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Challenges in the Development of Bioequivalent Topically Applied Drug Products

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Outline

- Background
  1) Skin Structure
  2) Percutaneous Absorption Process
  3) Factors Influencing Percutaneous Absorption ➔ Heat
  4) Transdermal Delivery Systems (TDS) vs. Topical
  5) Methods to evaluate bioavailability (BA) of TDS and Topical

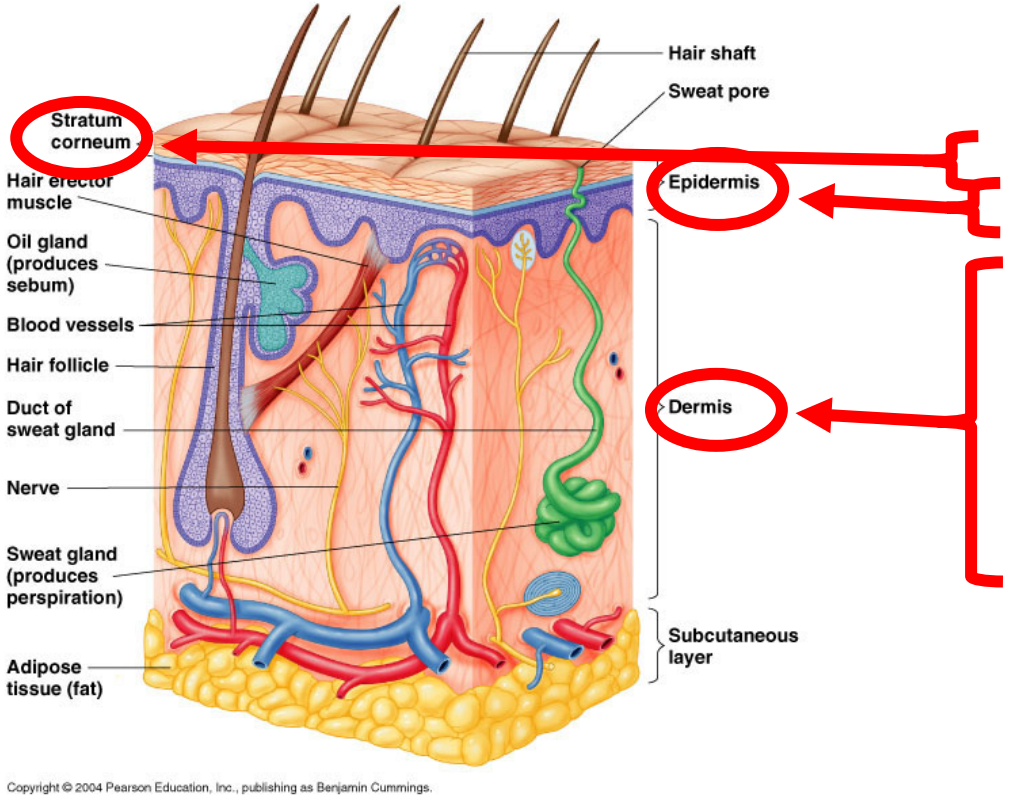
- Main Objectives

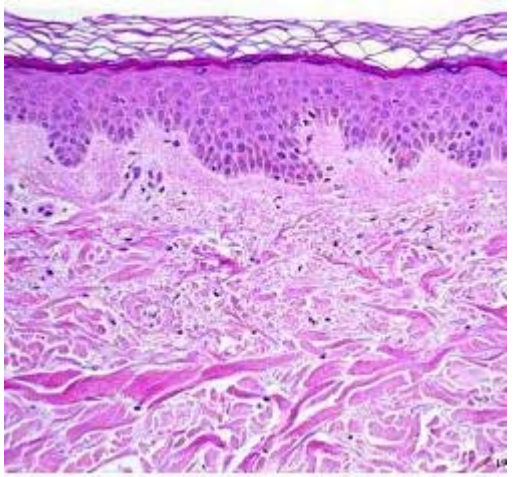
  Influence of Heat on TDS *in vitro*

  Influence of Heat on TDS *in vivo*

  Methods to Evaluate BA for Topical Drug Products

Skin Structure

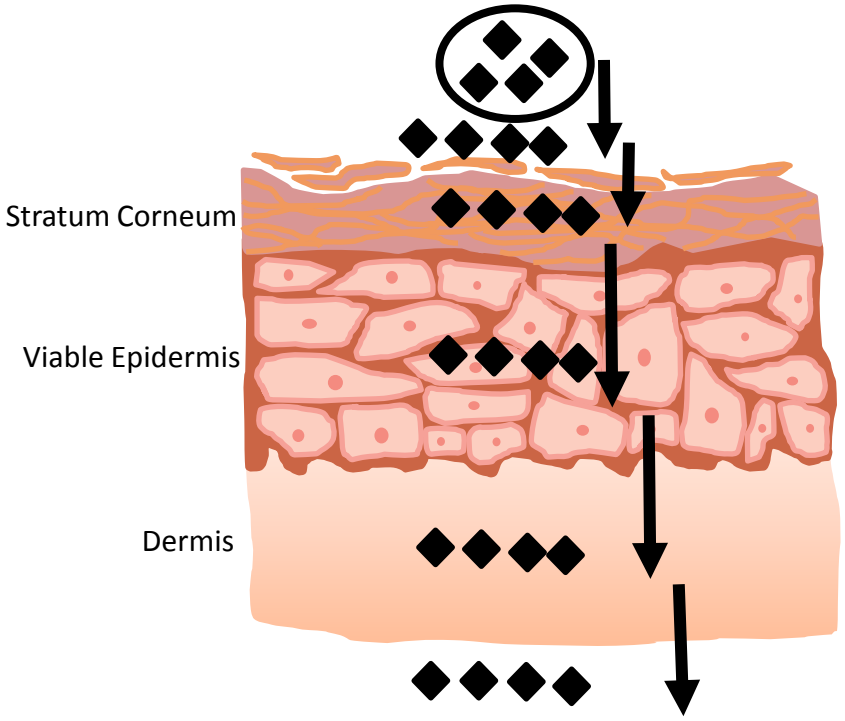




Images from http://classes.midlandstech.edu/carterp/courses/bio225/chap21/ss1.htm and http://www.scienceprog.com/skin-structure/

Percutaneous Absorption (Transepidermal route)

Release of drug from vehicle → Penetration through skin barriers → Activation of pharmacological response



- Dissolution of drug in vehicle
- Passive diffusion of drug out of its vehicle to skin surface
- Drug partition into SC
- Drug diffusion through SC
- Drug partition into viable epidermis
- Drug diffusion through viable epidermis
- Drug partition into dermis
- Drug diffusion through dermis
- Drug partition into blood capillary
- Systemic uptake

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 faster

Vehicle/Formulation

(Inactive Ingredients)

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

Skin

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

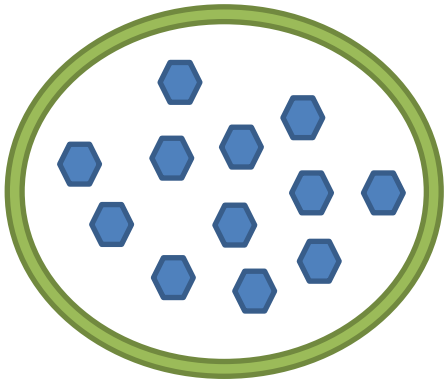
Environmental factors

- Humidity
- Occlusion
- Heat (high temperature)

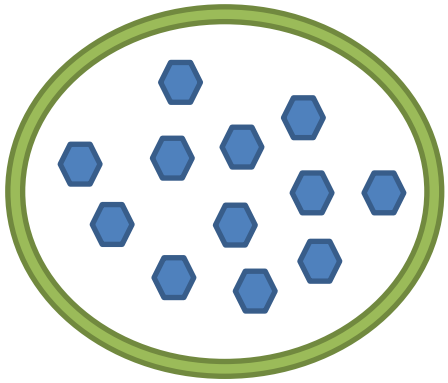
Flynn G.L. (2002). Cutaneous and Transdermal Delivery – Processes and Systems of Delivery. In *Modern Pharmaceutics* (pp. 187-235).
Barry B.W. (2007). Transdermal Drug Delivery. In *Aulton's Pharmaceutics: The Design and Manufacture of Medicines* (pp. 565-597).

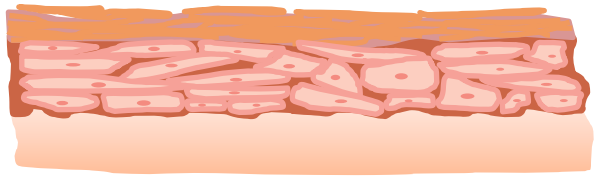
Influence of Heat on Percutaneous Absorption

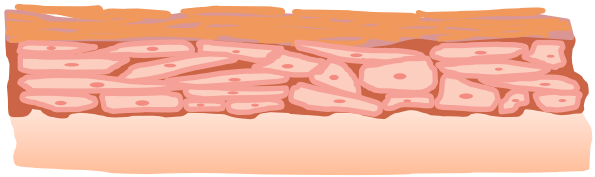
1) ↑ Diffusivity of Drug from its Vehicle



+ Heat ➜

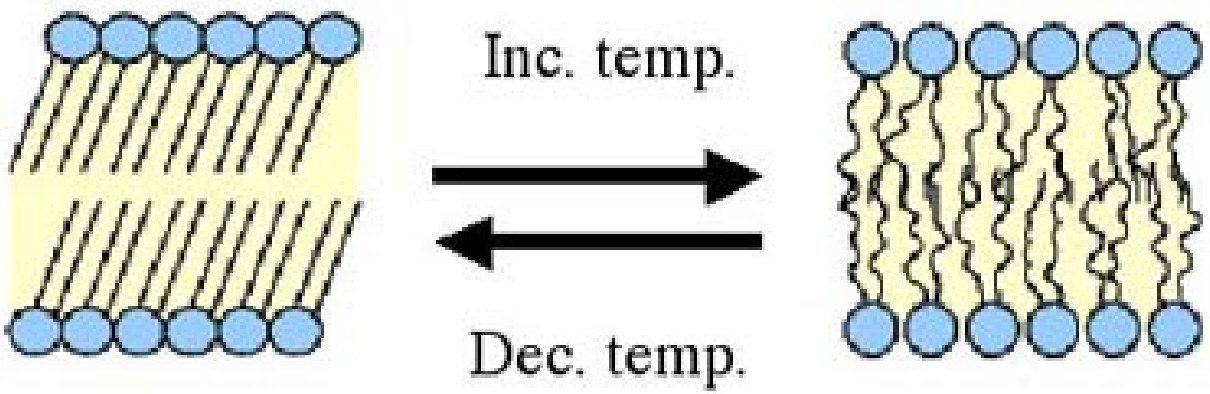






Influence of Heat on Percutaneous Absorption

2) ↑ Fluidity of Stratum Corneum Lipids



Very regular,
Ordered structure

Less tightly packed,
Hydrocarbon tails
Disordered.

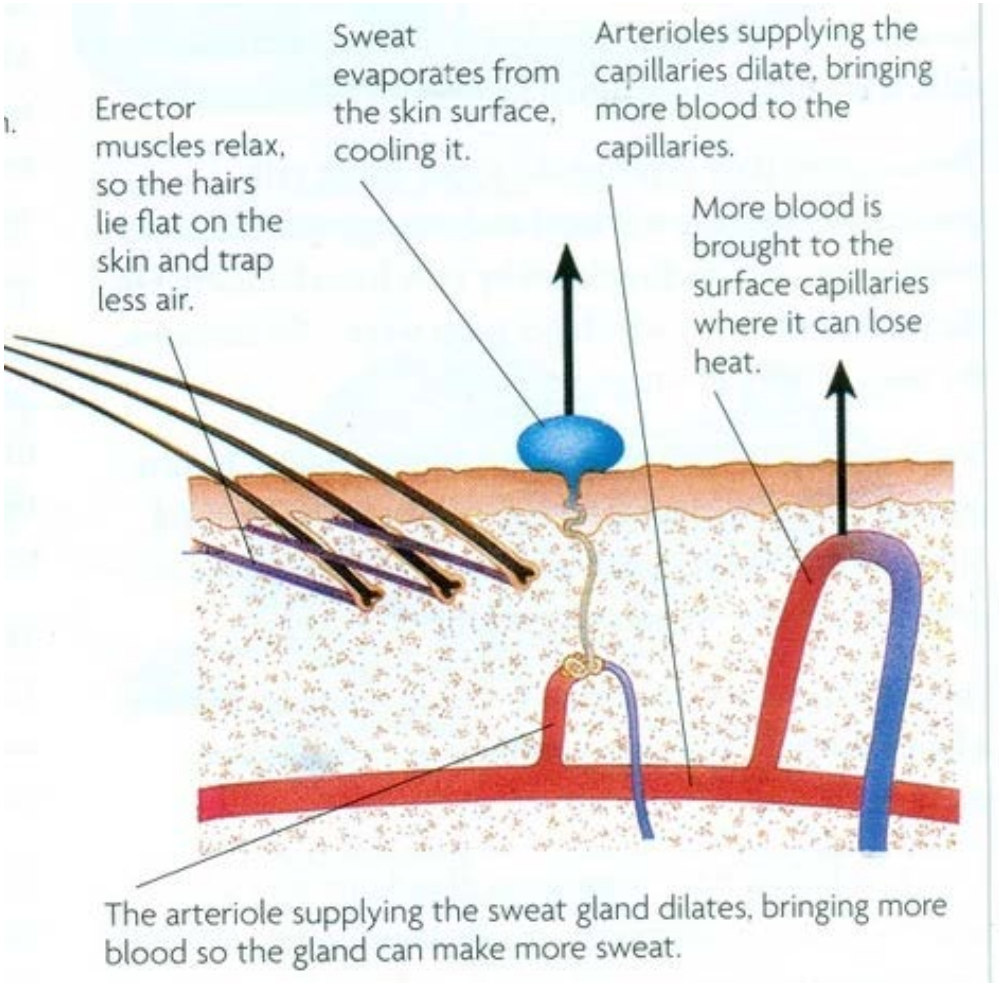
https://biochemistry3rst.wordpress.com/tag/phosphodiate/

Influence of Heat on Percutaneous Absorption

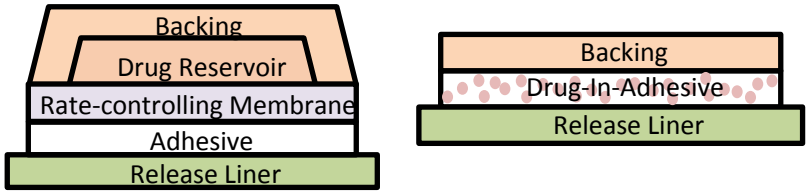
3) ↑ Cutaneous Vasodilation

Body temperature regulation

When the body is too hot



Transdermal Delivery Systems (TDS)



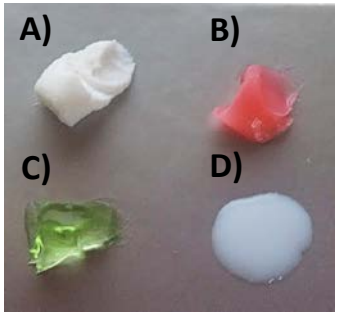
Reservoir Type **Matrix Type**

- Therapy can be interrupted
- Low drug 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

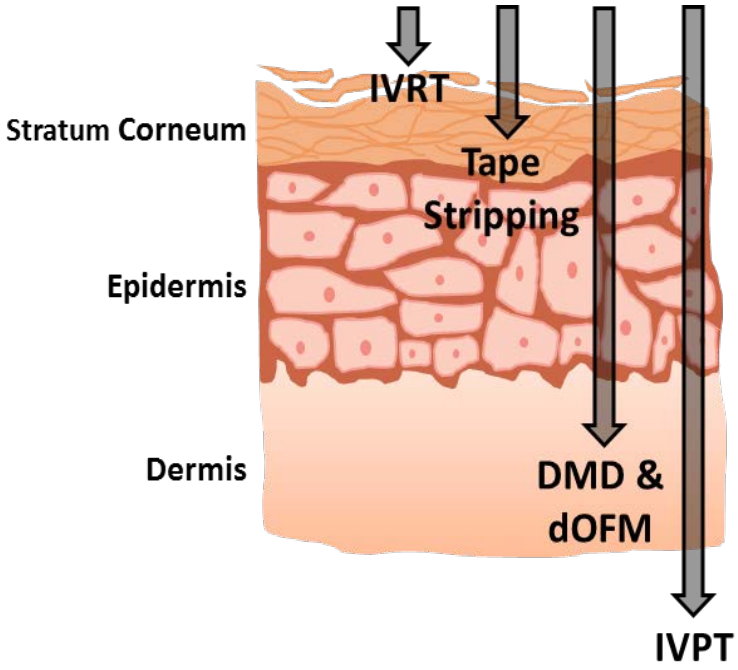
- Therapy can be interrupted
- Low drug efficiency

- Systemic Absorption is NOT desirable
- Local tissue levels ≈ Efficacy
- Open applications
- Highly individualized application techniques
- Short-acting

- 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.

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

Question

Among so many methodologies, which one is considered the best?

The likely answer may be a combination of the different tests, depending on the drug, product, dosing frequency, tissue target, etc.

➪ A **Clinical Trial** is the only approval route for generic transdermal & topical products

※ Except VCA for glucocorticoids
and
Acyclovir Draft Guidance

Active ingredient: Acyclovir

- **Form/Route:** Ointment; Topical
- **Recommended study: 2 Options: *In Vitro* or *In Vivo* Study**
- **I. In Vitro option:**
- To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:
- i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).
- ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.
- iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD formulations.
- **II. In Vivo option:**
- Type of study: BE Study with Clinical Endpoint Design: Randomized, double-blind, parallel, placebo-controlled in vivo

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm296733.pdf

Problems/Limitations of Clinical Studies

- Clinical trials are time-consuming and costly in general

For **Topical** Drug Products:

- Comparative clinical endpoint trials are relatively insensitive
- PK-based clinical trials
  - Amount of drug in blood is very small and difficult to quantify
  - Drug levels in blood can potentially be irrelevant to therapeutic activity at the site of action

→ Slows development of generic drug products

→ Burdens ($$$) healthcare system and patients

Objective

- 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

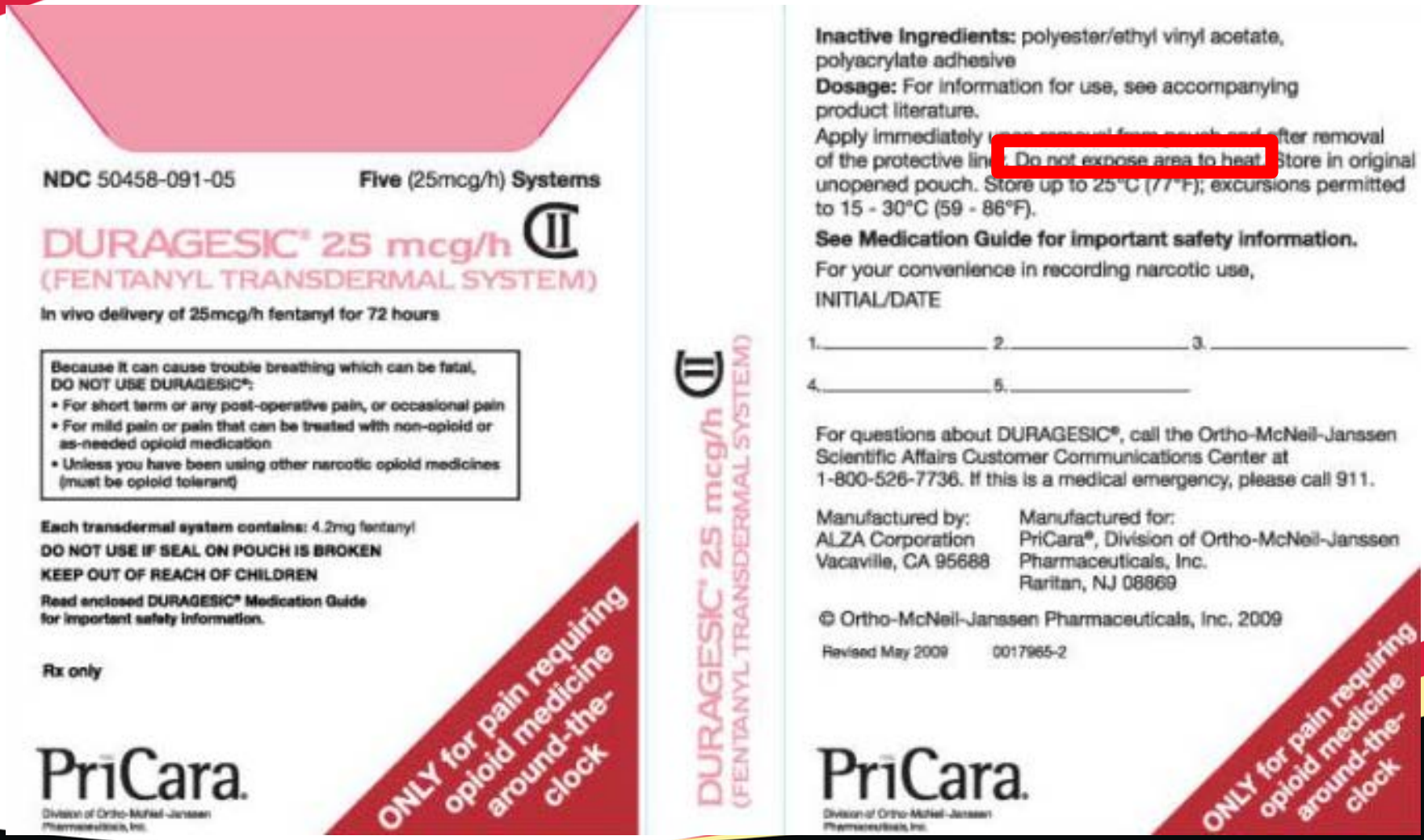
Experiments Underway and Planned

I. Evaluation of the influence of heat on the release and permeation of drug from nicotine and fentanyl TDS using IVPT

II. Evaluation of the relative bioavailability of nicotine and fentanyl TDS under the influence of heat in healthy human subjects and development of IVIVC

III. Evaluation of the relative bioavailability of topical drug products by various surrogate methods and development of IVIVC

Why is Heat effect on TDS of Interest?



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

DURAGESIC® 25 mcg/h (II)
(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 (II)
(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 lin[redacted]. 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.

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

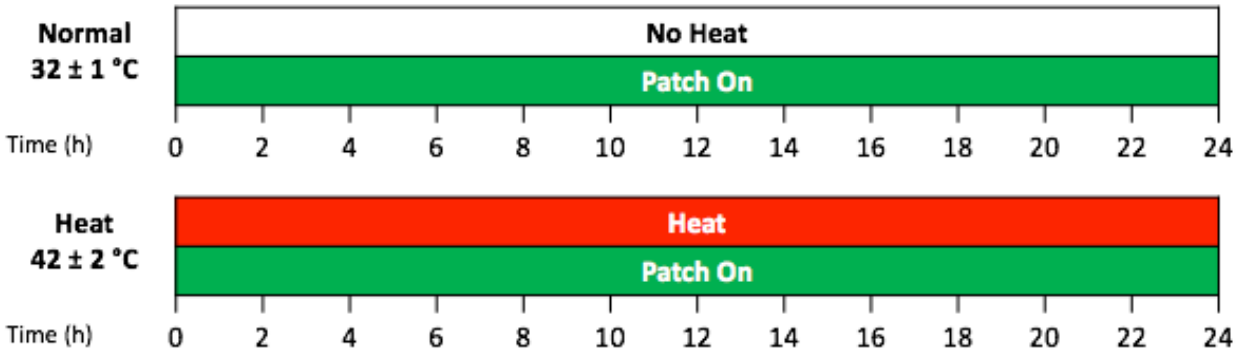
Revised May 2009 0017965-2

PriCara
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

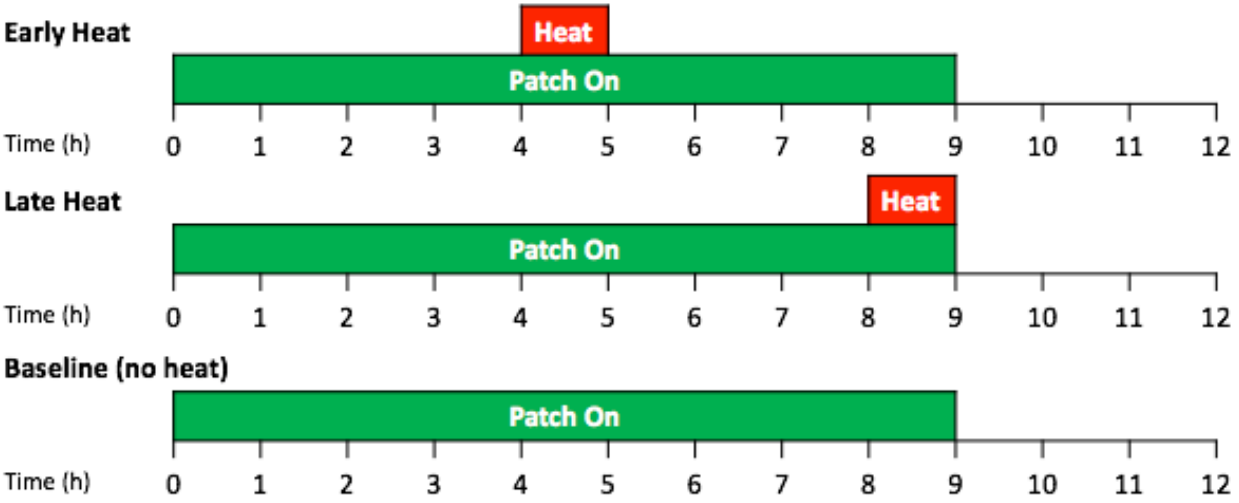
ONLY for pain requiring opioid medicine around-the-clock

IVPT Study Designs: Nicotine With and Without Heat

24h Study Designs



12h Study Designs



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, polyisobutene adhesive

Skin Preparation

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

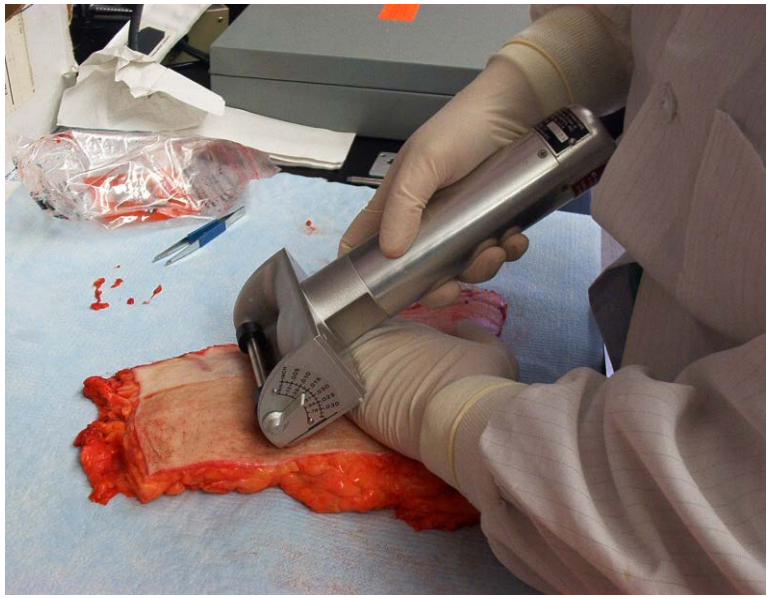
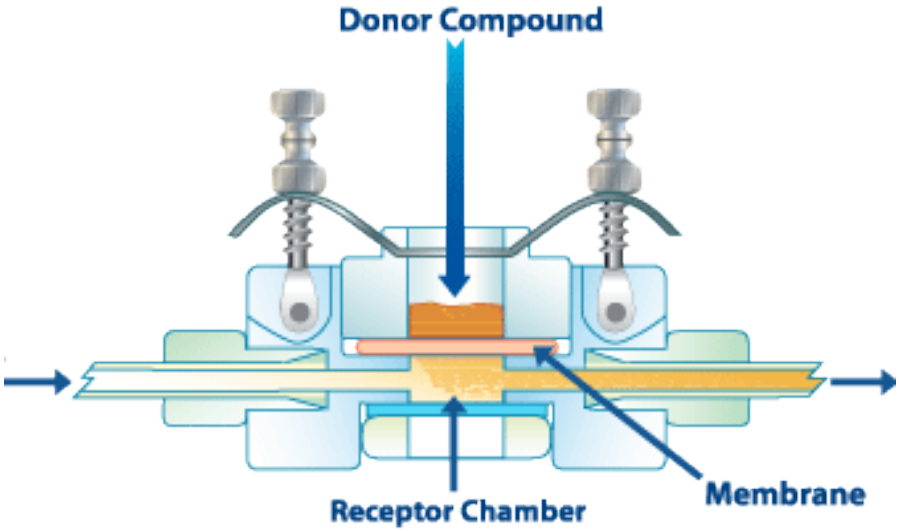
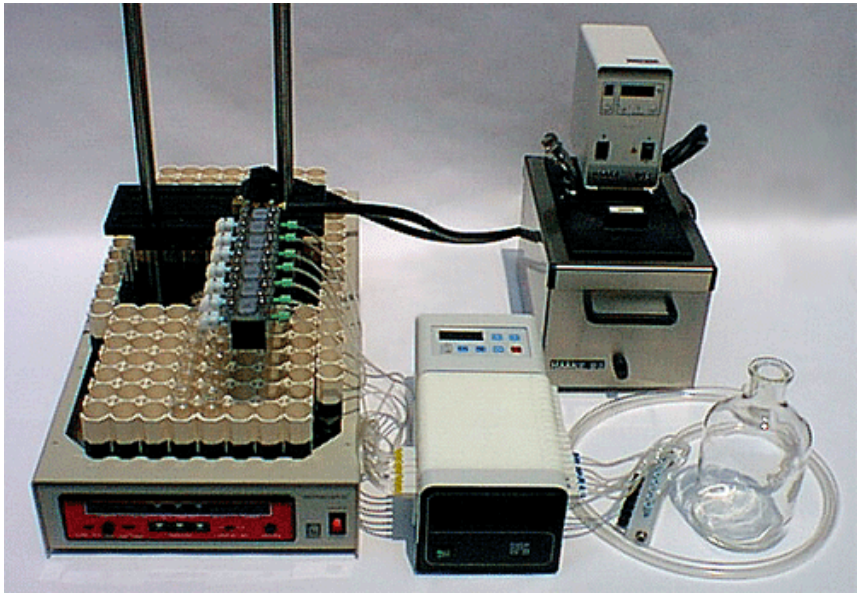


Image obtained from the Stinchcomb Lab's SOP

IVPT Setup

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

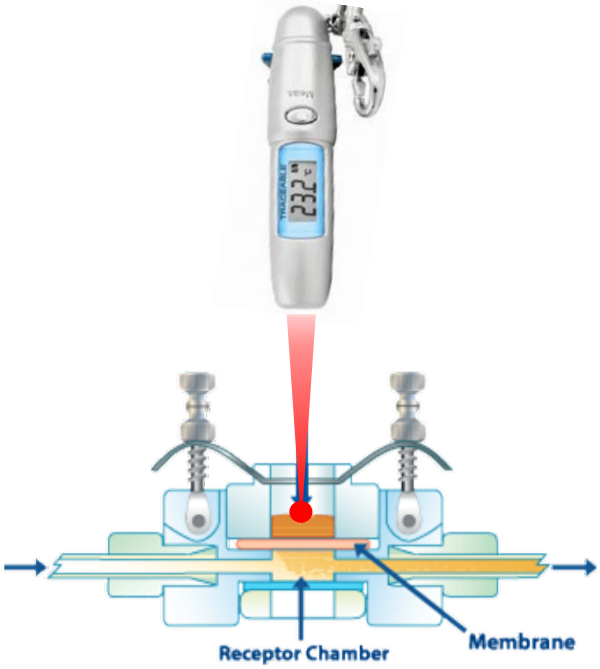


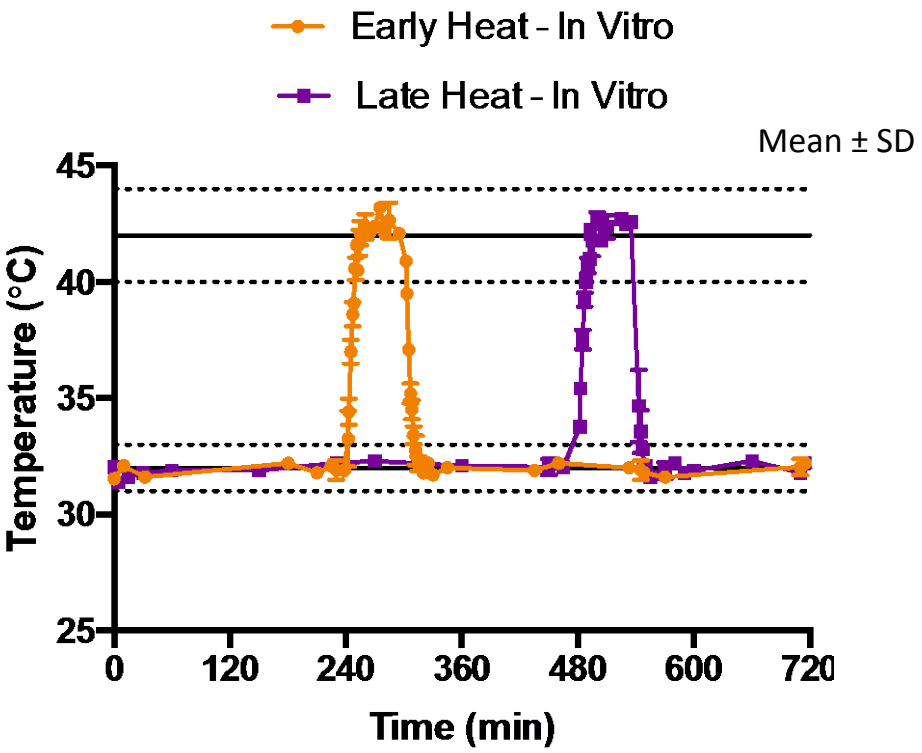


Images from www.ibric.org and www.permegear.com

Temperature Monitoring

- Infrared Thermometer





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

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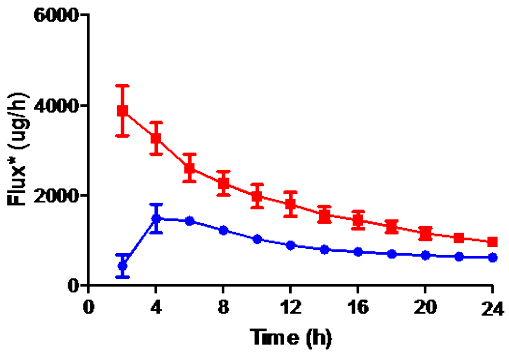
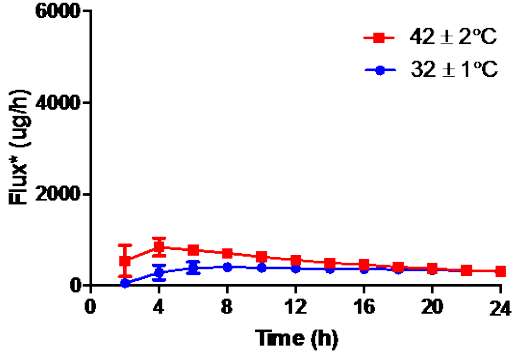
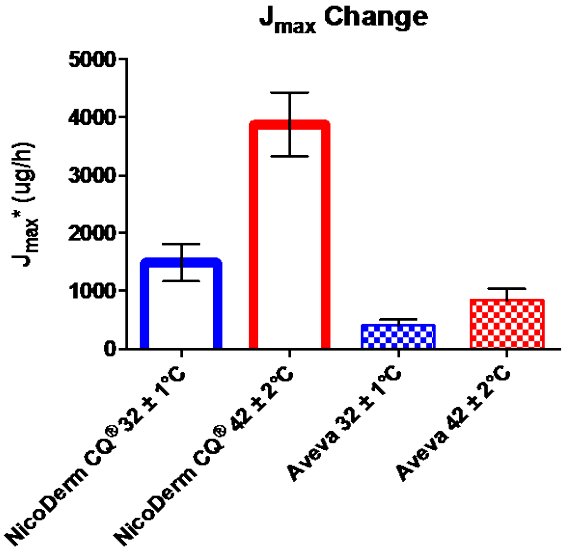
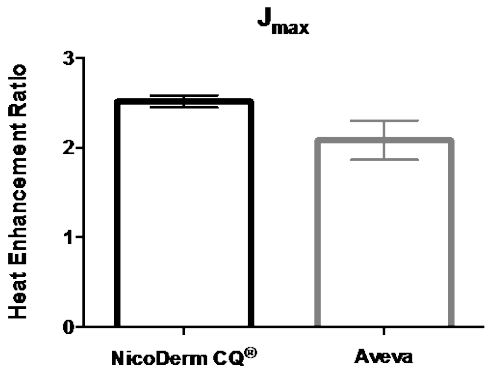
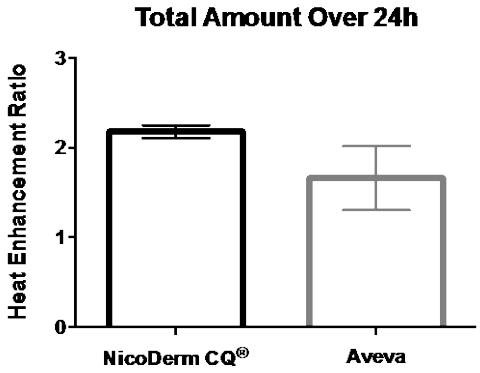
Preliminary: IVPT Continuous Heat Effect











Yucatan Miniature Pig Skin Data

Mean ± SD from with n=3

Image from Sinclair Bio Resources, LLC.

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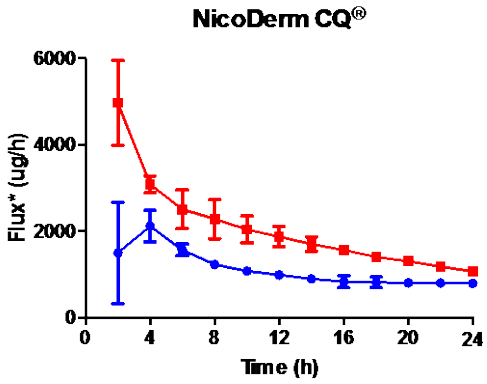
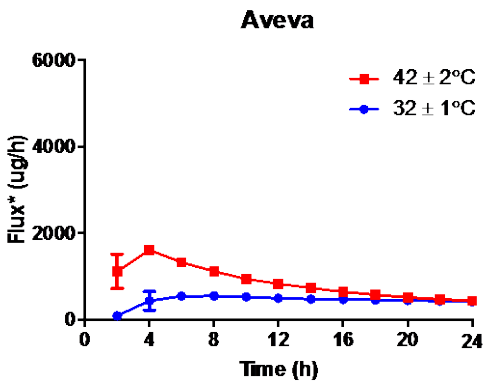
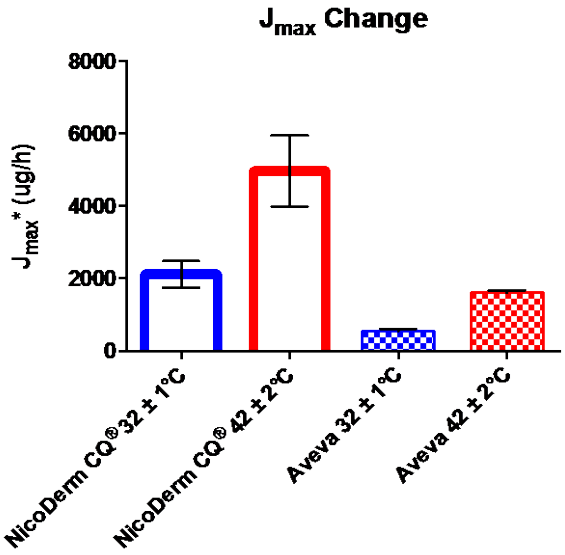
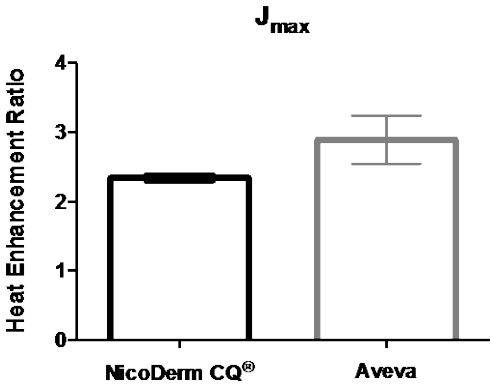
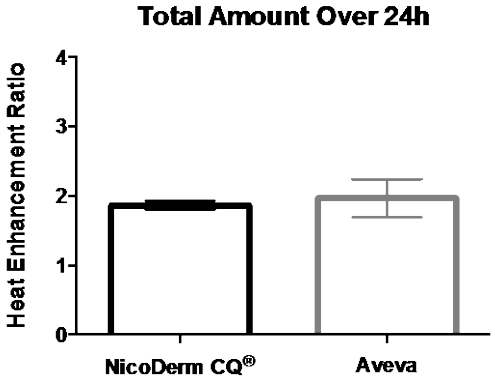
Preliminary: IVPT Continuous Heat Effect







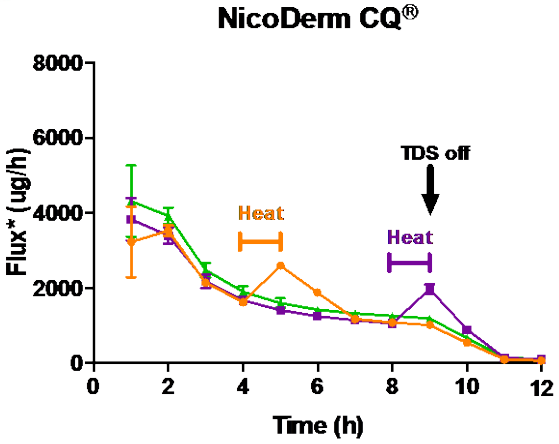


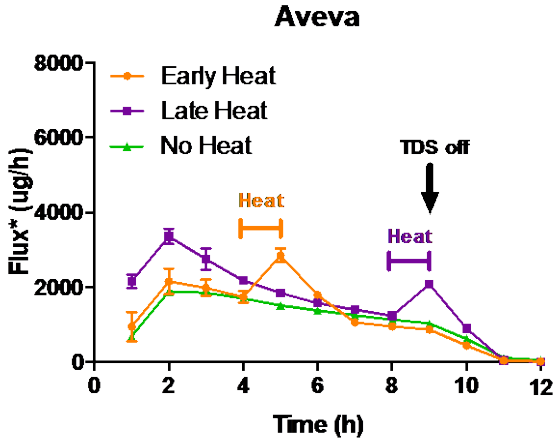


Human Skin Data

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

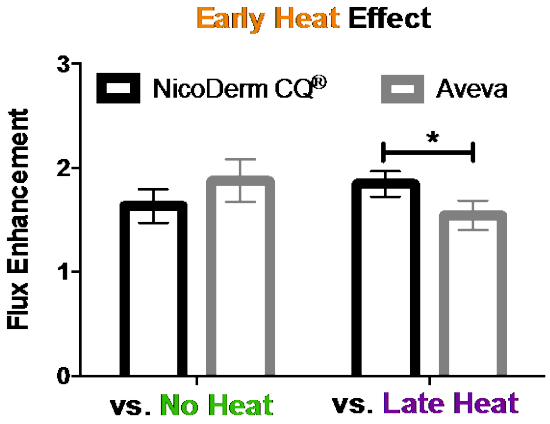
Preliminary: IVPT Temporary (1h) Heat Effect

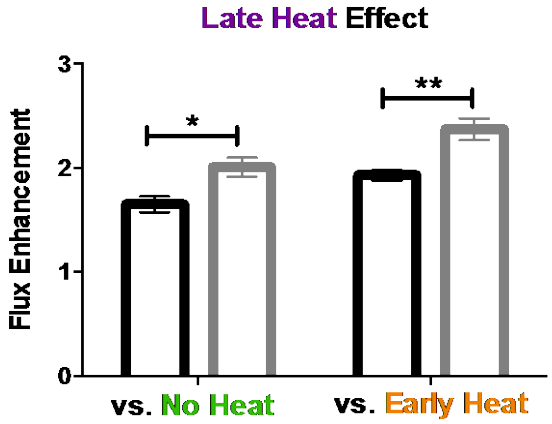




Yucatan Miniature Pig Skin Data

Mean ± SD from with n=4





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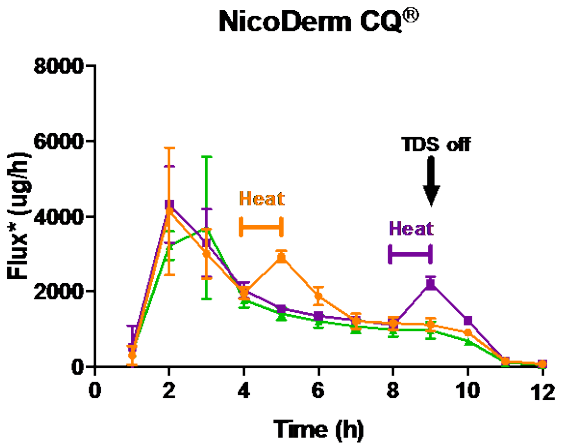

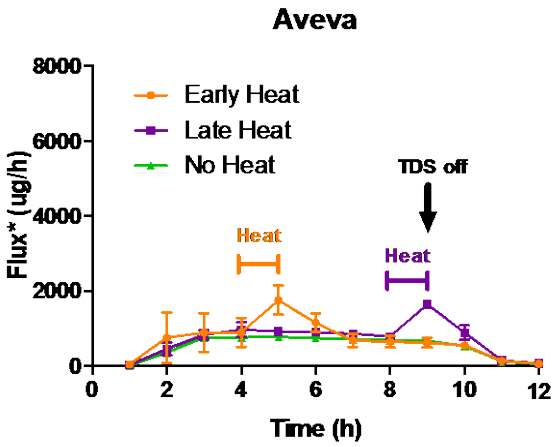

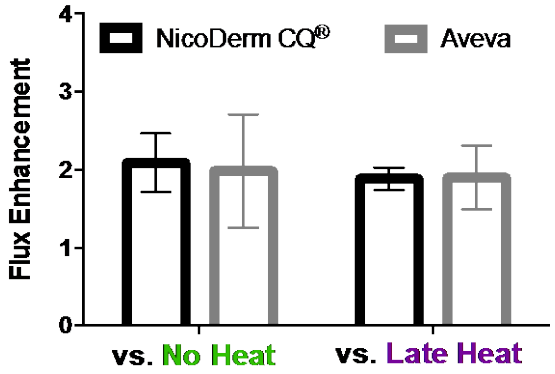

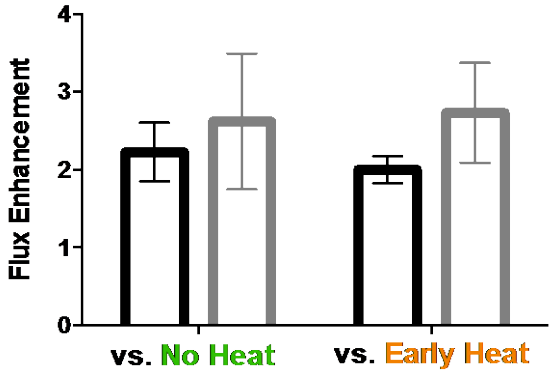

Human Skin Data

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

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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
- For nicotine TDS, the total drug content is unknown:

Therefore, unused patch was extracted using the selected extraction method

Amount extracted from unused patch − Amount extracted after IVPT = Amount expected to be delivered

$$\frac{\text{Amount remaining after IVPT}}{\text{Amount extracted from unused patch}} \times 100 = \%\ \text{drug remaining}$$

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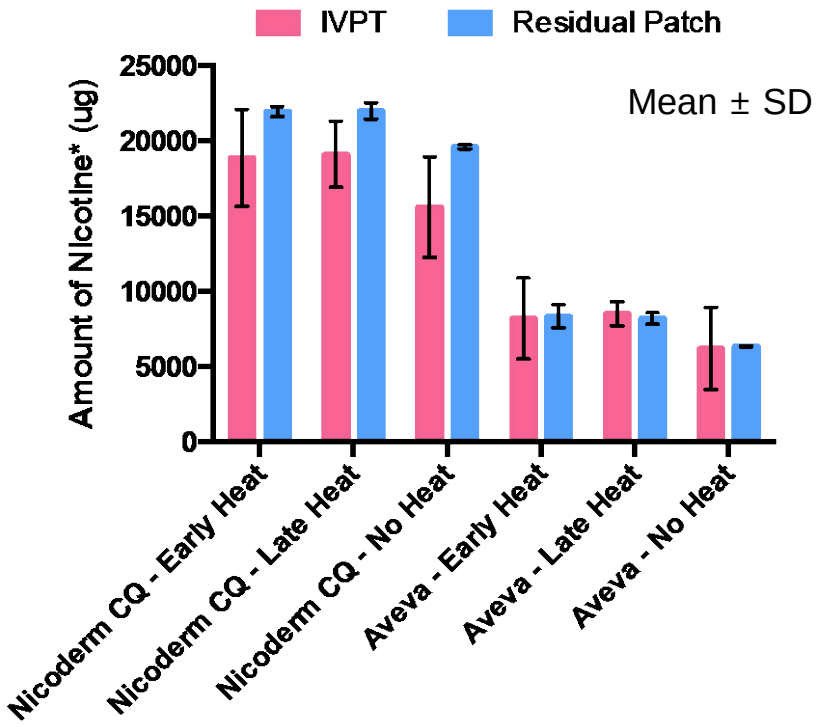
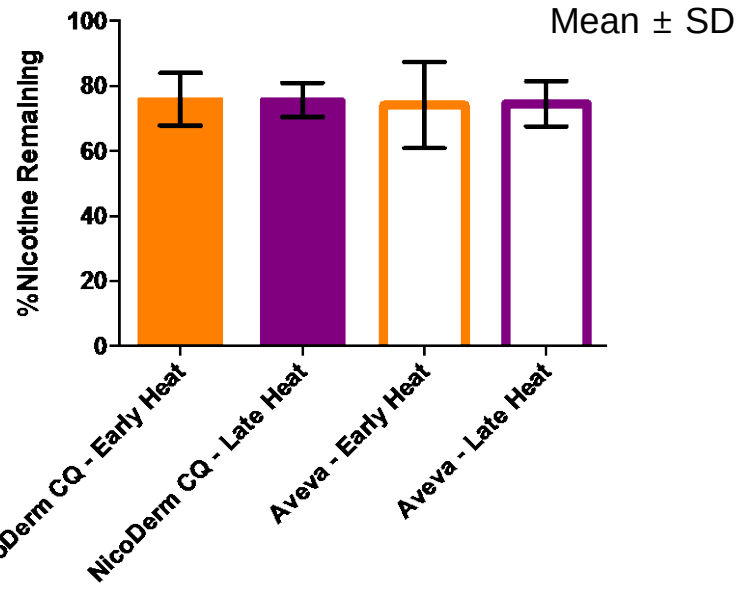
Preliminary: Nicotine Residual TDS Extraction



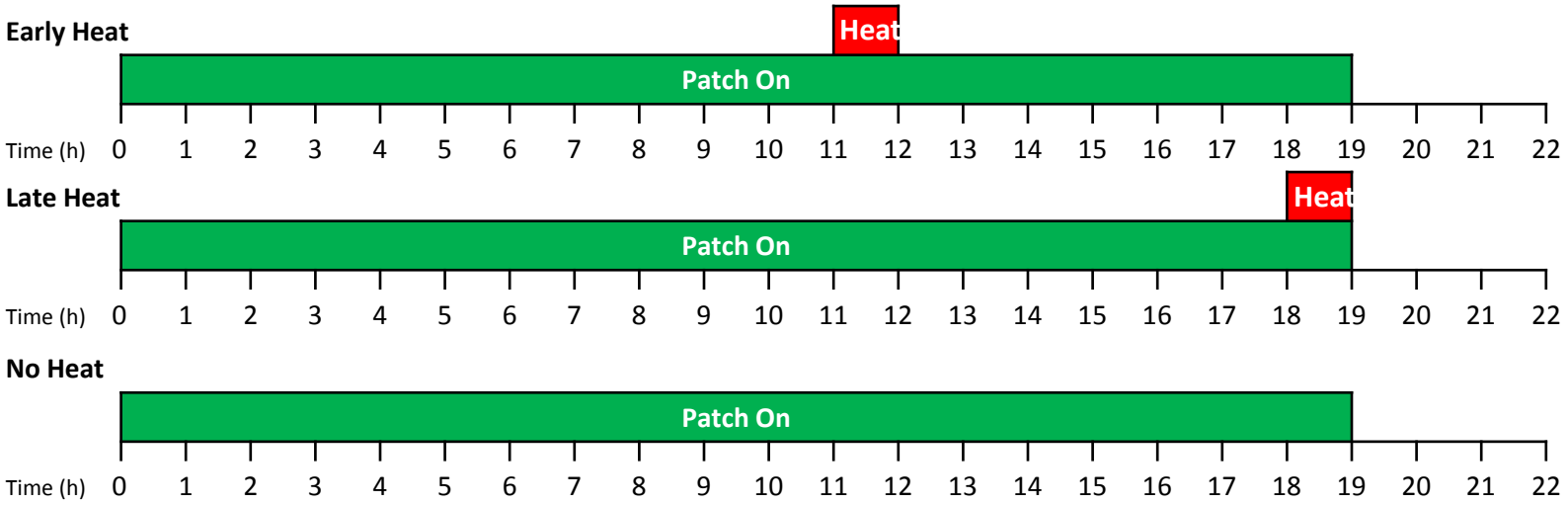
p > 0.05 for all treatment groups between IVPT and Residual Patch Analysis Data



p > 0.05 between early vs. late heat
⇒ paralleled the results from IVPT

Planned Studies with Fentanyl TDS

- IVPT experiments with three fentanyl TDS



- Validation of extraction method for each fentanyl TDS
- Analysis of residual fentanyl in TDS after IVPT

Evaluation of the relative bioavailability of nicotine and fentanyl TDS under the influence of heat in human subjects and development of IVIVC

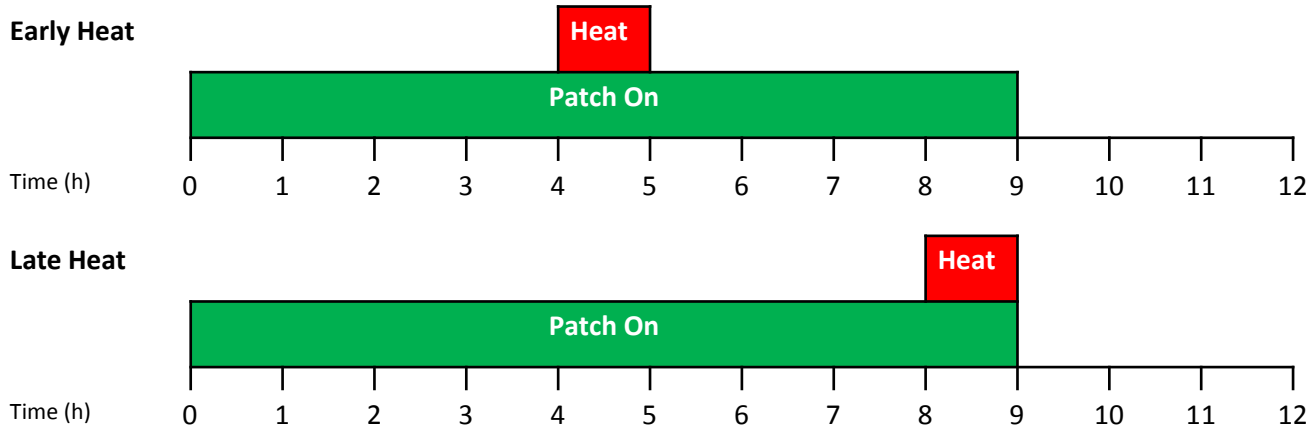
Hypothesis: TDS with different formulations behave differently under the influence of heat *in vivo*, which can be predicted by the *in vitro* permeation tests.

Approaches:

1) A crossover pharmacokinetic clinical study, with study designs mimicking the *in vitro* experimental designs
   - Sample analysis by a validated LC-MS/MS method
2) Analysis of residual drug content in patch after patch removal from clinical study
   - Sample analysis by a validated HPLC method
3) Evaluate relationships between *in vitro* and *in vivo* data
4) Develop IVIVC models in which IVPT data can predict the performance of TDS *in vivo*

Clinical Study Designs – Nicotine

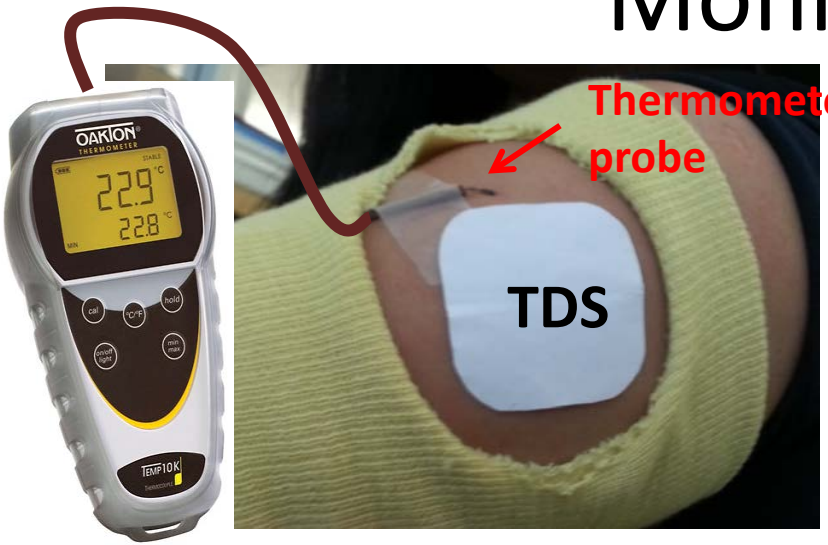
- A four-way crossover PK study in 10 adult smokers (two nicotine TDS)



- Residual amount of nicotine in TDS was analyzed

- Temperature of skin surface was monitored throughout the study

Heat application and Temperature Monitoring

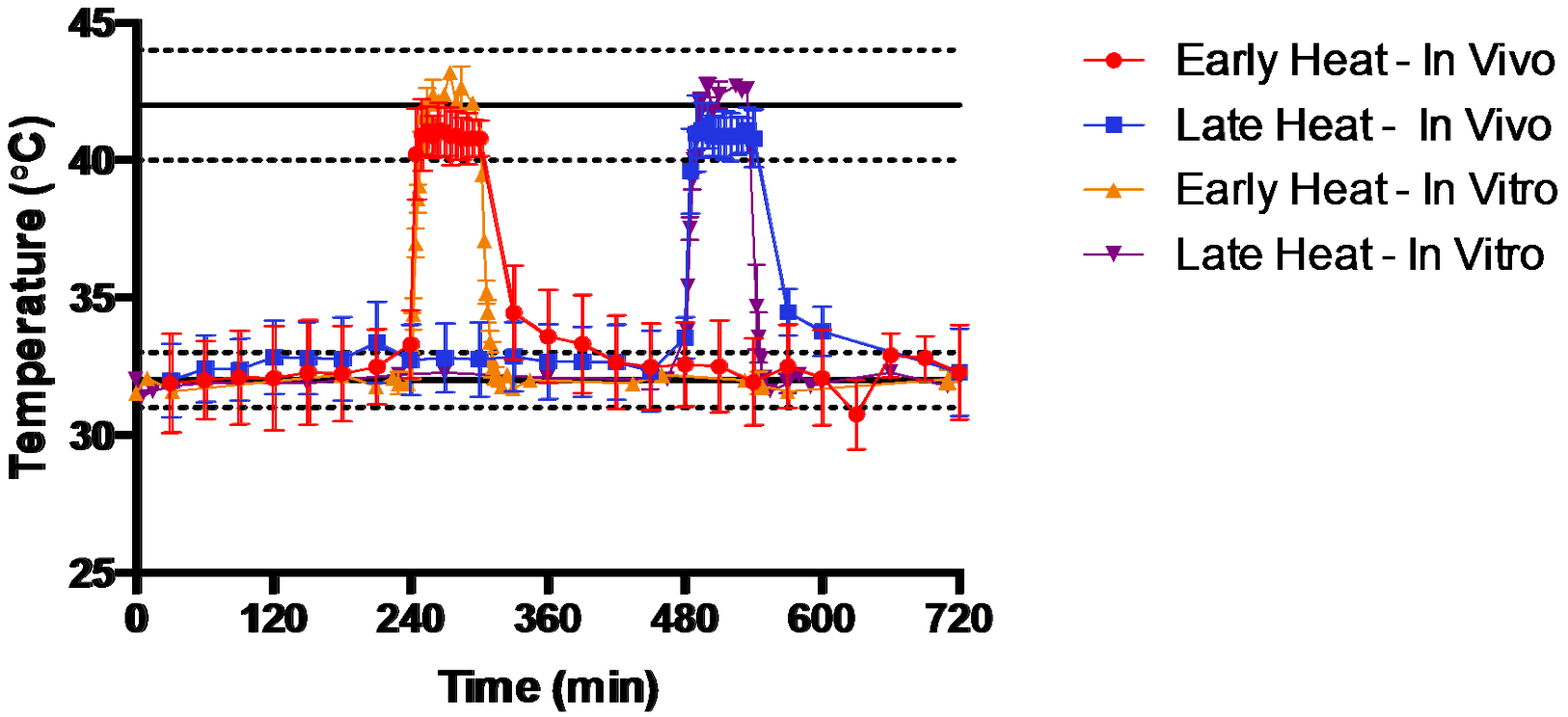


- Kevlar sleeve with an opening to expose TDS, while protecting skin from other areas
- Thermometer probe adjacent to TDS

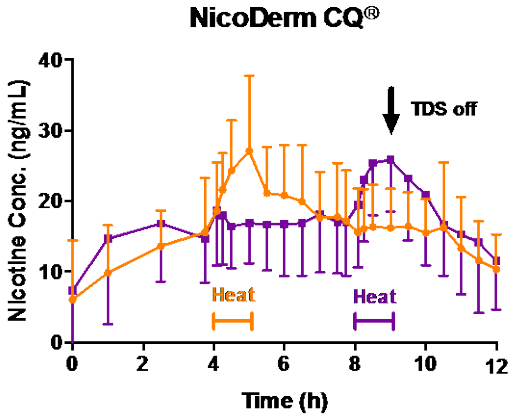
- Pre-heated heating pad
- ACE™ Bandage to ensure good contact between TDS and heating pad

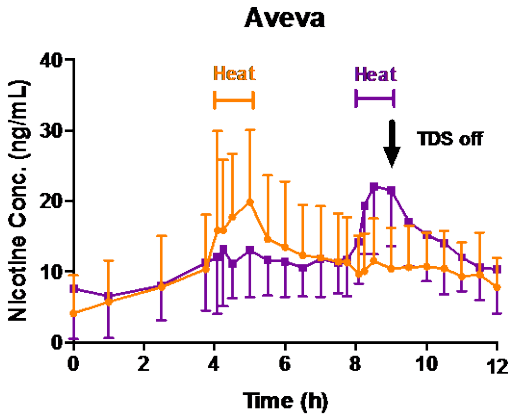
Image from http://static.coleparmer.com/large_images/91427_10_5.jpg

Preliminary: Temperature Monitoring



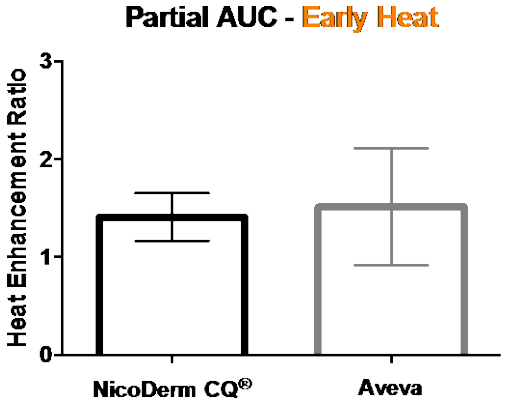
Preliminary: Nicotine PK profiles

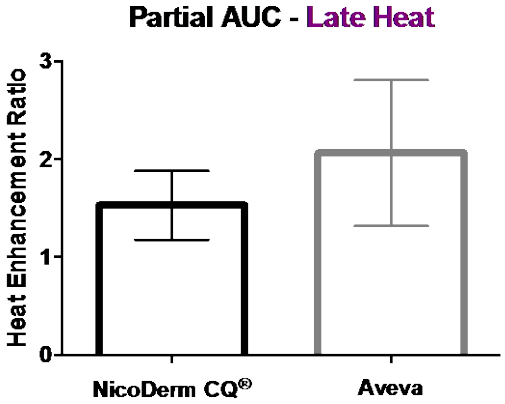




Early Heat
Late Heat

Mean ± SD from 10 Subjects





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

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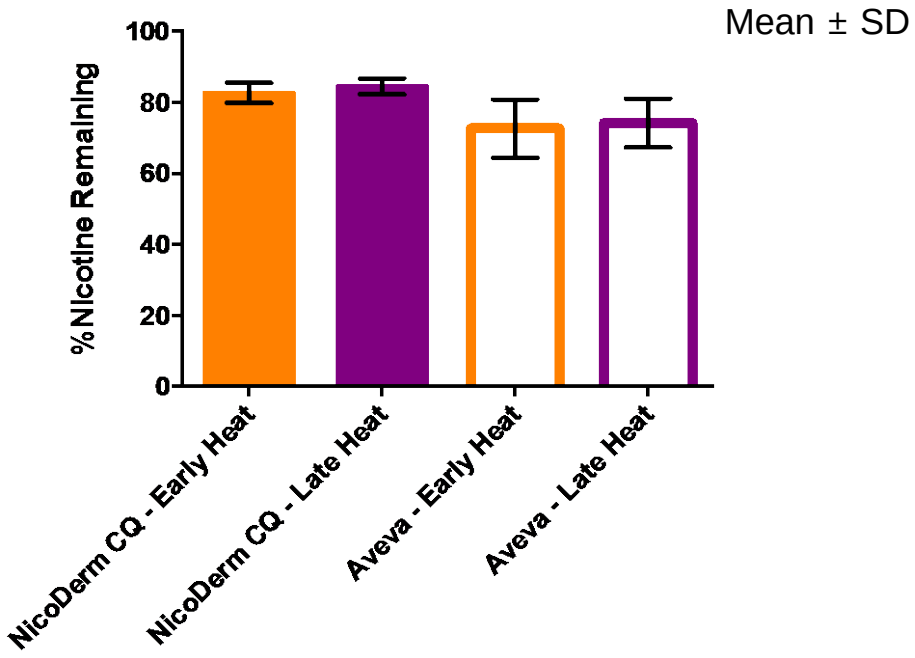
Preliminary: Nicotine Residual TDS Extraction



$p > 0.05$ between early vs. late heat

⇒ paralleled the results from *in vivo* PK and IVPT

Preliminary:

In Vitro – In Vivo Correlations

Nicotine TDS

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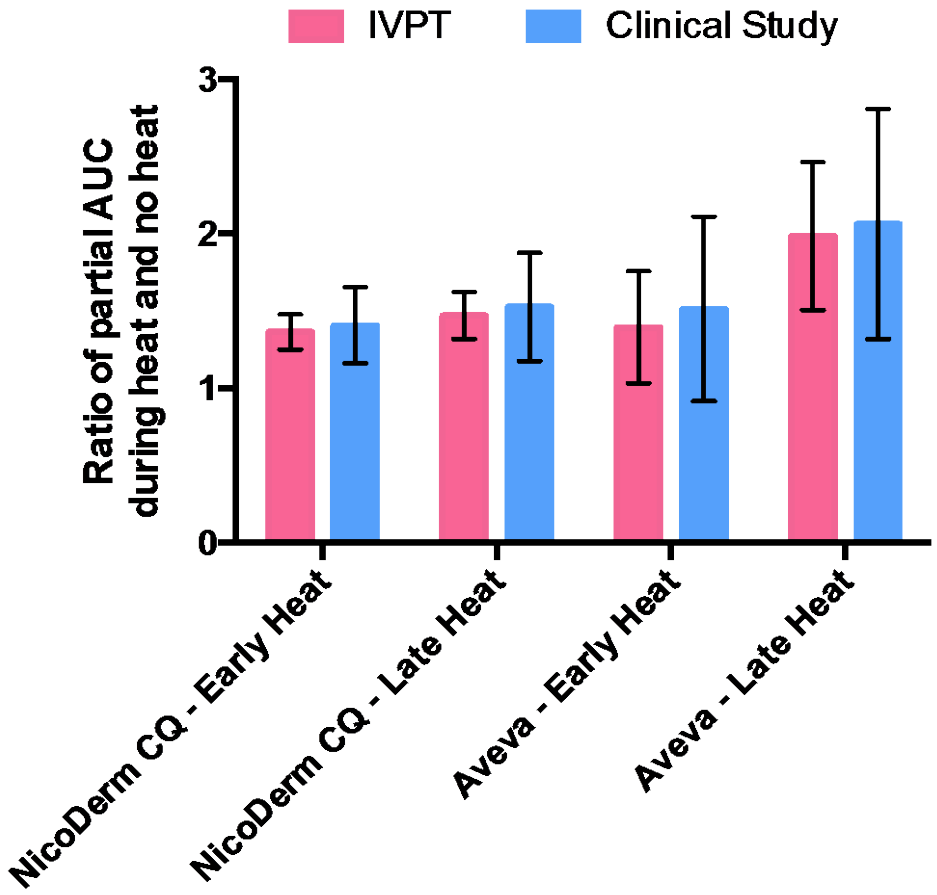
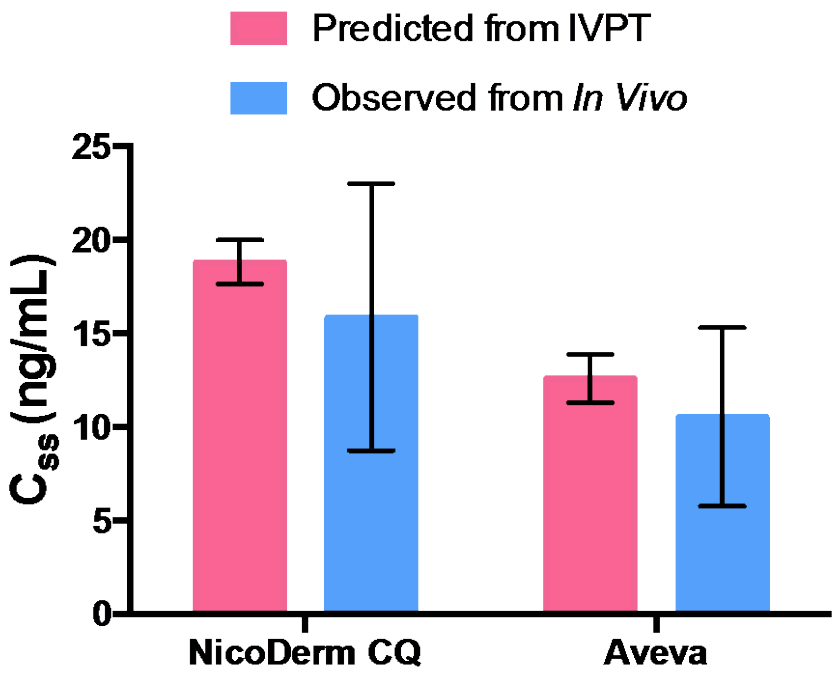
Preliminary: IVIVC – Heat Effect on Nicotine TDS



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

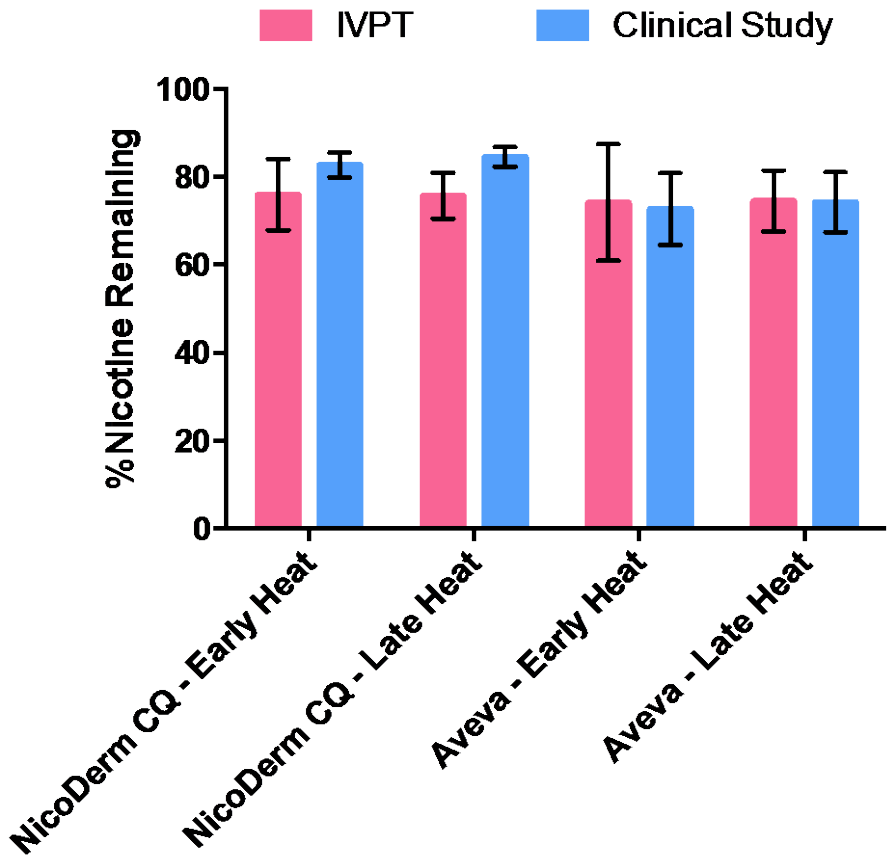
Preliminary: IVIVC – Absence of Heat



- 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*

Preliminary: IVIVC – Residual TDS Analysis



- $p > 0.05$ between IVPT and clinical study results

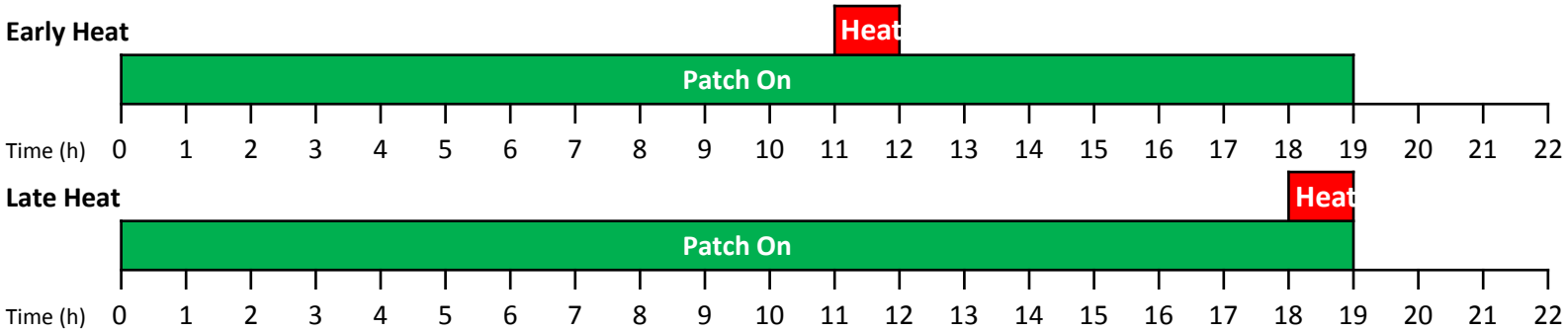
Summary

- IVIVC between IVPT and clinical human PK studies under the matched study conditions and designs, even with an external factor of temporary heat exposure

- Residual drug in TDS results paralleled the results from IVPT and clinical study, suggesting its potential as a surrogate measure to determine the extent of drug delivery and/or absorption

Planned Studies with Fentanyl TDS

- A six-way, crossover PK study in 10 healthy adults (3 fentanyl TDS)



- Evaluate IVIVC from fentanyl data
- Develop IVIVC models for nicotine and fentanyl TDS

Evaluation of the relative bioavailability of topical drug products by various surrogate methods and development of IVIVC

Hypothesis: Well-designed and optimized surrogate method(s) can be used to predict bioavailability and performance of topical drug products *in vivo.*

Planned Approach

1) IVPT experiments will be done with a focus of investigating effects of different experimental conditions and techniques involved in IVPT

- Dose amount selection
- Dose administration techniques & rubbing effect
- Multiple-dosing designs

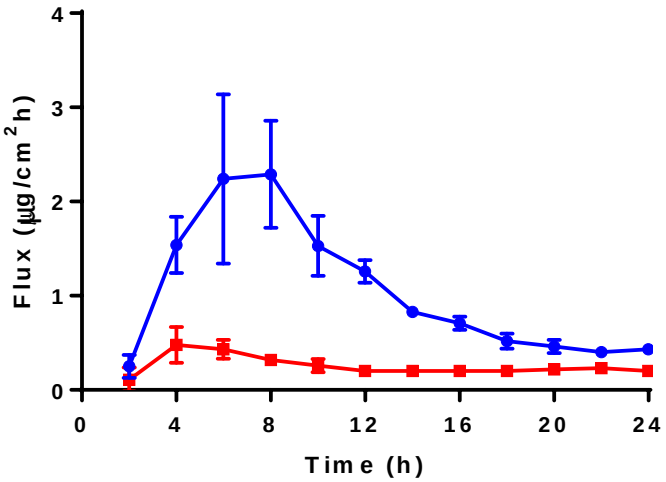
2) Other surrogate methods which evaluate the drug retention within skin layers will be investigated and performed

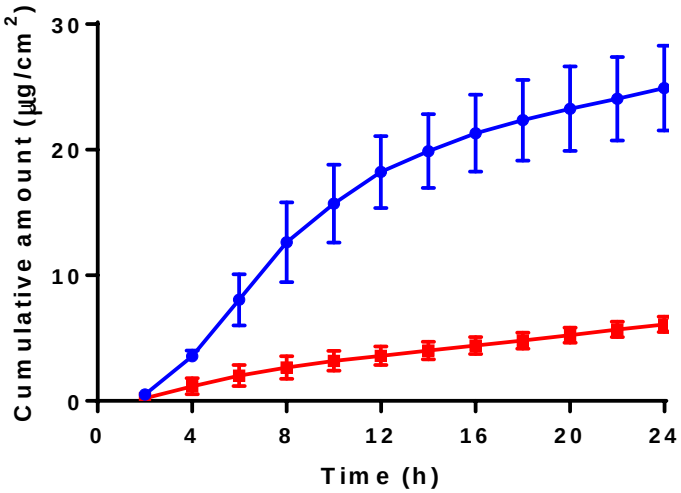
Biosensors

Infrared Spectroscopy

3) Obtained data through experiments, literature, and collaborators will be compared to determine which method(s) best predict the performance of topical drug products *in vivo*

Preliminary: Importance of Dose – Voltaren® gel

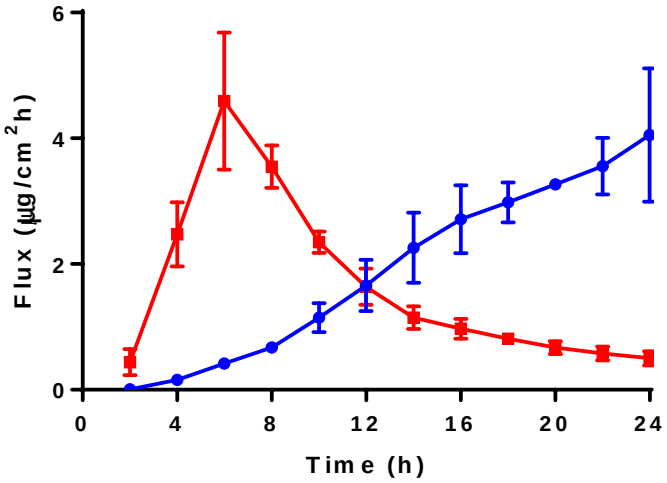


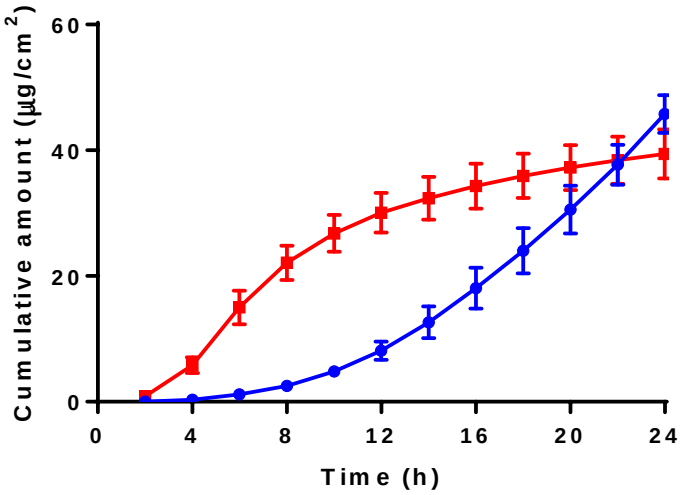


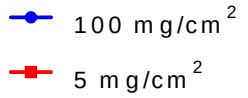
Mean ± SD (n=3)
Yucatan Miniature Pig Skin

	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

Preliminary: 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

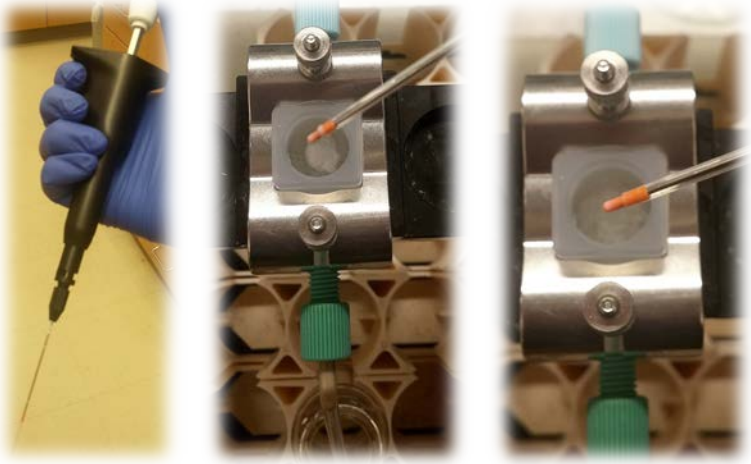
Dose Administration Techniques

- 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

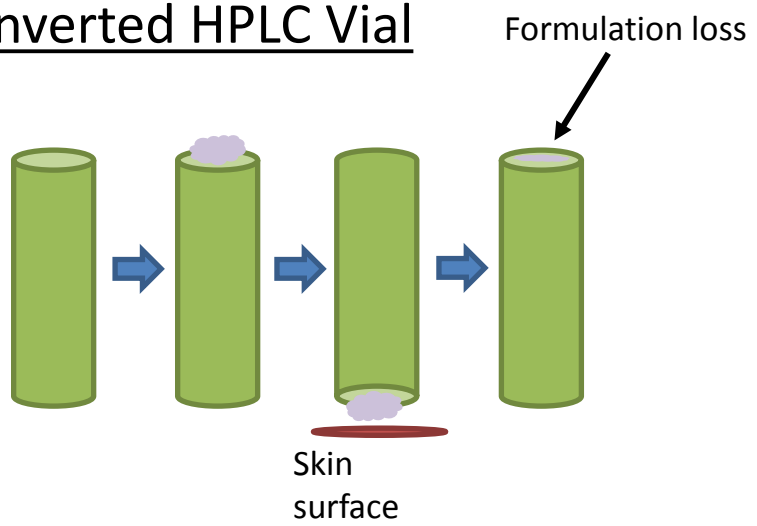
Dose Administration Techniques

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

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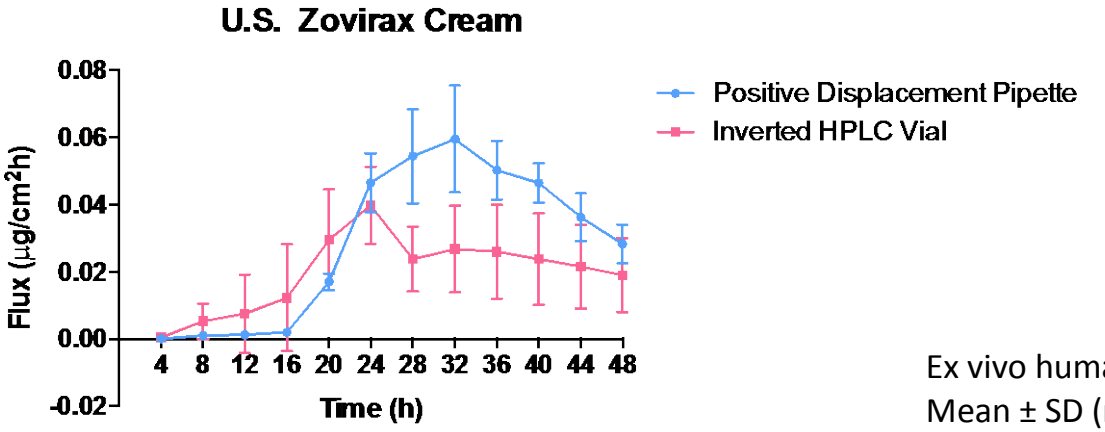
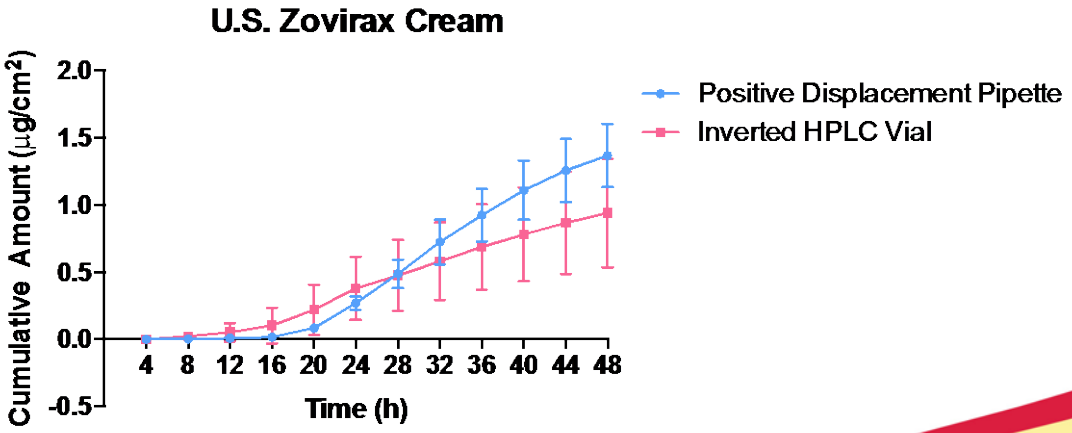
Preliminary: Dose Administration Techniques





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

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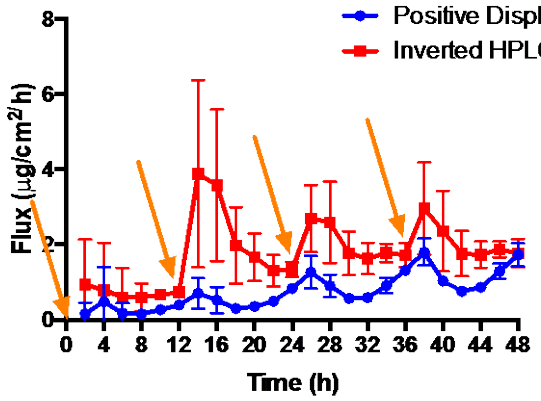
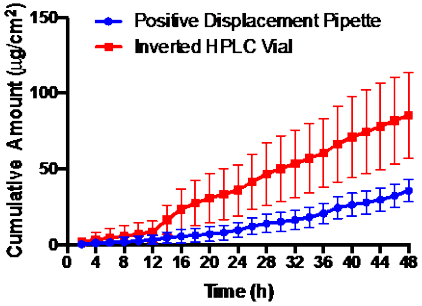
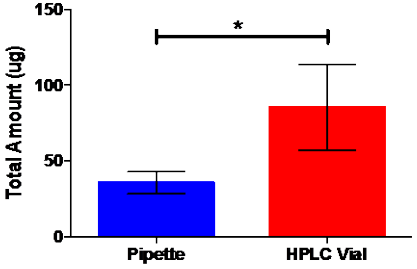
Preliminary: Dose Administration Techniques

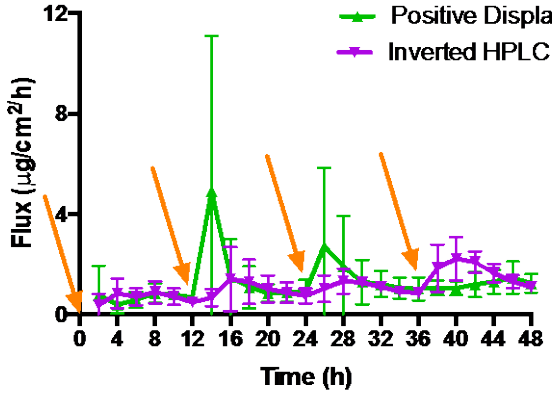
Pennsaid® 2% (more viscous)

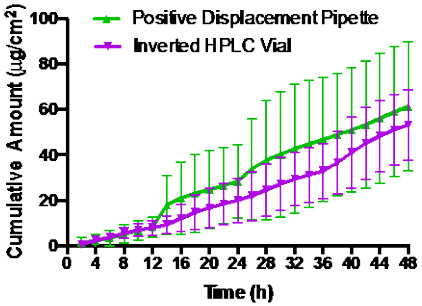


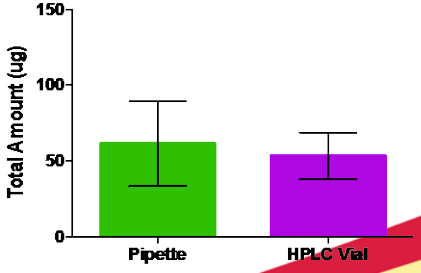




Pennsaid® 1.5%







Orange Arrow: dosing (~5 mg/cm² of formulation)

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

Planned Studies

- Optimizing techniques for IVPT experiments
  - Needs to be product-specific

→ Perform IVPT experiments to collect reliable data set

- Investigate other surrogate methods and optimize techniques involved in the selected surrogate methods

→ Perform experiments to collect reliable data set

- Gather data and information for the selected products

→ Compare and correlate data set from various surrogate methods

→ Determine surrogate method(s) that best predict *in vivo* performance

Conclusions

- Limitations of clinical studies for topical drug products highlight the needs for developing surrogate methods to evaluate BA
- 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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- Dr. Bryan Newman
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- Dr. Elena Rantou

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- Dr. Richard Guy
- Dr. Begoña Delgado-Charro
- Dr. Frank Sinner

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- Dr. Wilbur Chen
- Melissa Billington
- GCRC nurses

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- 1U01FD004955-01

Back Up

Dermatopharmacokinetics(DPK, tape-stripping)

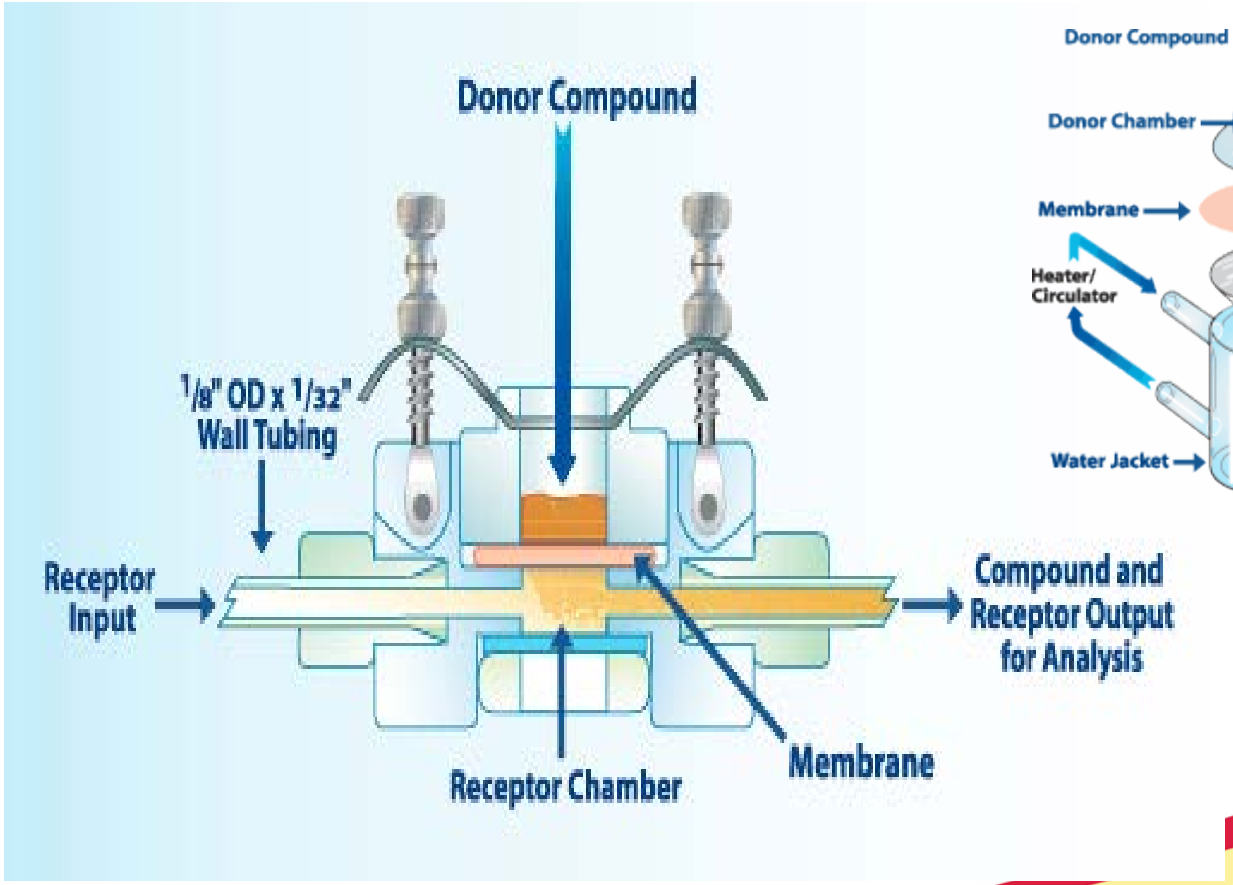
- Measures amount in SC measured in time after application and cleaning
- Analysis of PK parameters: AUC (area under amount in SC versus time curve), T_{max}, C_{max}
  - e.g., Pershing & Franz tretinoin studies (FDA guidance 1998-2002)
  - Complicated and same BE answer is achievable with a simpler 1-uptake and 1-clearance analysis (Bunge and Guy et al.)
  - Navidi, W, Hutchinson, A, N'Dri-Stempfer, B and Bunge, A (2008). Determining bioequivalence of topical dermatological drug products by tape-stripping. *J Pharmacokin Pharmacodyn*, 35:337-348
  - N'Dri-Stempfer, B, Navidi, WC, Guy, RH and Bunge, AL (2008). Optimizing metrics for the assessment of bioequivalence between topical drug products. *Pharm Res*, 25:1621-1630
  - Nicoli S, Bunge AL, Delgado-Charro MB, Guy RH. Dermatopharmacokinetics: factors influencing drug clearance from the stratum corneum. Pharm Res. 2009; 26: 865-71
  - N'Dri-Stempfer, B, Navidi, WC, Guy, RH and Bunge, AL (2009). Improved bioequivalence assessment of topical dermatological drug products using dermatopharmacokinetics. *Pharm Res*, 26:316-328

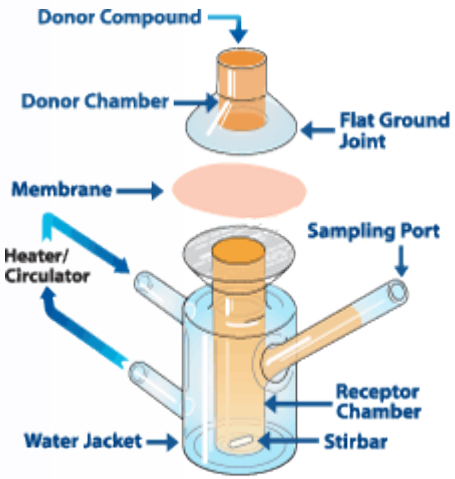
Dermatopharmacokinetics (DPK, tape-stripping)

- four improvements made by Bunge and Guy et al. to the original DPK methodology
  - improved cleaning of excess drug from each test site at the end of the uptake period
  - determination and inclusion of drug from the first two tape strips in the reported total amount taken up into the SC
  - an increase in the number of tape strips collected combined with a method to ensure reliable collection of nearly all the SC
  - improved control of the tape strip sampling area within the drug application area (to avoid edge effects)

In Vitro Skin Permeation Study (IVPT)

Automated
In-Line
Flow Through
System





Standard
Franz cell

www.permegear.com

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

Historical IVIVC for Bioequivalence

- Previous examples of IVIVC*
  - IVPT compared with total absorption after 1 application in humans
  - Studied same drug products with same methodology (harmonization)
  - Measured the same metric (usually total % absorbed)
  - *In vivo* and *in vitro* results were the same
  - Relatively robust set of data demonstrates that *in vitro* measurements are good representations of the *in vivo* system
  - Rate and extent are coupled in the total % absorbed (i.e., rate and extent are not determined separately, 1 time point)
- Total % absorbed is not typically measured by other *in vivo* methods; for example:
  - Pharmacokinetic (i.e., blood levels)
  - DPK
  - We will be incorporating this metric with DPK and PK

*Lehman, PA, Raney, SG and Franz, TJ (2011). Percutaneous absorption in man: In vitro-in vivo correlation. *Skin Pharmacol Physiol*, 24:224-230.

*Franz, TJ, Lehman, PA and Raney, SG (2009). Use of excised human skin to assess the bioequivalence of topical products. *Skin Pharmacol Physiol*, 22:276

*also Chapter 9 in Transdermal and Topical Drug Delivery, Benson ed., Lehman et al. 2012