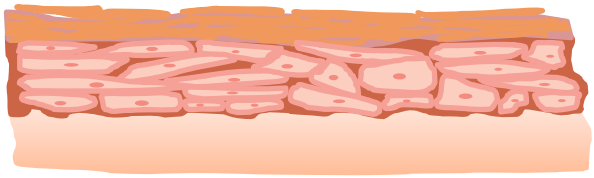
1) ↑ Diffusivity of Drug from its Vehicle

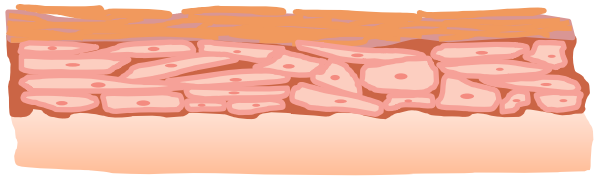


+ Heat

➜

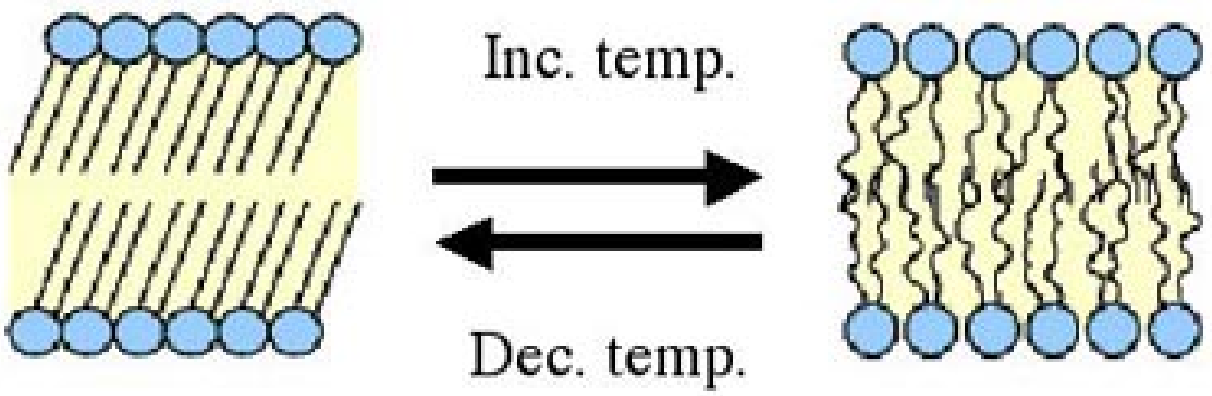






Influence of Heat on Percutaneous Absorption

2) ↑ Fluidity of Stratum Corneum Lipids



Very regular,
Ordered structure

Less tightly packed,
Hydrocarbon tails
Disordered.

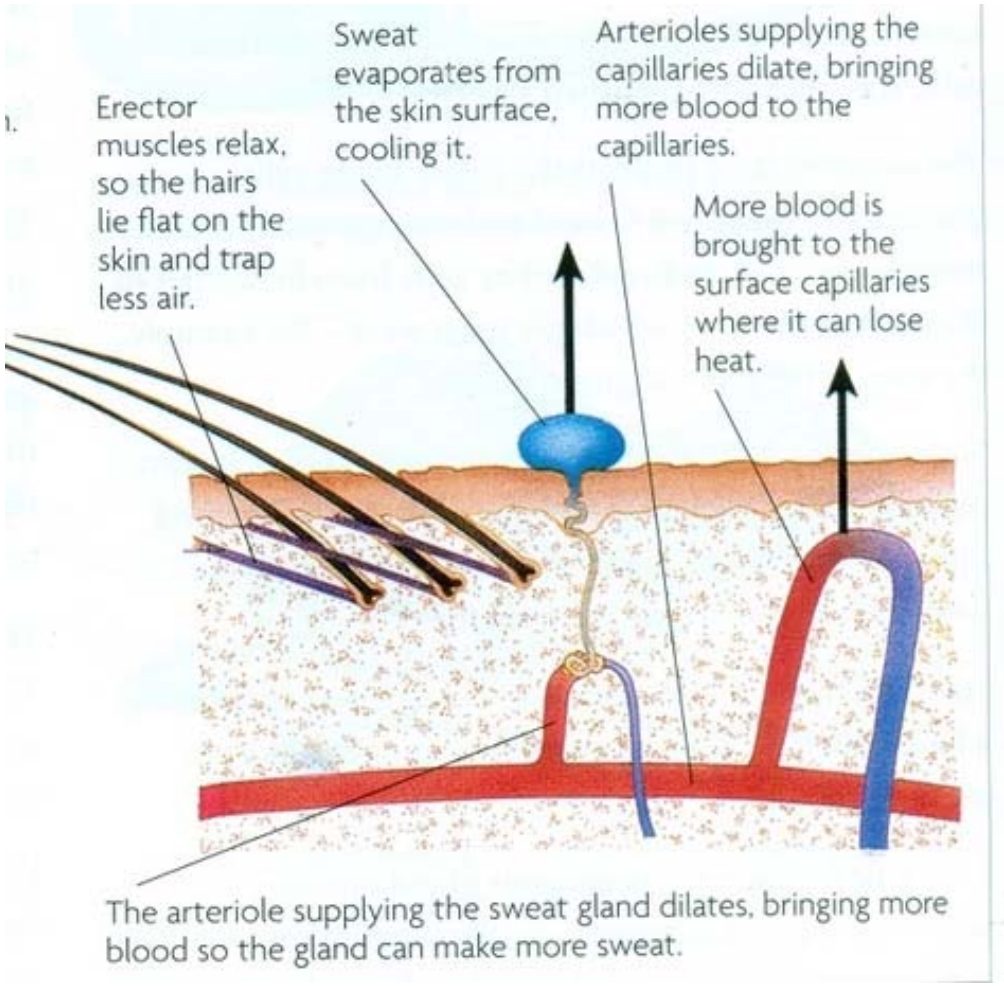
https://biochemistry3rst.wordpress.com/tag/phosphodiate/

Influence of Heat on Percutaneous Absorption

3) ↑ Cutaneous Vasodilation

Body temperature regulation

When the body is too hot



UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Selected TDS

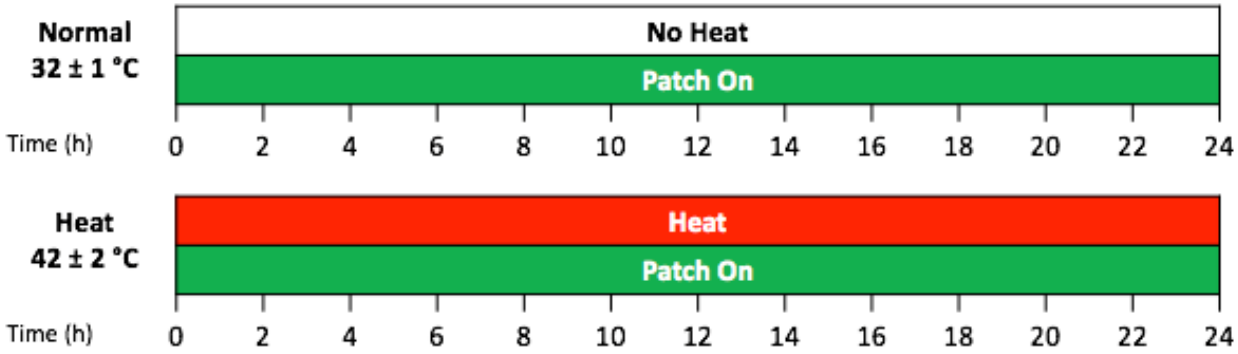
Nicotine TDS

Fentanyl TDS

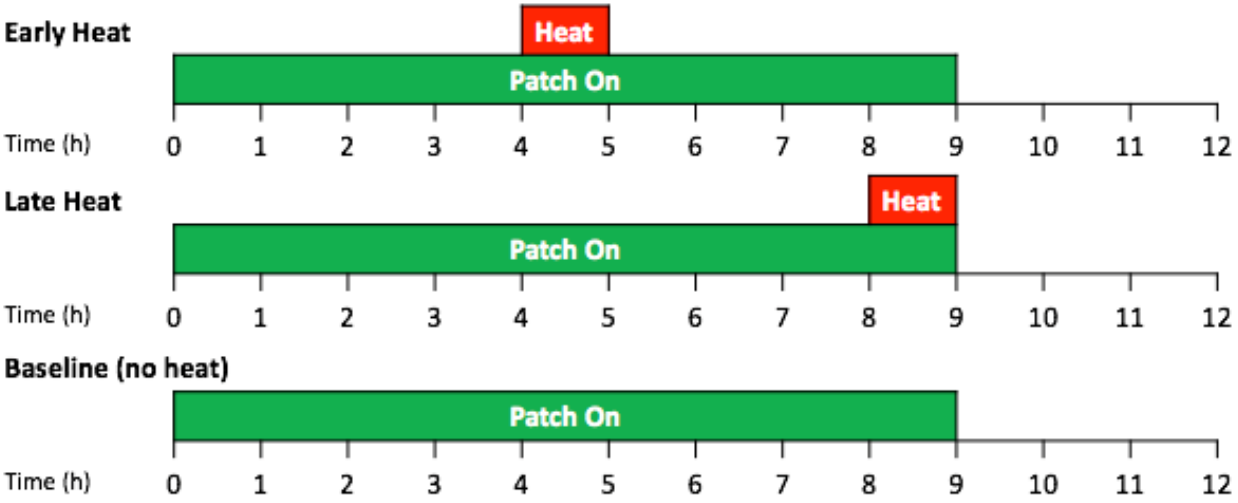
	NicoDerm CQ®	Aveva	Duragesic®	Mylan	Apotex
Patch size (cm^2)	15.75	20.12	10.5	6.25	10.7
Drug content (mg)	Not available	Not available	4.2	2.55	2.76
Rate/Area ($\mu g/h/cm^2$)	37	29	2.4	4.0	2.3
Inactive ingredients	Ethylene vinyl acetate-copolymer, **polyisobutylene** and high density polyethylene between 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

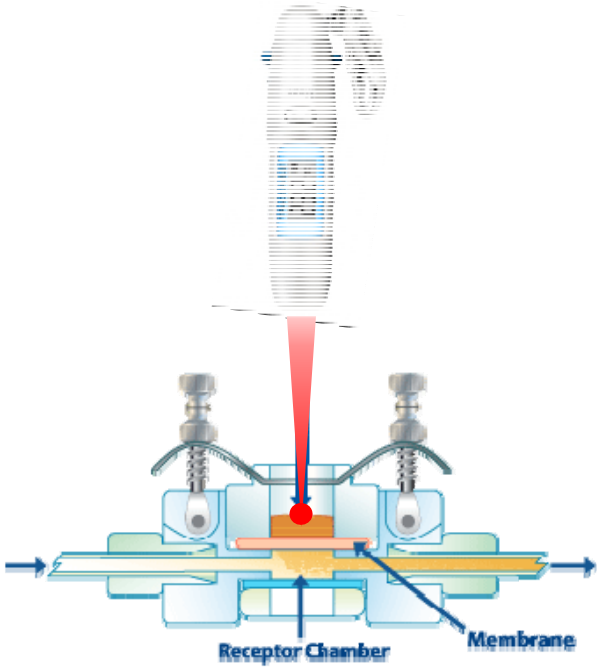


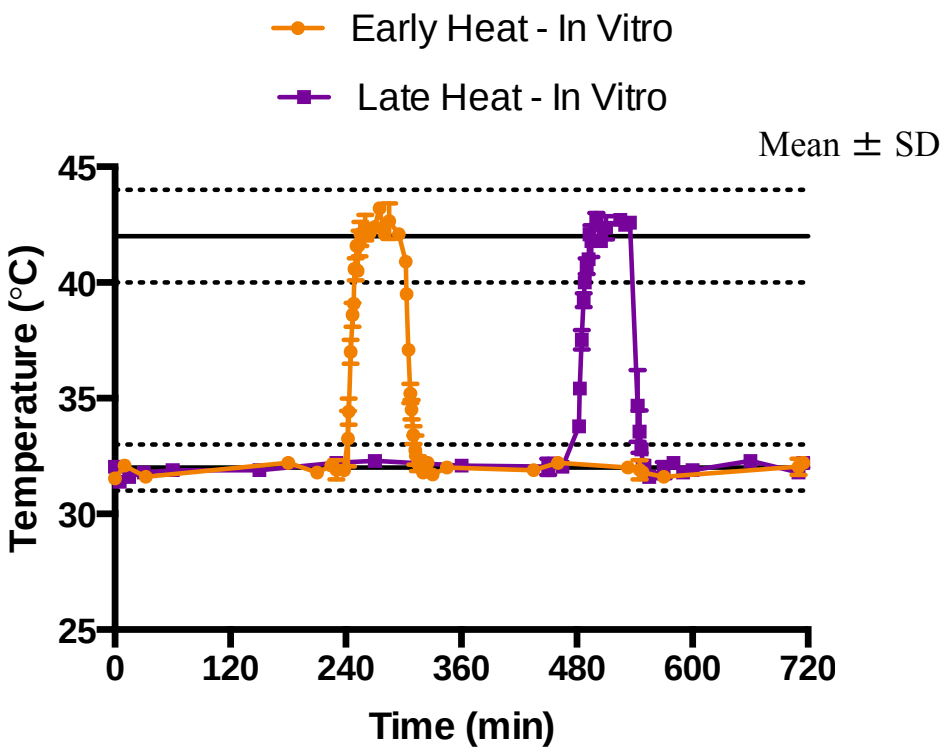
12h Study Designs



Temperature Monitoring

- Infrared Thermometer





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

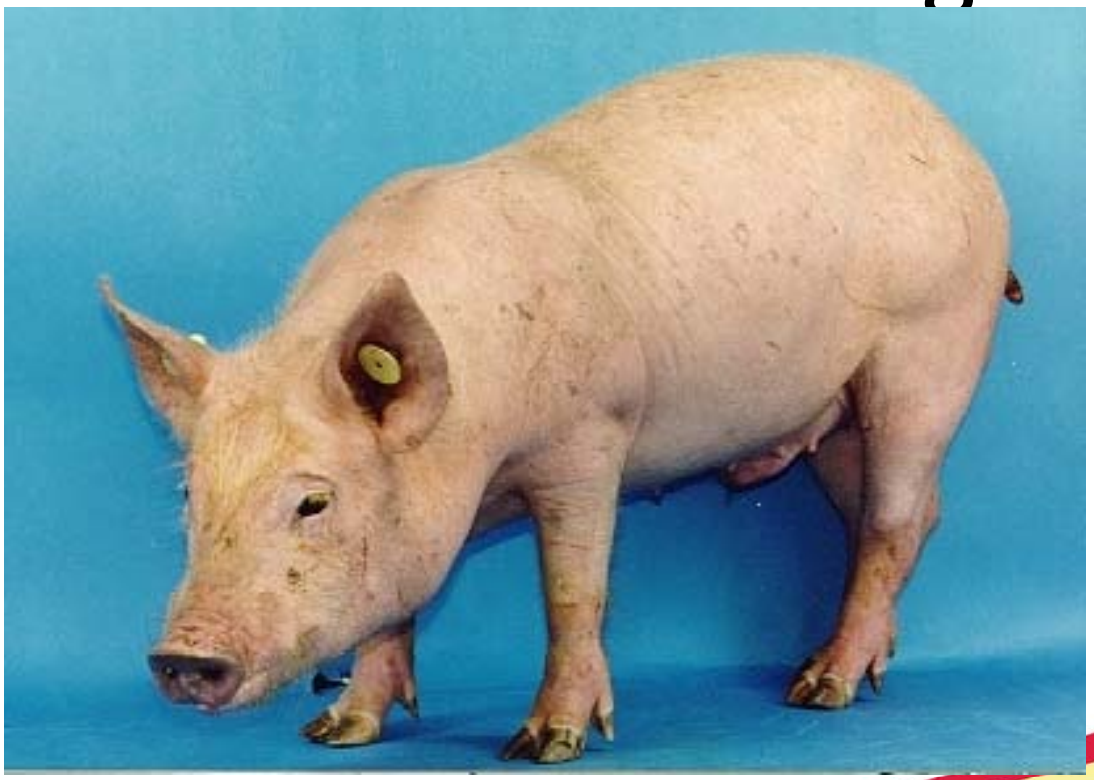
UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

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

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Yucatan Miniature Swine: Pre-human skin screening in vitro



UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Skin Preparation

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

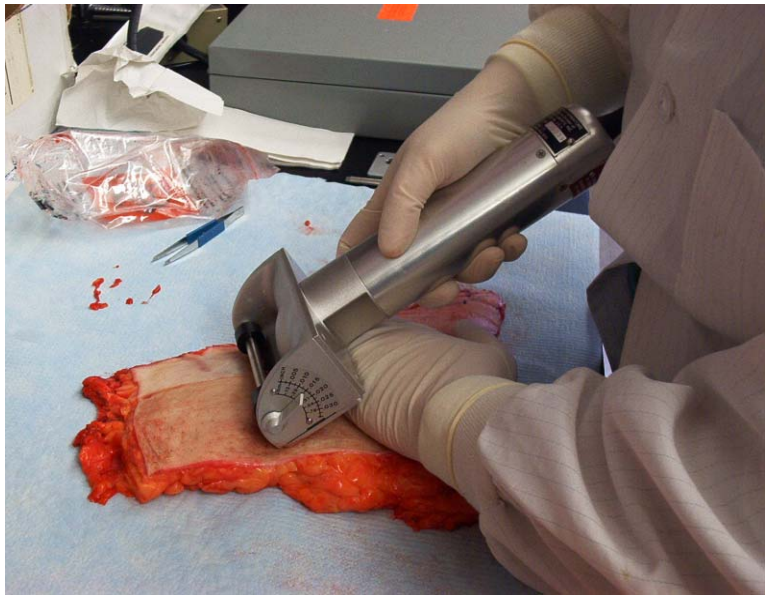
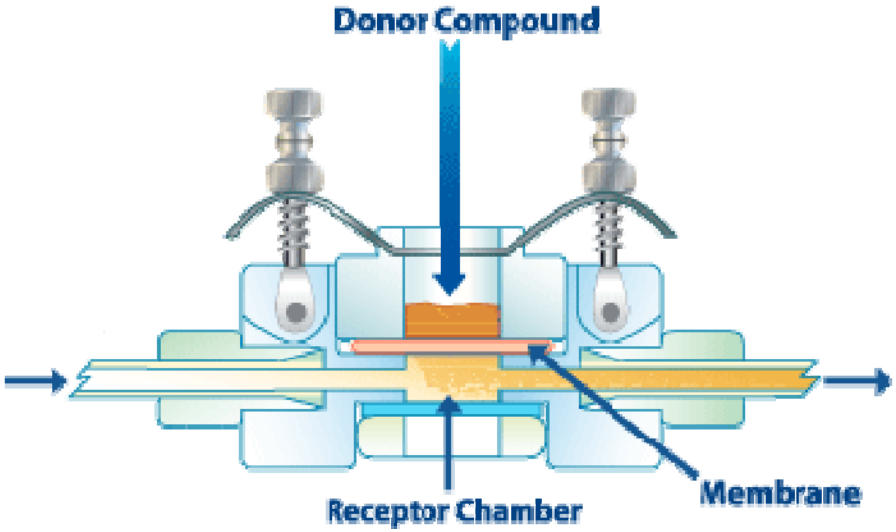
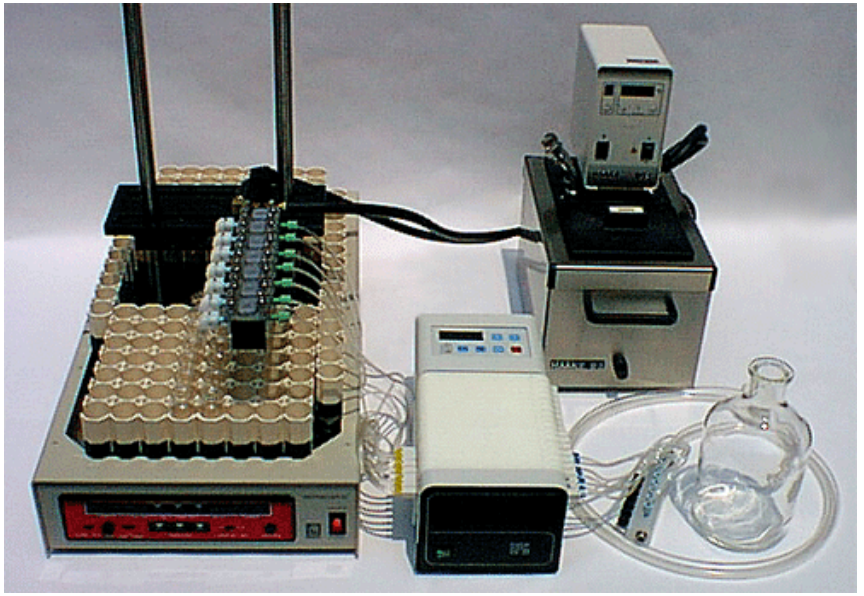


Image obtained from the Stinchcomb Lab's SOP

IVPT Setup
In Vitro Permeation Test

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



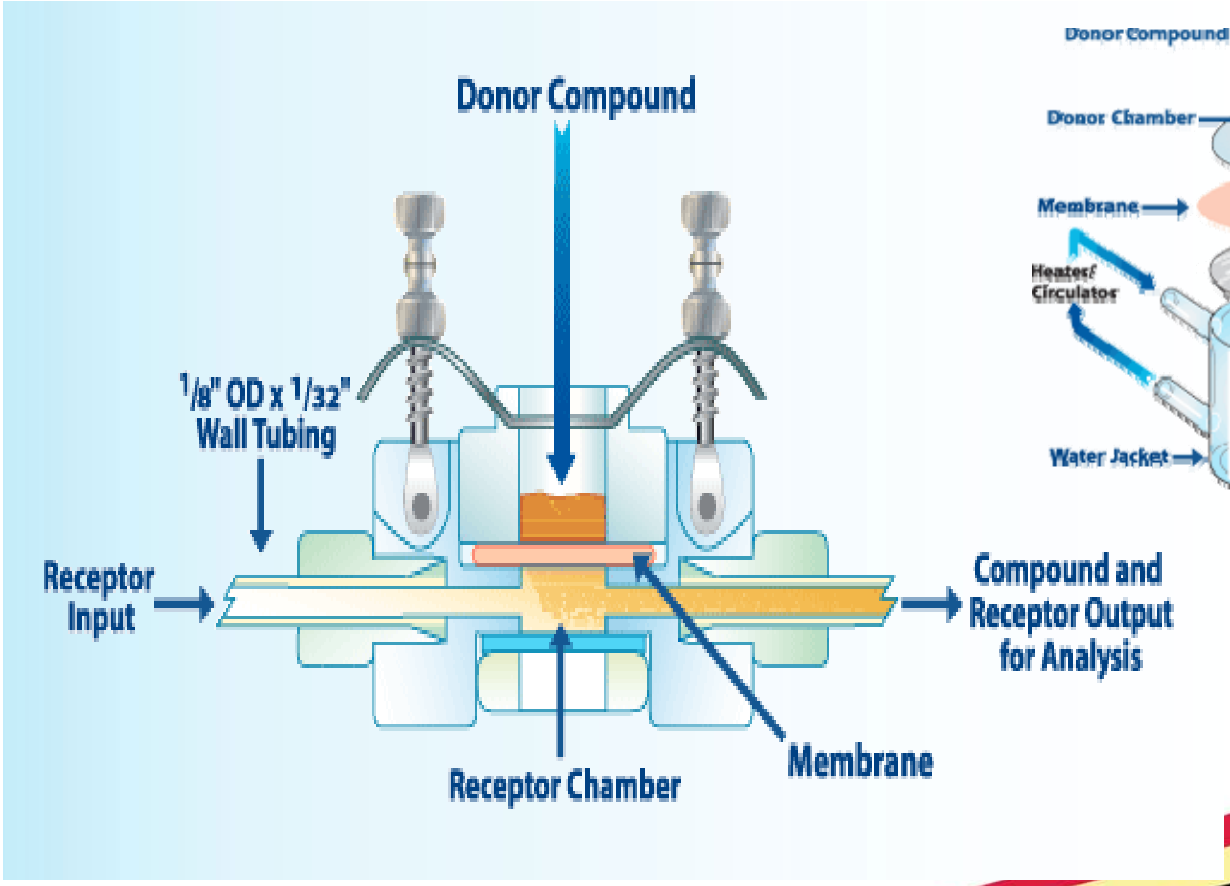


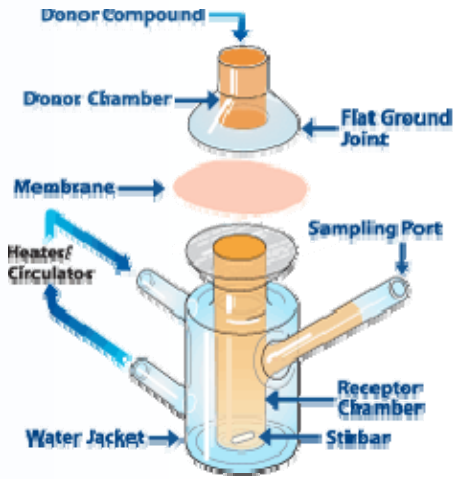
Images from www.ibric.org and www.permegear.com

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

In Vitro Skin Permeation Study (IVPT)

Automated
In-Line
Flow Through
System





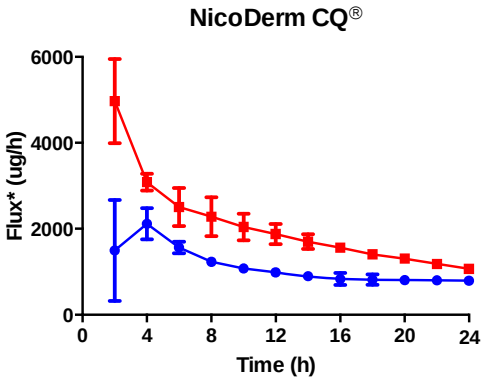
Standard
Franz cell

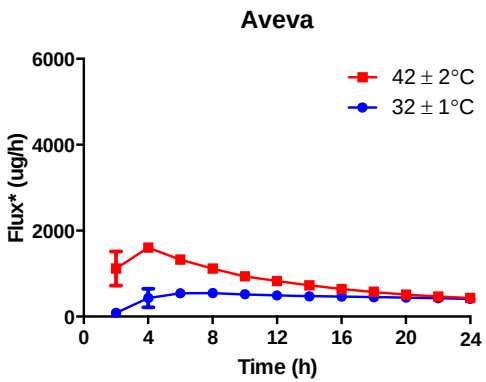
www.permegear.com

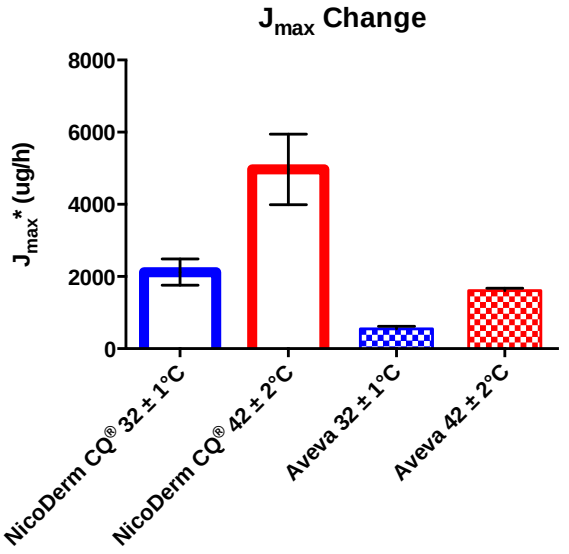
http://www.permegear.com/inline.htm

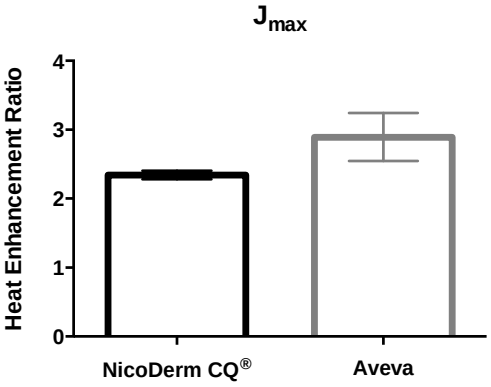
UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

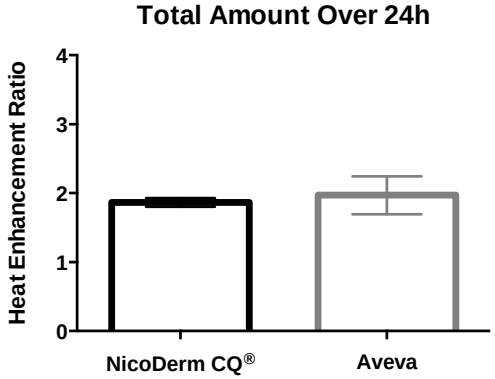
IVPT Continuous Heat Effect









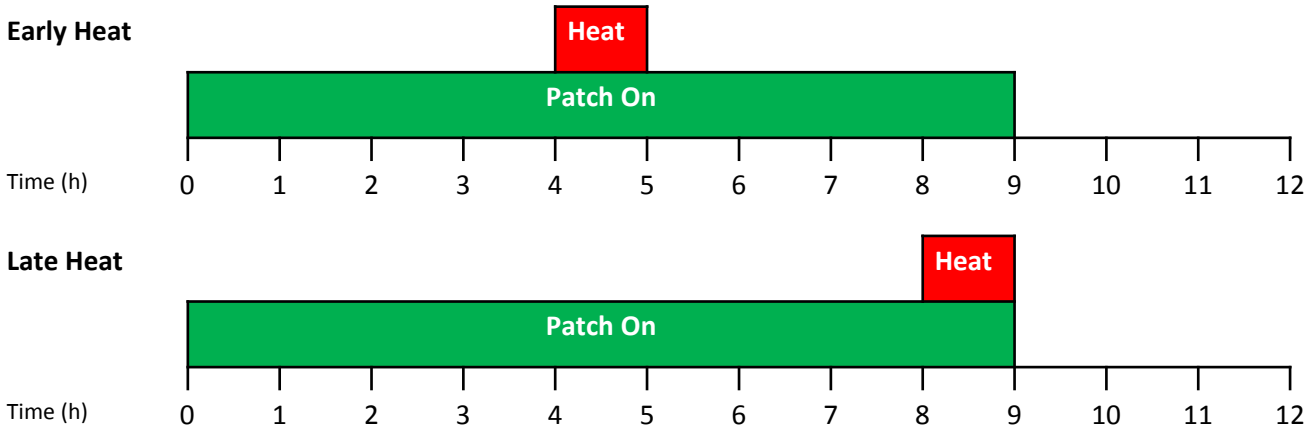


Human Skin Data

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)

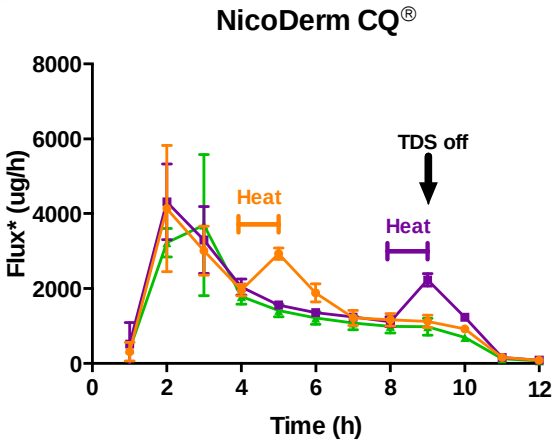


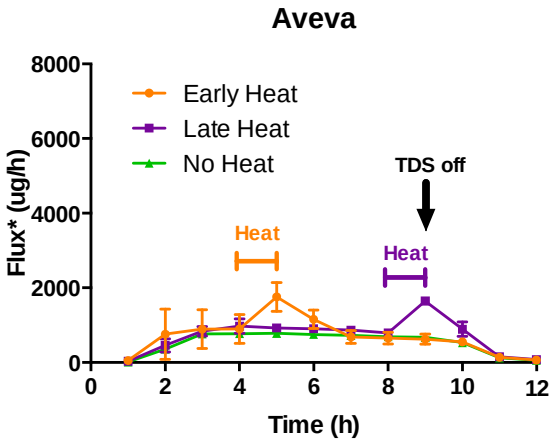
- Residual amount of nicotine in TDS was analyzed

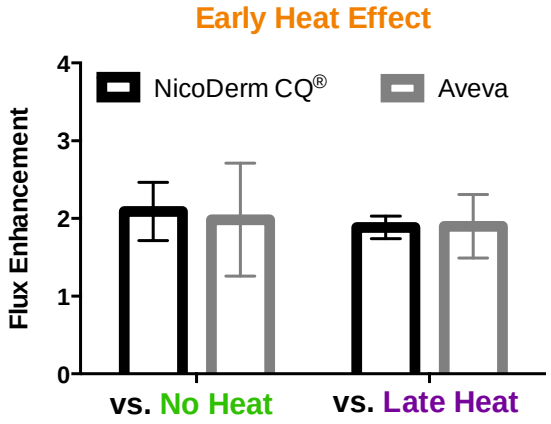
- Temperature of skin surface was monitored throughout the study

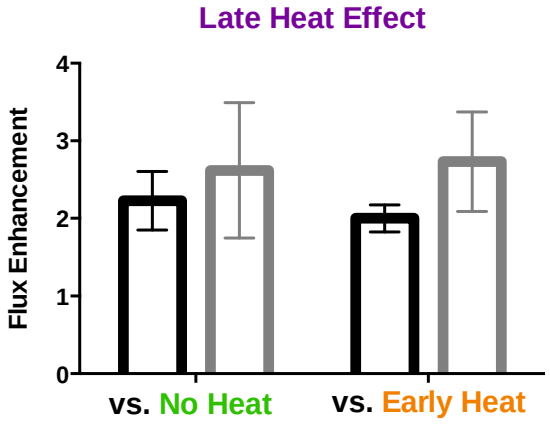
UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Preliminary: IVPT Temporary (1h) Heat Effect







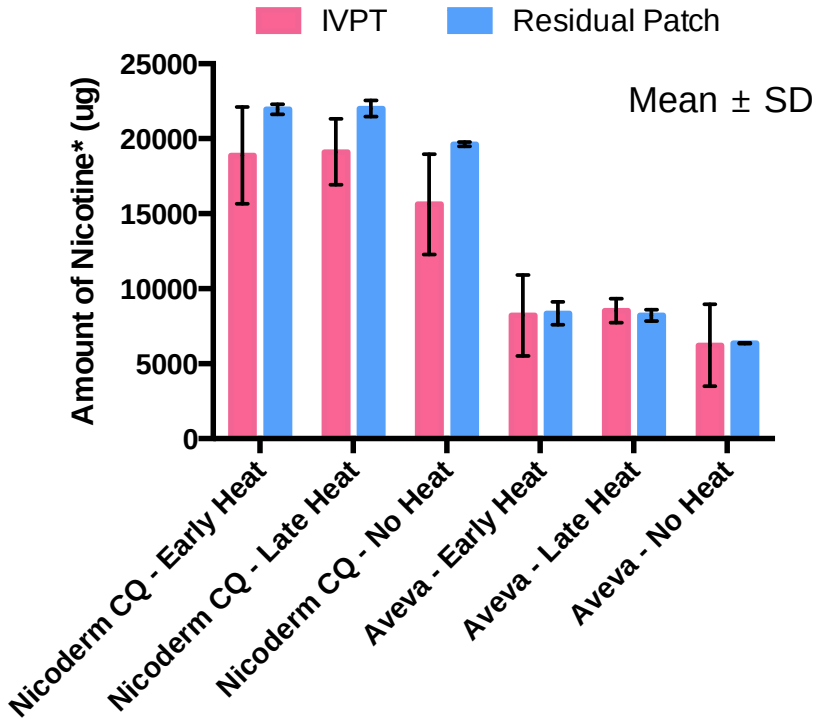


Human Skin Data

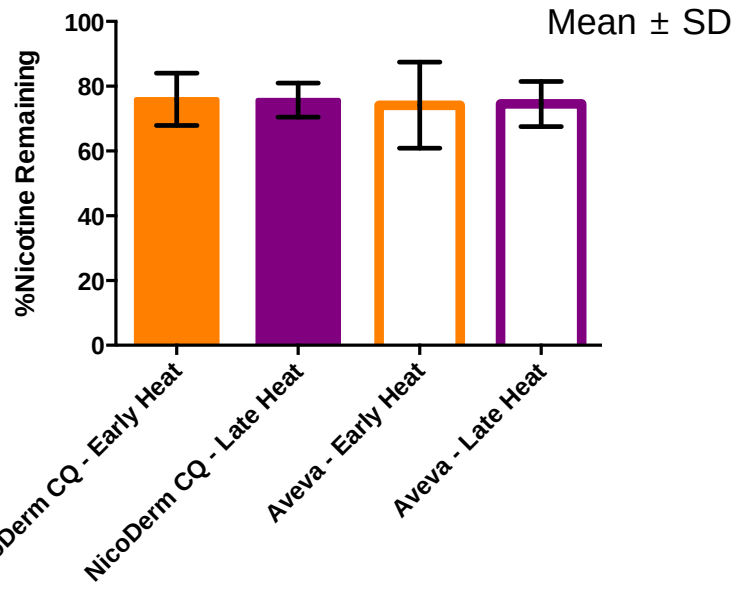
Mean ± SD from 4 donors for Heat and 2 donors for No Heat with n=4 per each donor

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

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
⇒ paralleled the results from IVPT

IVPT

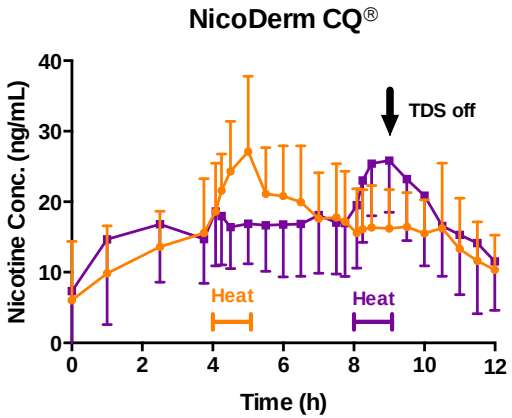
Heat application and Temperature Monitoring

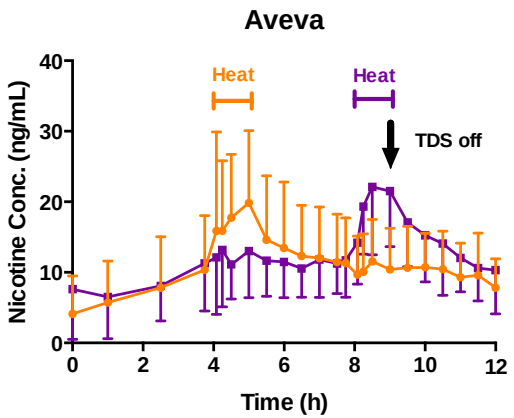
- Kevlar sleeve with an opening to expose TDS, while protecting skin from other areas
- Thermometer probe adjacent to TDS

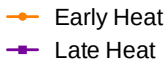
- Pre-heated heating pad
- ACE™ Bandage to ensure good contact between TDS and heating pad

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

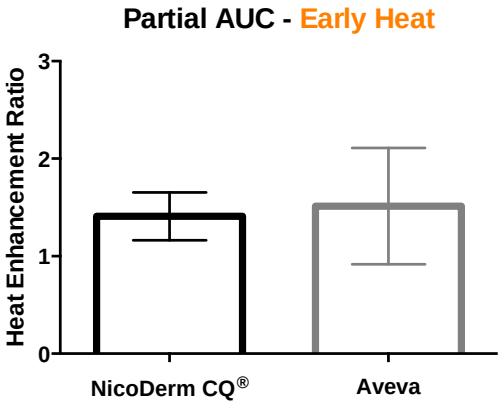
Nicotine PK profiles

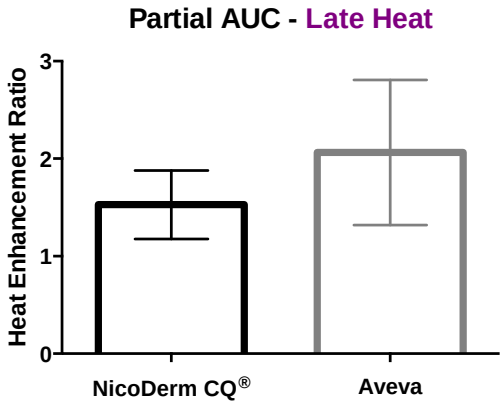






Mean ± SD from 10 Subjects

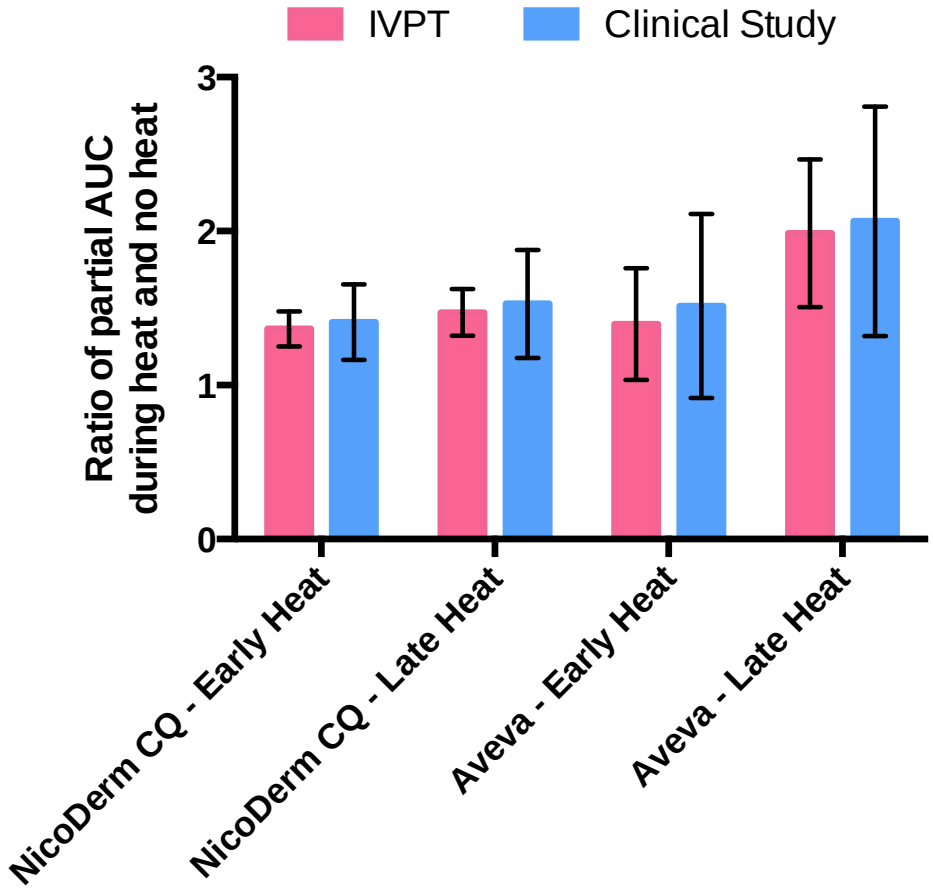




- Serum samples analyzed by S. Thomas
- LC-MS/MS method developed by I. Abdallah

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

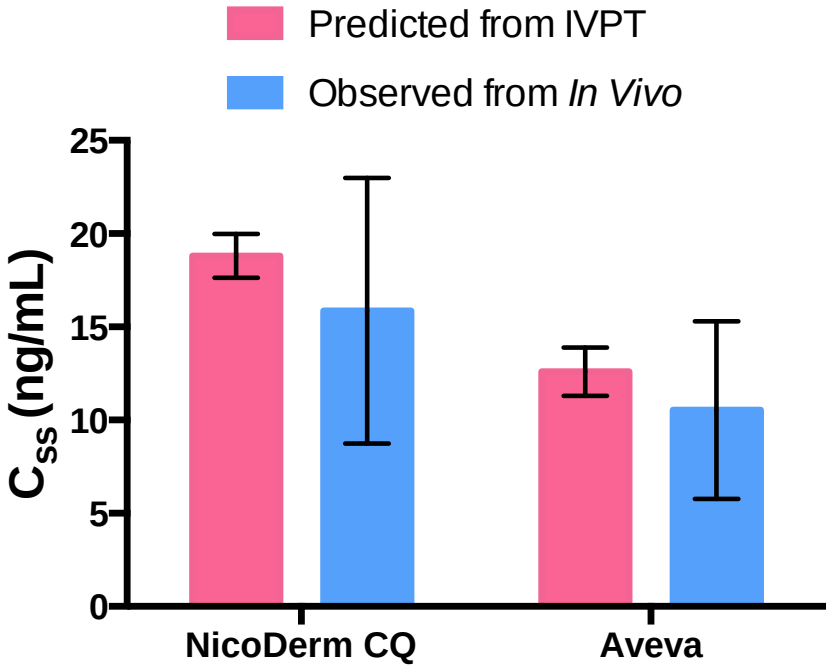
IVIVC – Heat Effect on Nicotine TDS



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

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Nicotine IVIVC – Absence of Heat



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

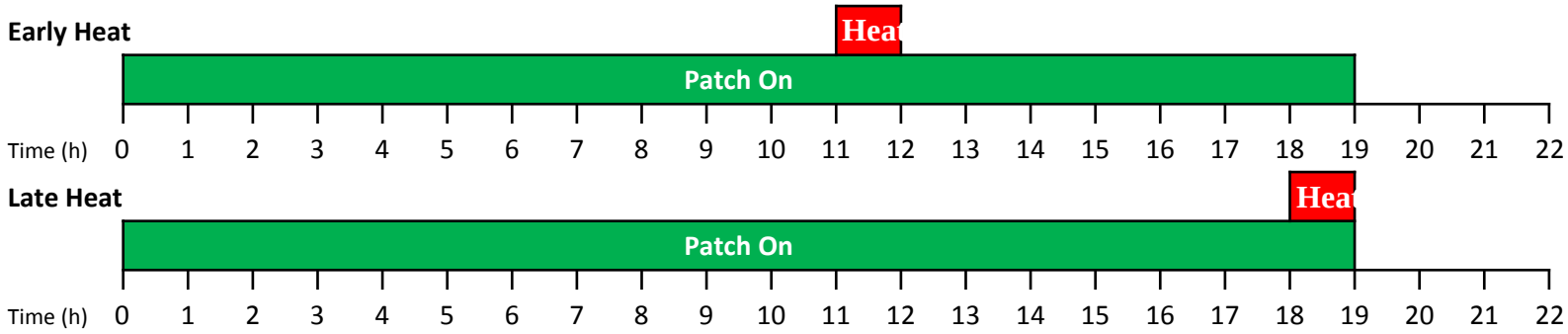
- $p > 0.05$ between predicted and observed C_{ss}
- IVPT can predict the performance of TDS *in vivo*

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Fentanyl

Heat with Fentanyl TDS

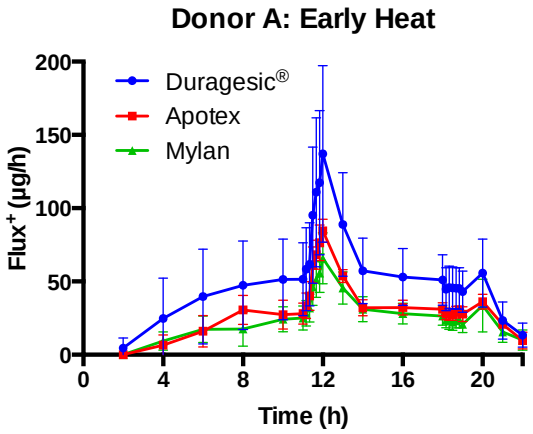
- A six-way, crossover PK study in 10 healthy adults

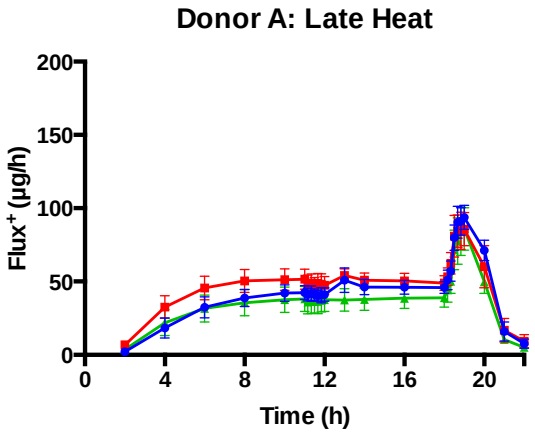


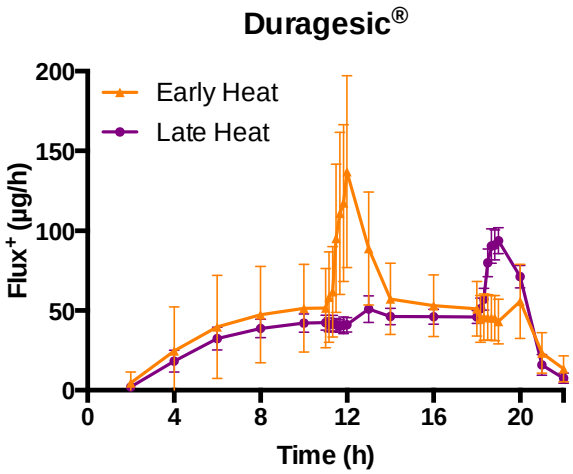
- 3 Fentanyl Patches
- Duragesic, Apotex generic, Mylan generic
- 1 hr heat

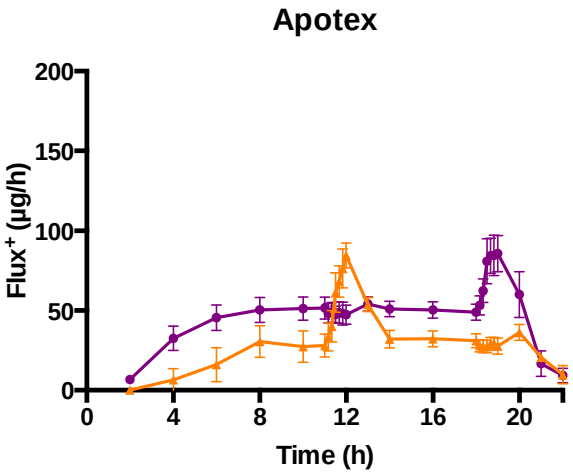
Fentanyl Heat-IVPT

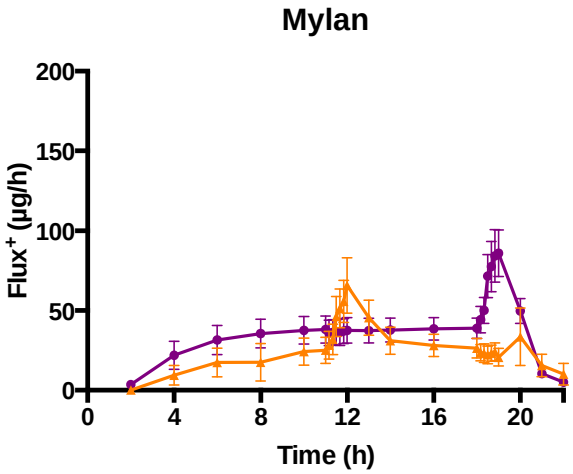
6 samples during 1 h of heat application (same number of samples as in vivo)











Mean +/- S.D. n=4

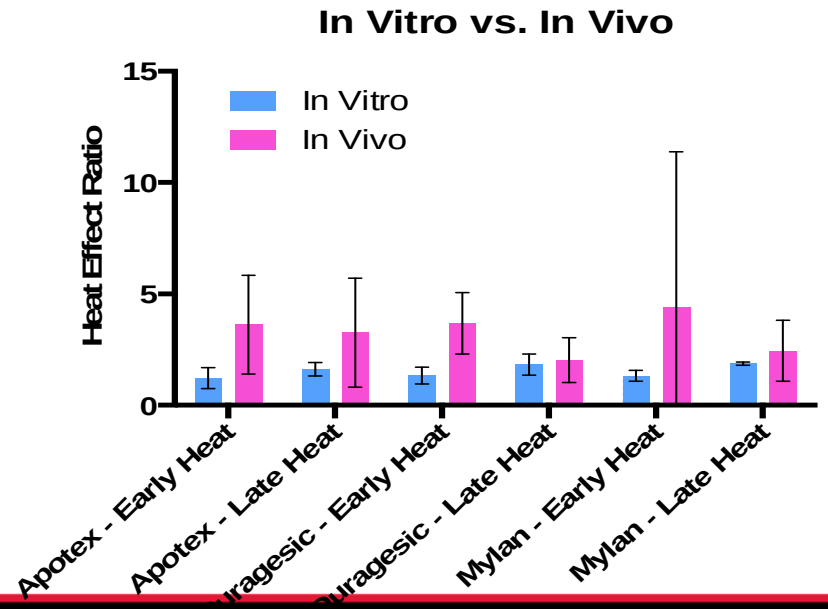
Fentanyl Heat: Ratio IVPT amt & partial AUC

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 21h

Early Heat Effect	In Vitro			In Vivo (n=7)
	Donor A,B,C	D1	D2	
Duragesi®	1.3 ± 0.4	1.1	2.0	3.7 ± 1.4
Apotex	1.2 ± 0.5	1.5	1.8	3.6 ± 2.2
Mylan	1.3 ± 0.2	1.6	1.8	4.4 ± 7.0

Late Heat Effect	In Vitro			In Vivo (n=7)
	Donor A,B,C	D1	D2	
Duragesic	1.8 ± 0.5	1.9	1.2	2.0 ± 1.0
Apotex	1.6 ± 0.3	1.3	1.5	3.3 ± 2.4
Mylan	1.9 ± 0.1	1.4	1.3	2.5 ± 1.4



In vitro data from Donor A,B,C

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 seven subjects

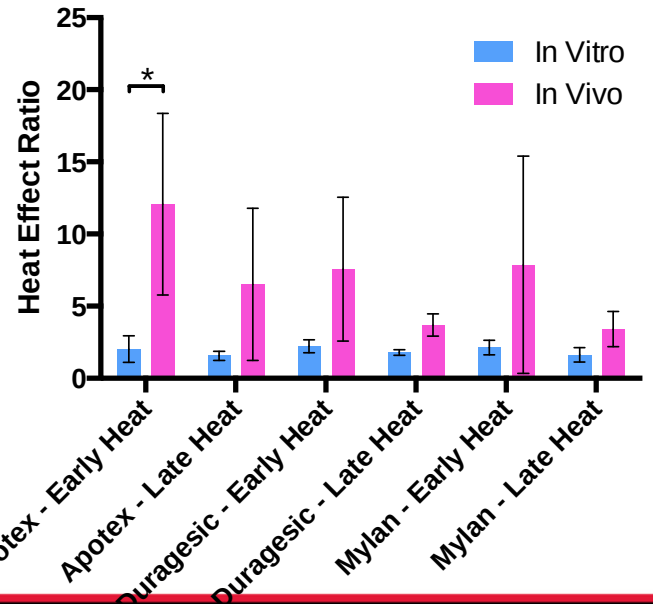
Fentanyl Heat: Ratio IVPT Jmax & Cmax

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: Jmax			In Vivo Cmax
	Donor A,B,C	D1	D2	
Duragesic®	2.7 ± 0.3	2.2	1.8	7.0 ± 4.8
Apotex	2.5 ± 0.6	1.5	1.5	10.7 ± 6.8
Mylan	2.6 ± 0.0	1.9	1.8	7.4 ± 7.0

Late Heat Effect	In Vitro: Jmax			In Vivo Cmax
	Donor A,B,C	D1	D2	
Duragesic	2.2 ± 0.2	1.6	1.8	3.7 ± 0.7
Apotex	2.0 ± 0.2	1.2	1.8	6.1 ± 4.9
Mylan	2.4 ± 0.2	1.4	1.3	3.4 ± 1.1

In Vitro vs. In Vivo



In vitro data from Donor A,B,C

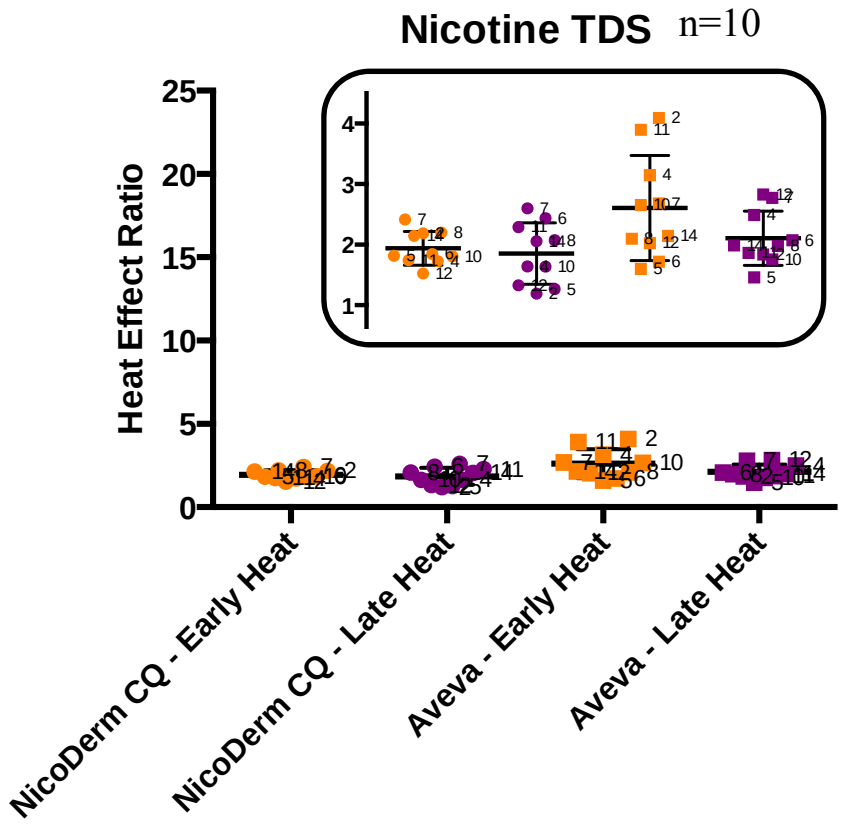
* p=0.0433

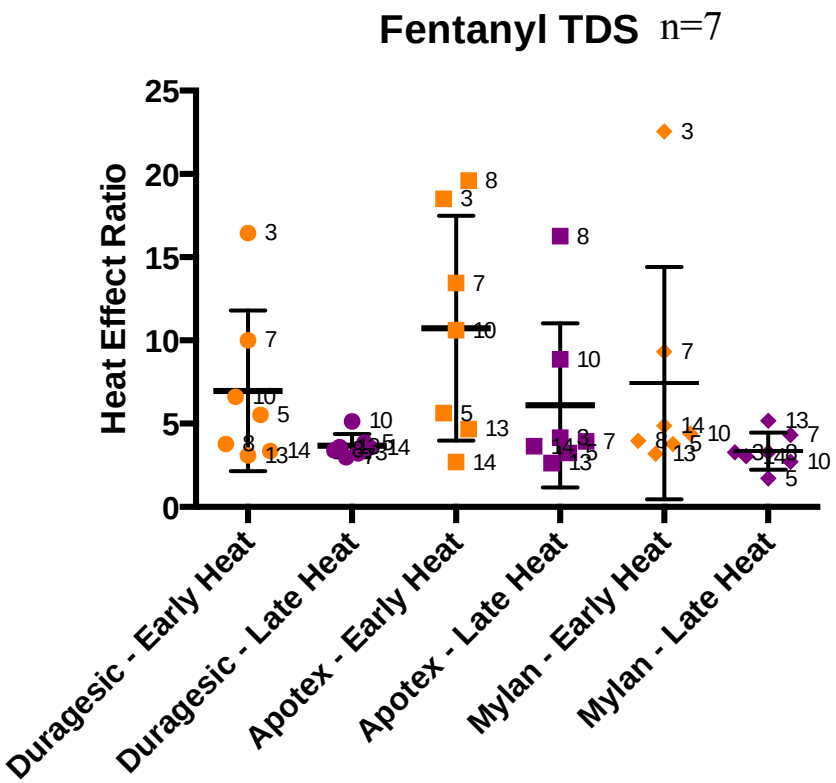
(Two-way ANOVA followed by Bonferroni's post-hoc analysis)

In vivo data from seven subjects

In Vivo Heat Effect Ratio of Nicotine TDS vs. Fentanyl TDS

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





In Vivo Heat Effect Ratio of Nicotine TDS vs. Fentanyl TDS

Nicotine TDS

Early Heat Effect	In Vivo										Mean ± SD (% CV) n=10
	4	6	2	10	11	8	7	14	12	5	
NicoDerm CQ®	1.7	1.8	2.2	1.8	1.7	2.2	2.4	2.1	1.5	1.8	**1.9 ± 0.3 (14)**
Aveva	3.1	1.7	4.1	2.7	3.9	2.1	2.7	2.1	2.0	1.6	**2.6 ± 0.9 (33)**

Late Heat Effect	In Vivo										Mean ± SD (% CV) n=10
	4	6	2	10	11	8	7	14	12	5	
NicoDerm CQ®	1.6	2.4	1.2	1.6	2.3	2.1	2.6	2.1	1.3	1.3	**1.9 ± 0.5 (27)**
Aveva	2.5	2.1	1.8	1.8	1.9	2.0	2.8	2.0	2.8	1.5	**2.1 ± 0.4 (21)**

Fentanyl TDS

Early Heat Effect	In Vivo							Mean ± SD (% CV) n=7
	3	5	7	8	10	13	14	
Duragesic	16.4	5.5	10.0	3.8	6.6	3.1	3.4	**7.0 ± 4.8 (69)**
Apotex	18.5	5.6	13.4	19.6	10.6	4.7	2.7	**10.7 ± 6.8 (63)**
Mylan	22.6	3.8	9.3	4.0	4.4	3.2	4.9	**7.4 ± 7.0 (94)**

Late Heat Effect	In Vivo							Mean ± SD (% CV) n=7
	3	5	7	8	10	13	14	
Duragesic	4.2	3.2	3.9	16.3	8.9	2.6	3.7	**6.1 ± 4.9 (81)**
Apotex	3.2	3.9	3.0	3.4	5.1	3.6	3.6	**3.7 ± 0.7 (19)**
Mylan	3.3	1.7	4.3	3.3	2.7	5.2	3.1	**3.4 ± 1.1 (33)**

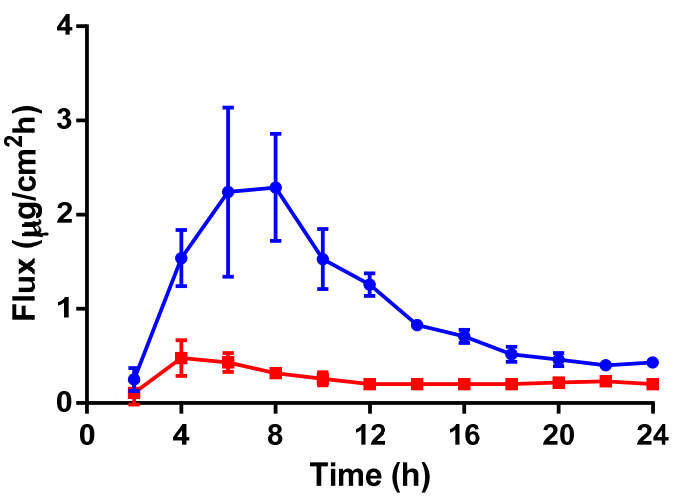
UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

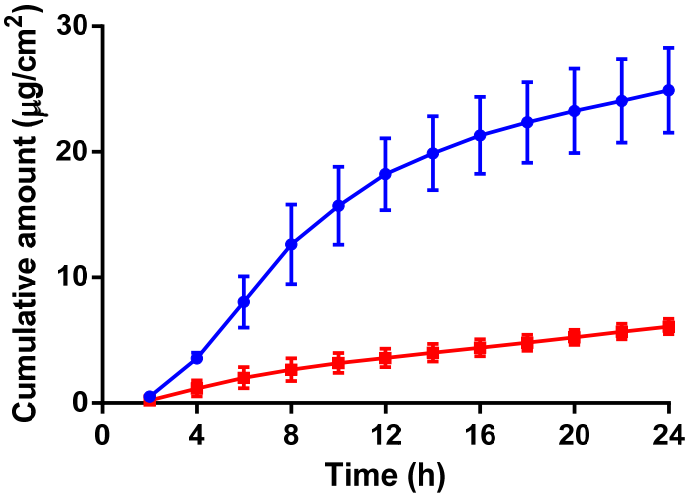
IVPT

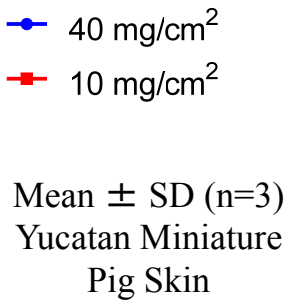
in vitro permeation testing

Dose Selection and Application Methods for Semisolids

Importance of Dose – Voltaren® gel



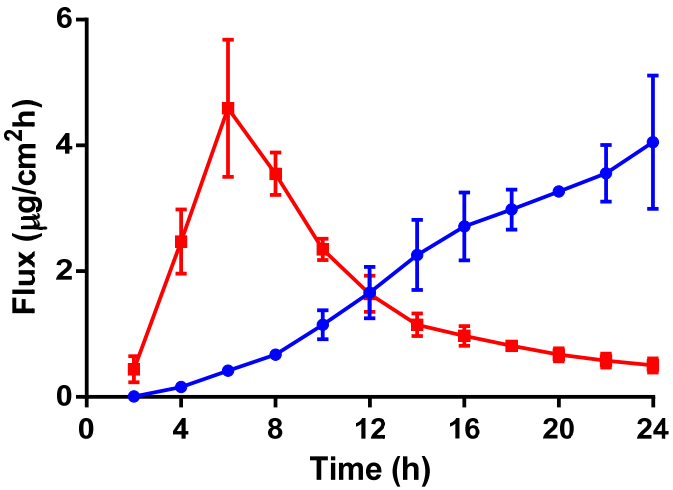


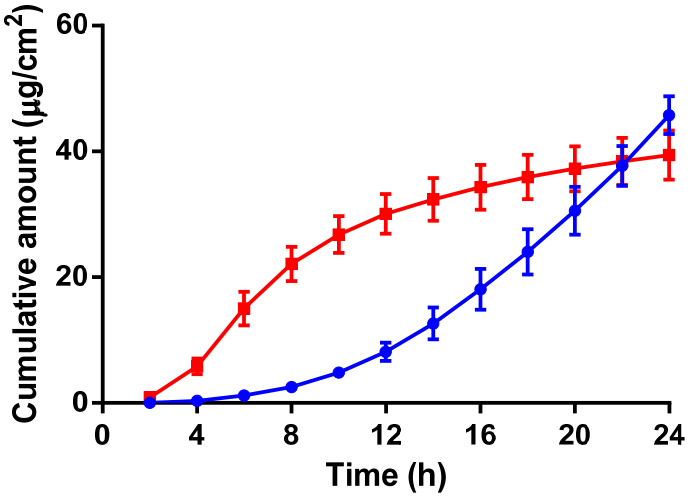


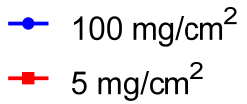
Mean ± SD (n=3)
Yucatan Miniature
Pig Skin

	J_{max} ± SD (µg/cm²/h)	T_{max} (h)	Cumulative Amount ± SD (µg/cm²)
40 mg/cm²	2.29 ± 0.57	8	24.91 ± 3.38
10 mg/cm²	0.48 ± 0.19	2	6.10 ± 0.61

Importance of Dose – Pennsaid® 2%







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

	J_{max} ± SD (µg/cm²/h)	T_{max} (h)	Cumulative Amount ± SD (µg/cm²)
100 mg/cm²	4.05 ± 1.06	24	45.79 ± 3.00
5 mg/cm²	4.59 ± 1.09	6	39.43 ± 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

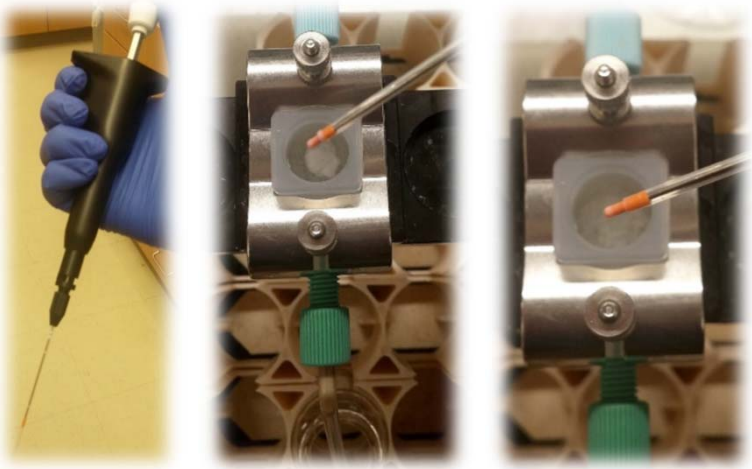
- Need a reproducible and clinically-relevant technique

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

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

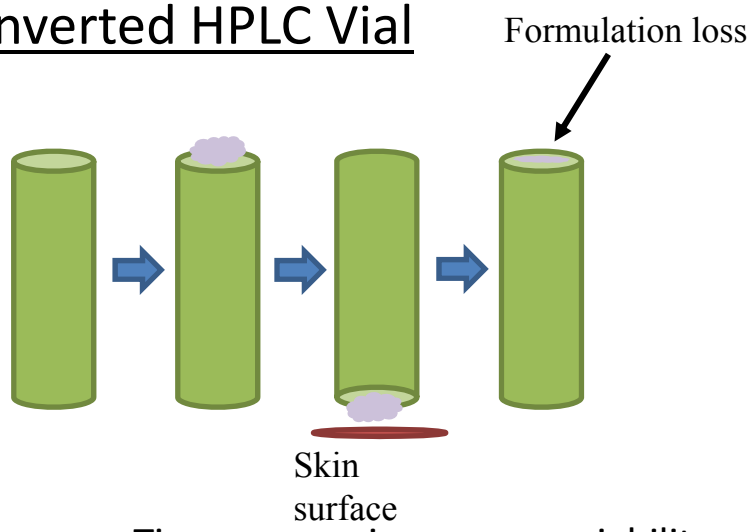
Dose Administration Techniques

Positive Displacement Pipette



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

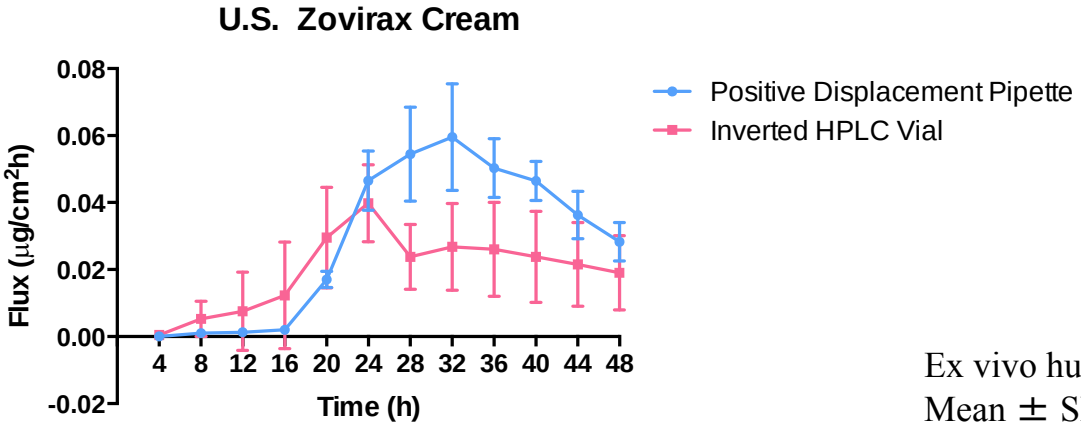
Inverted HPLC Vial



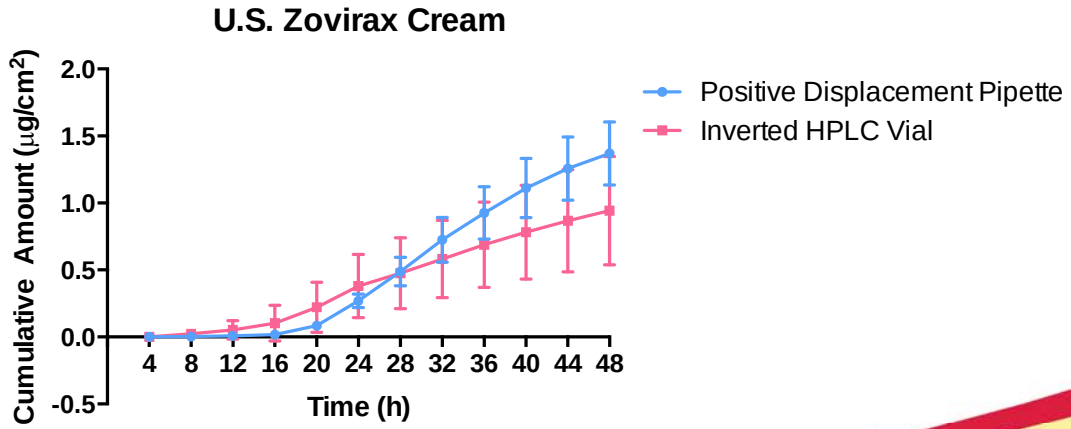
- Time-consuming, more variability
- Some formulation loss
- Simulates clinically-relevant rubbing effect

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Dose Administration Techniques



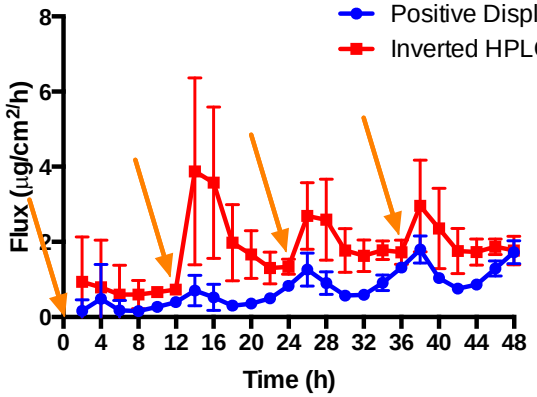
Ex vivo human skin
Mean ± SD (n=4 for each technique)

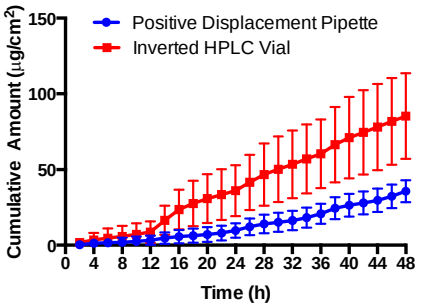


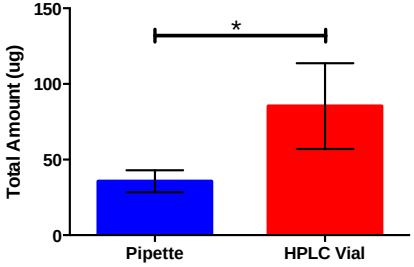
UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Preliminary: Dose Administration Techniques

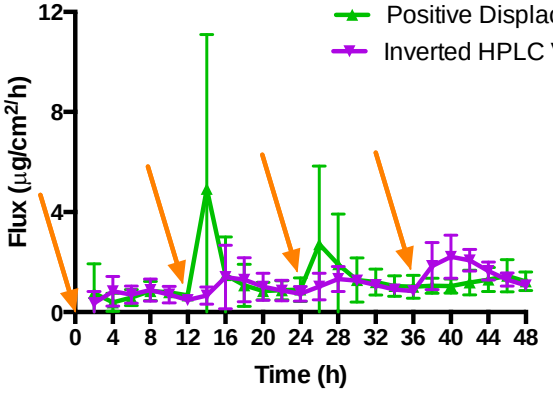
Pennsaid® 2% (more viscous)

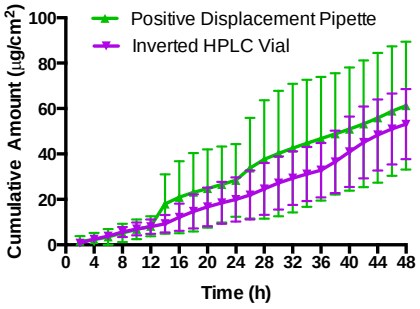


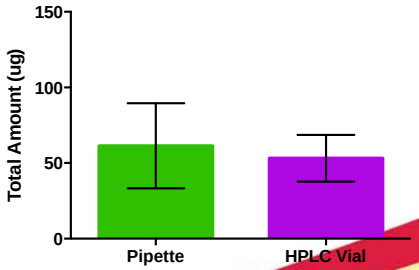




Pennsaid® 1.5%







Orange Arrow: dosing (~5 mg/cm^2 of formulation)

Mean ± 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

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Acknowledgments

UMB Collaborators
- Dr. Hazem Hassan
- CoPI

Lab Group
- Soo Shin
- Dr. Inas Abdallah
- Sagar Shukla
- Sherin Thomas
- Dana Hammell, M.S.
- Dr. Raghunadha Seelam
- Juliana Quarterman

U.S. FDA
- Dr. Sam Raney
- Dr. Bryan Newman
- Dr. Kaushalkumar Davé
- Dr. Priyanka Ghosh
- Dr. Elena Rantou

Collaborators
- Dr. Thomas Franz
- Dr. Annette Bunge
- Dr. Richard Guy
- Dr. Begoña Delgado-Charro

Clinical Study Team
- Dr. Samer El-Kamary
- Dr. Wilbur Chen
- Dr. Jeff Fink
- Melissa Billington
- GCRC nurses

Funding

FDA OGD

- 1U01FD004947-01
- 1U01FD004955-01

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Thank you for your attention!

Questions?