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Environmental Harmonization in Multi-Application Sunscreen Use: In Vitro Permeation Testing to Healthy Volunteers

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

- Chief Scientific Officer and Co-Founder of

  F6 Pharma

  – A company developing and testing topical drug products

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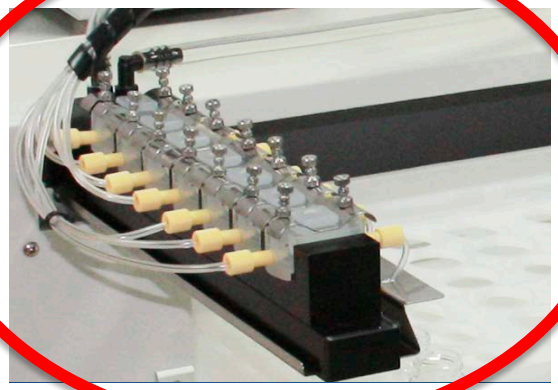
  - QingZhao Zhang
  - Paige Zambrana
  - Dana Hammell, M.S.
  - Danielle Fox

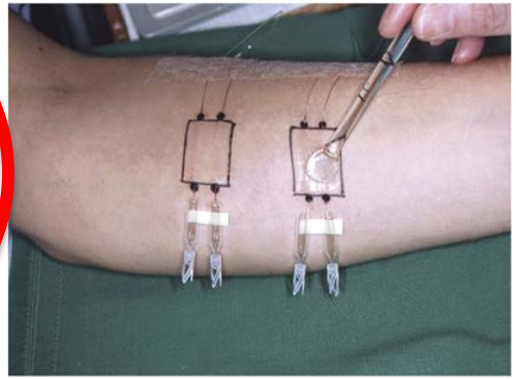
Paige Zambrana PhD thesis project

Methods of Assessment of Bioavailability

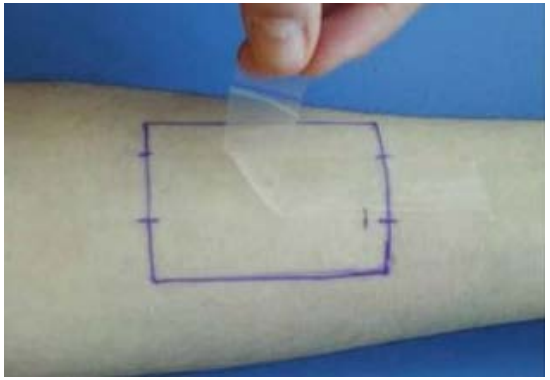
IVPT
In vitro permeation test



Microdialysis



Tape stripping



Blood levels

Pharmacodynamic assay
(vasoconstriction)

Urine levels

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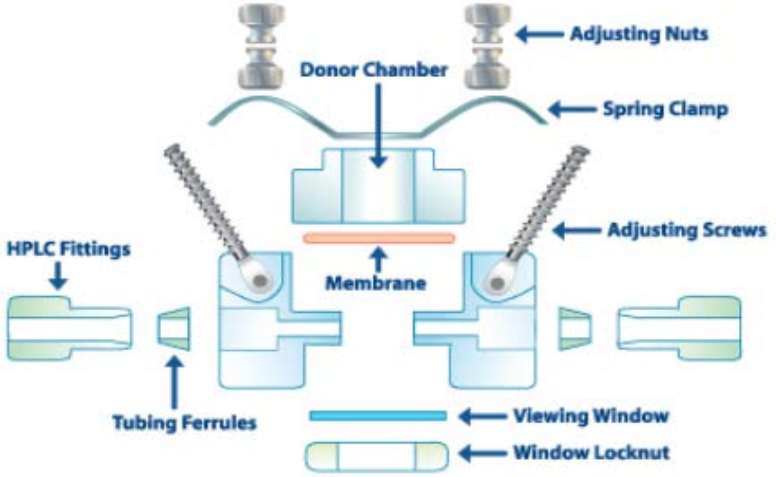
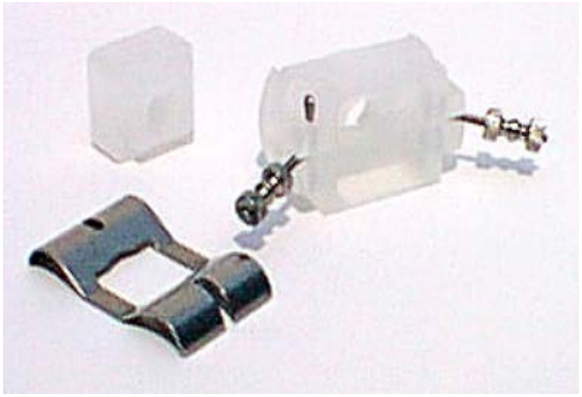
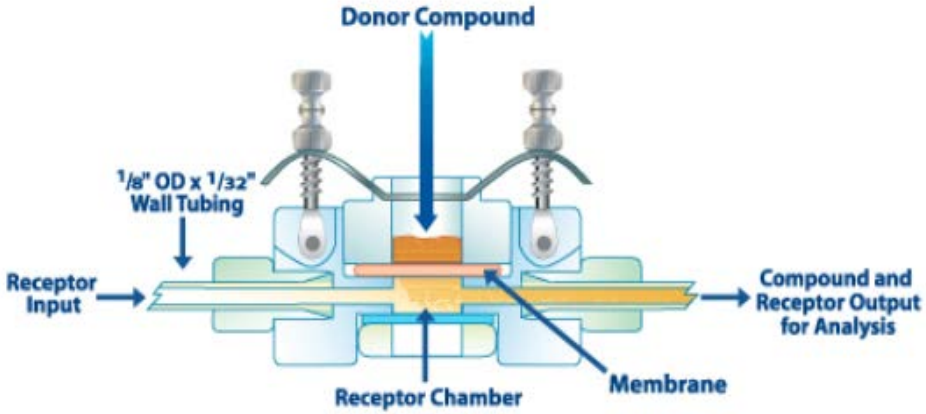
In-Line Diffusion Cells







http://permegear.com/in-line-cells/

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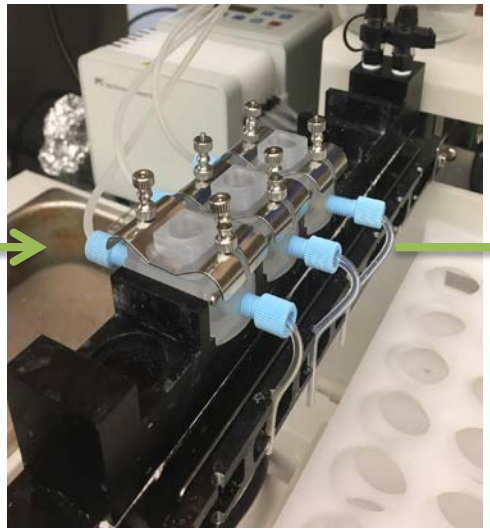
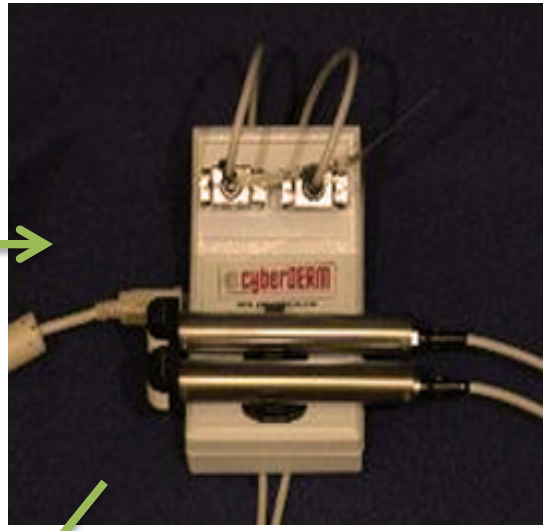
IVPT (In vitro permeation test)

1. Dermatome

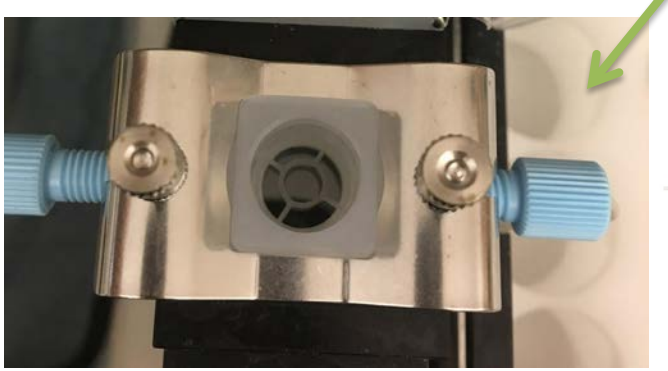
2. Assemble setup



3. Record TEWL



4. Dose Product



Inverted HPLC vial

Positive displacement pipette

Multiple Dosing

- Oxybenzone permeation with multi-application use of sunscreens on

1) in vitro permeation of oxybenzone across excised human skin
2) design an in vivo study, under harmonized conditions, to evaluate the pharmacokinetics of oxybenzone absorption in healthy human volunteers for four sunscreen products each containing 6% oxybenzone

Sunscreen Products

IVIVC: *In Vitro In Vivo* Correlation

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

→ Minimize/Reduce in vivo clinical studies

(Save 💰 & 🕓)

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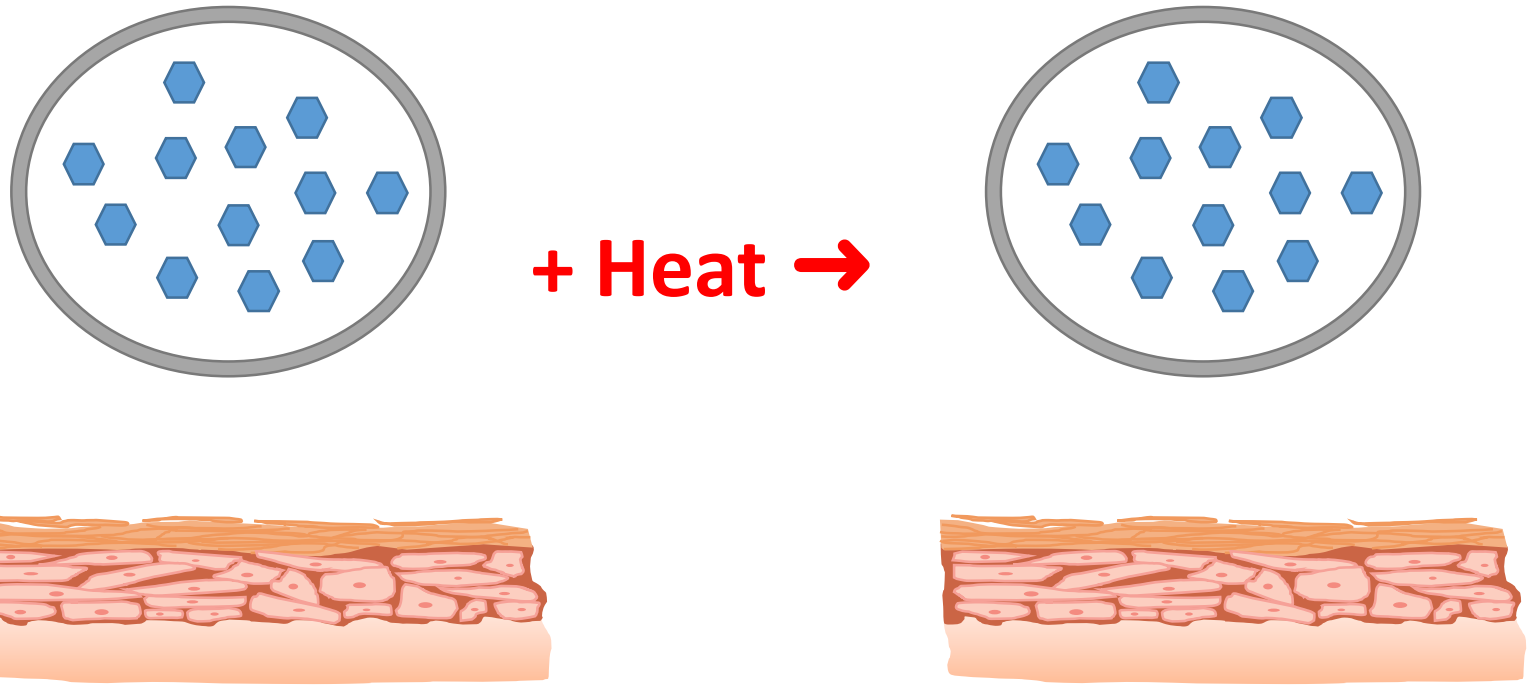
Influence of Heat

- Evaluate the effect of heat exposure
  - 37°C vs standard skin surface temperature of 32°C

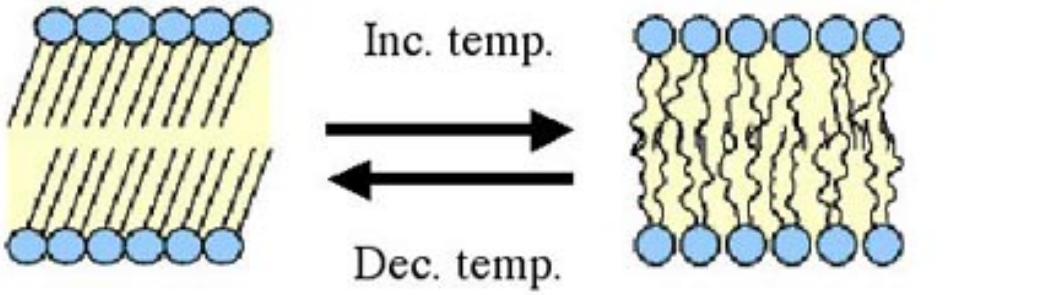
Influence of Heat on Percutaneous Absorption

1) ↑ Diffusivity of Drug from its Vehicle



Influence of Heat on Percutaneous Absorption

2) ↑ Fluidity of Stratum Corneum Lipids



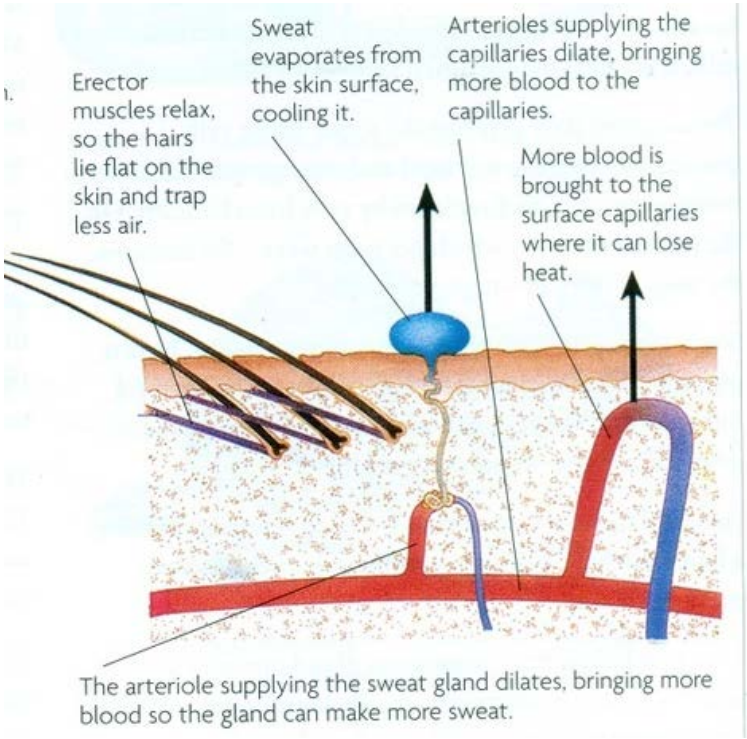
https://biochemistry3rst.wordpress.com/tag/phosphodiate/

Influence of Heat on Percutaneous Absorption

3) ↑ Cutaneous Vasodilation

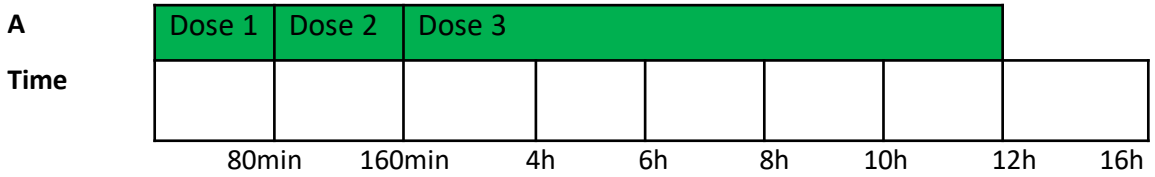
Body temperature regulation

When the body is too hot

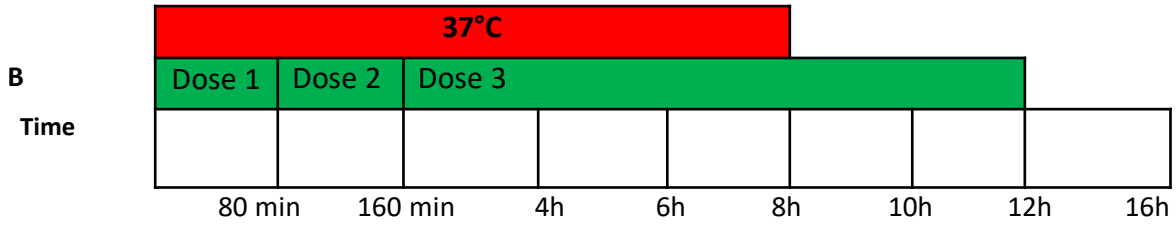


Initial MiniMUsT Study Design

Baseline arm

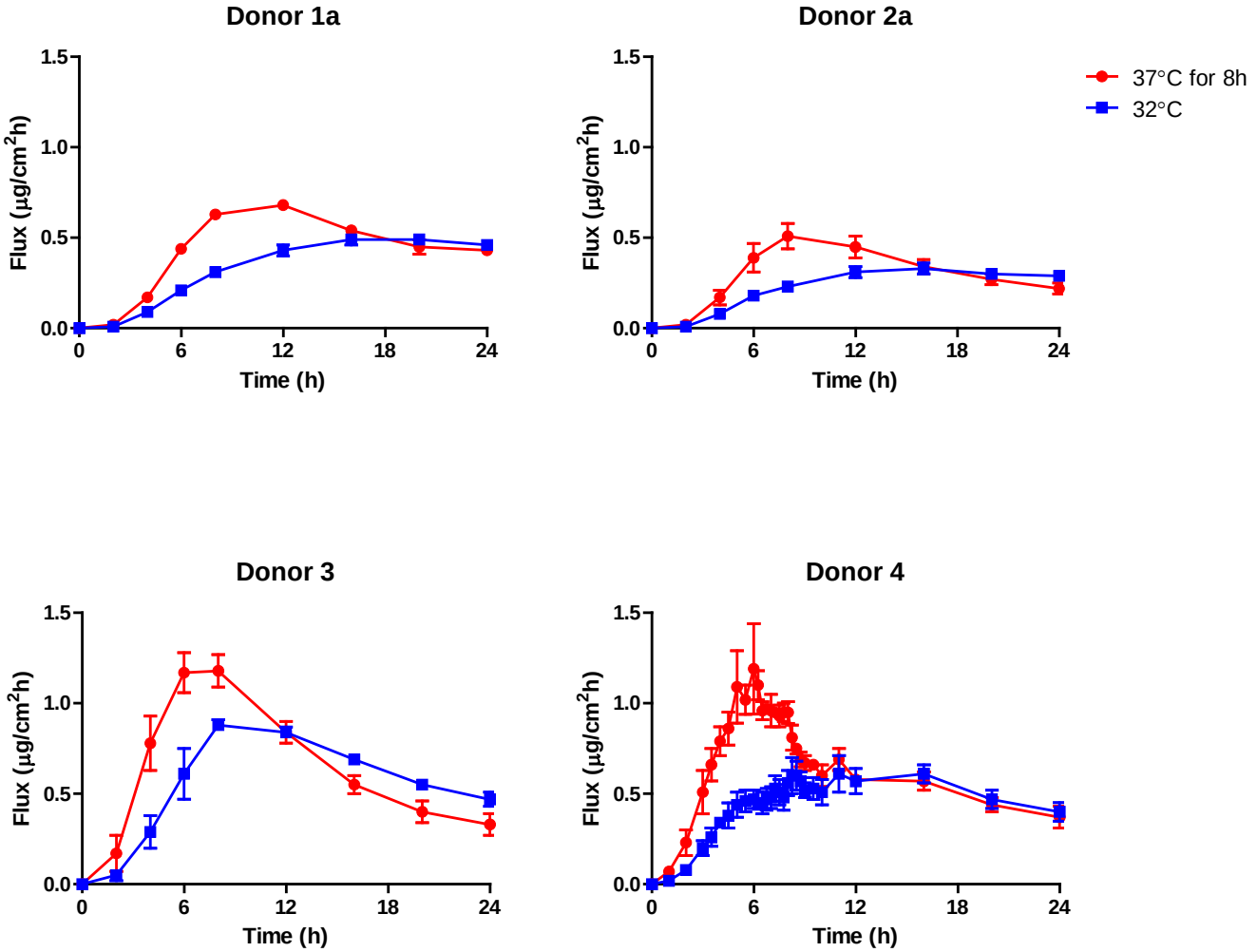


Heat arm



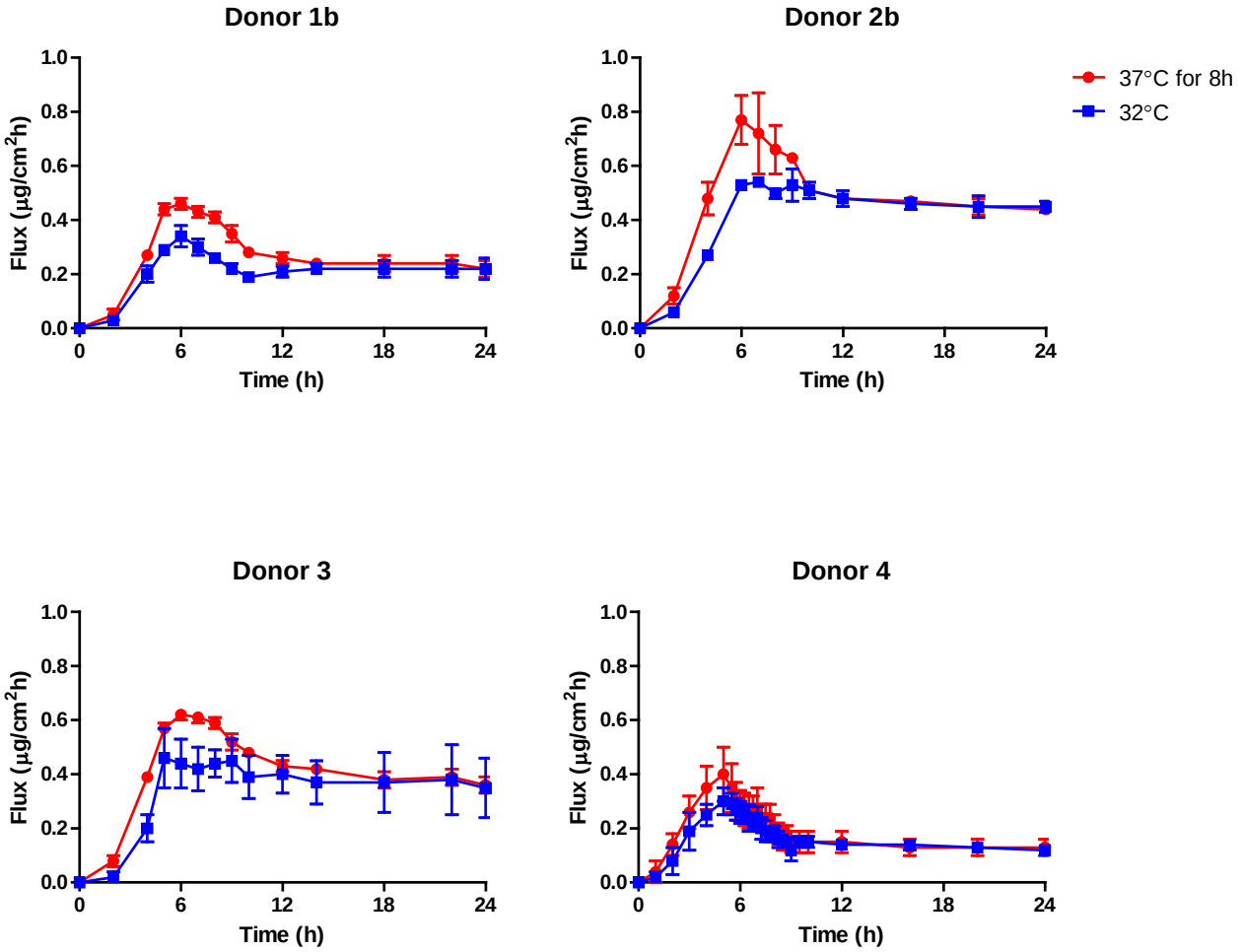
Both arms will be performed for Lotion 1 and Lotion 2
IVPT carried out for 24 hours

IVPT Data: Lotion 1 (Cream Emulsion)
Flux profile from human skin for Lotion 1 (mean ± SD) (3 replicates/donor)

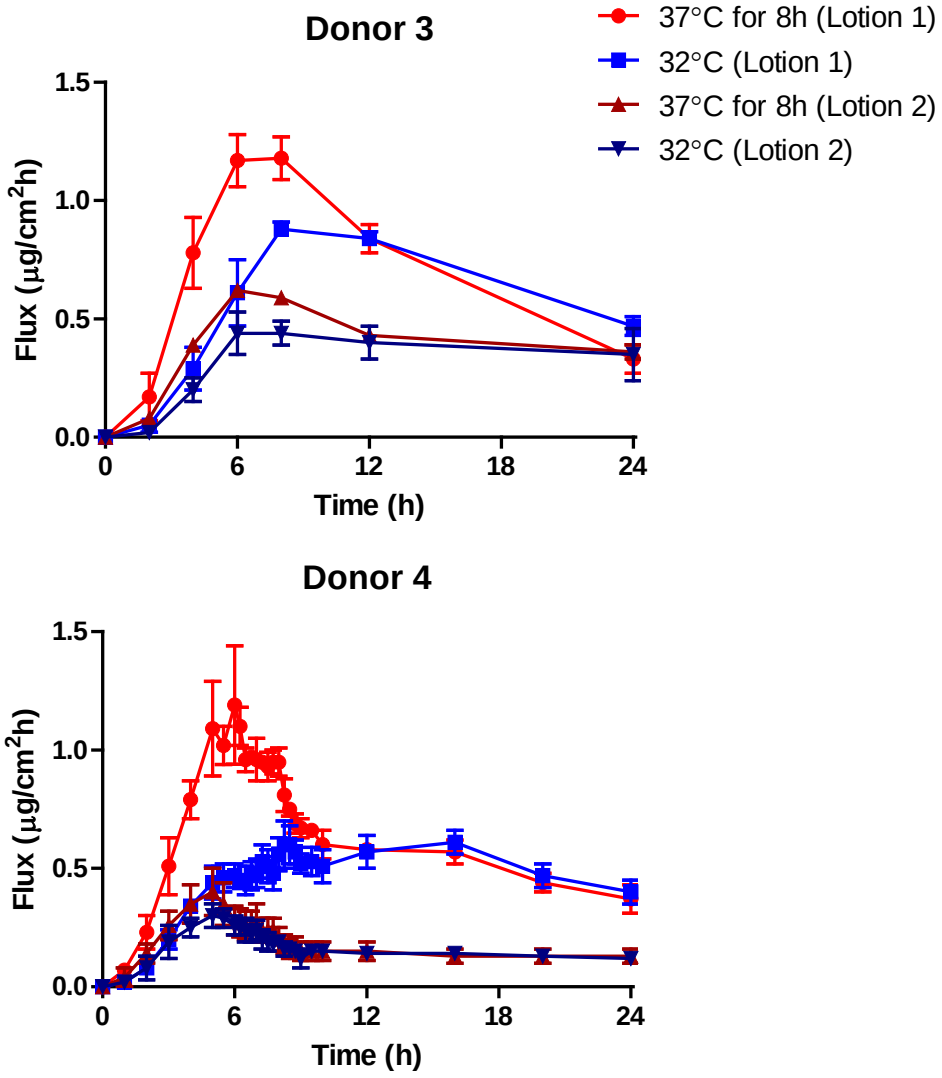


IVPT Data: Lotion 2 (Water washable lotion)

Flux profile from human skin for Lotion 2 (mean ± SD) (3 replicates/donor)



Flux profile comparison of Lotion 1 vs Lotion 2 for two human skin donors (mean ± SD)



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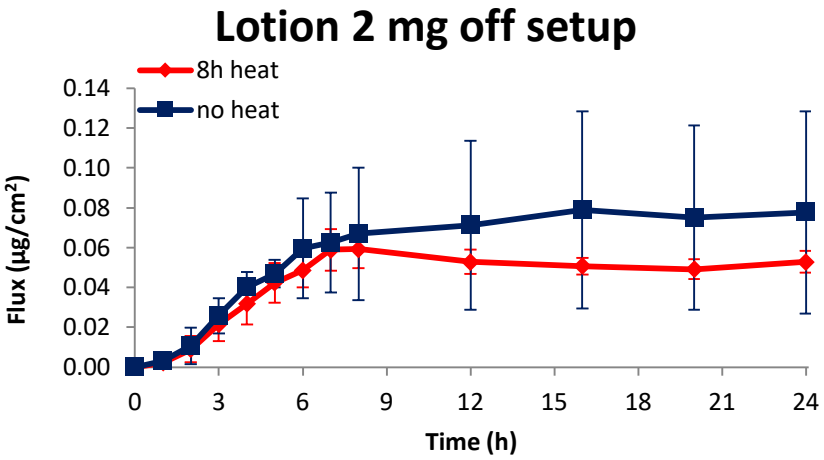
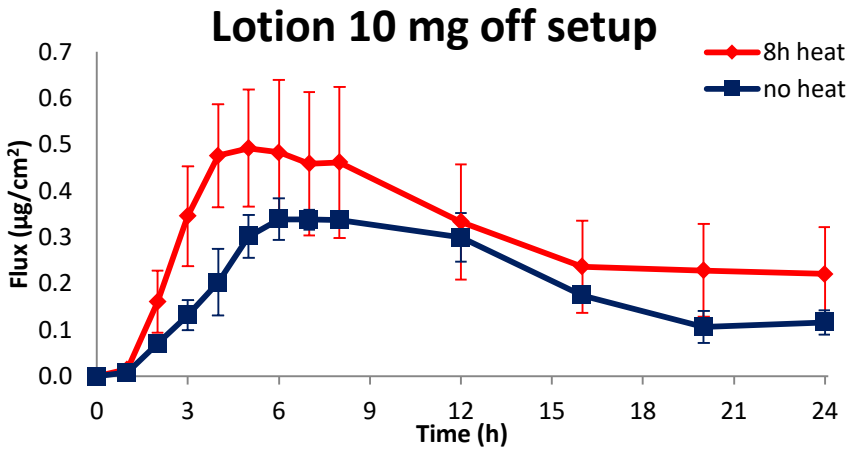
Lotion – 2 mg vs 10 mg Single Dose IVPT





2 mg lotion-off setup		
	heat	no heat
avg. cum (µg/cm²)	1.39	1.91
avg dose (mg)	2.02	2.07
avg skin thickness (µm)	290	300

10 mg lotion-off setup		
	heat	no heat
avg. cum (µg/cm²)	9.21	5.86
avg dose (mg)	9.8	10.35
avg skin thickness (µm)	313.3	306.7

Conclusions: When dosing 2 mg the no heat condition had a similar flux and avg cumulative amount permeated
When dosing 10 mg the heat condition had a higher flux and avg cumulative amount permeated

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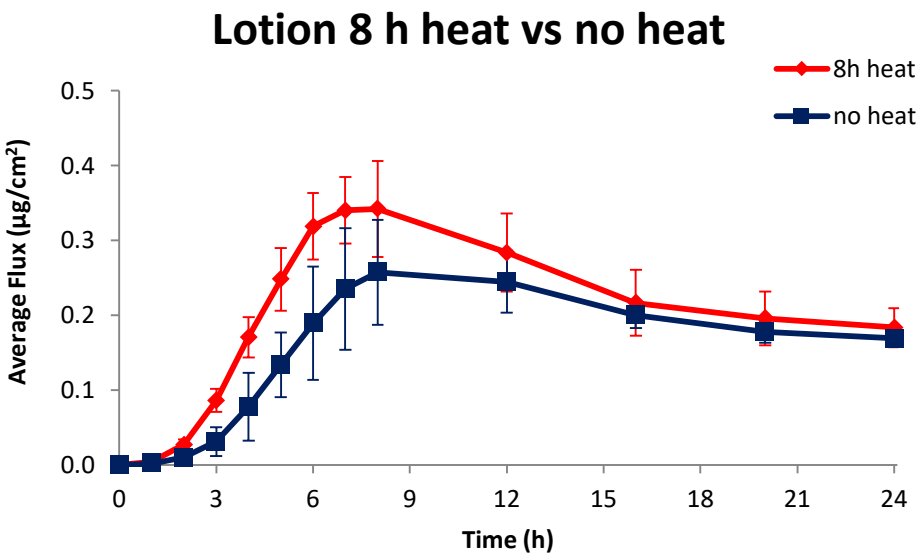
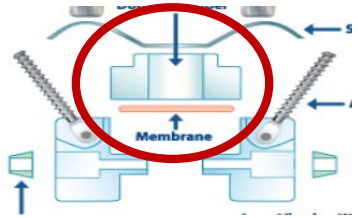
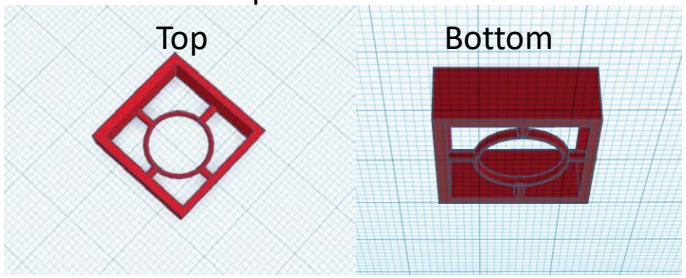
Lotion – 2 mg multidose IVPT



Current cell insert



Proposed cell insert

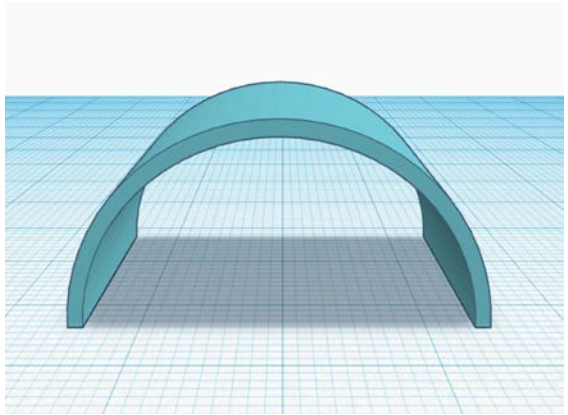


Conclusions: For this study used a new membrane support system but heat flux goes back to being higher when multiple doses are applied

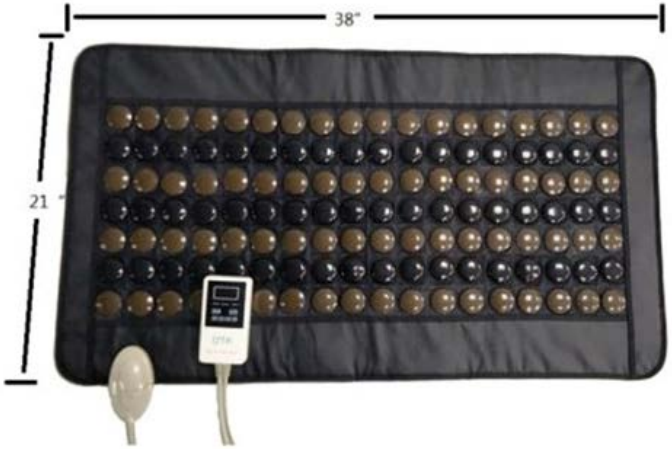
~potential for higher humidity environment occurring since cell insert dosing area is tall not allowing for adequate evaporation??? Potentially need to make a new version of a cell insert so that skin is more exposed to air (see above)

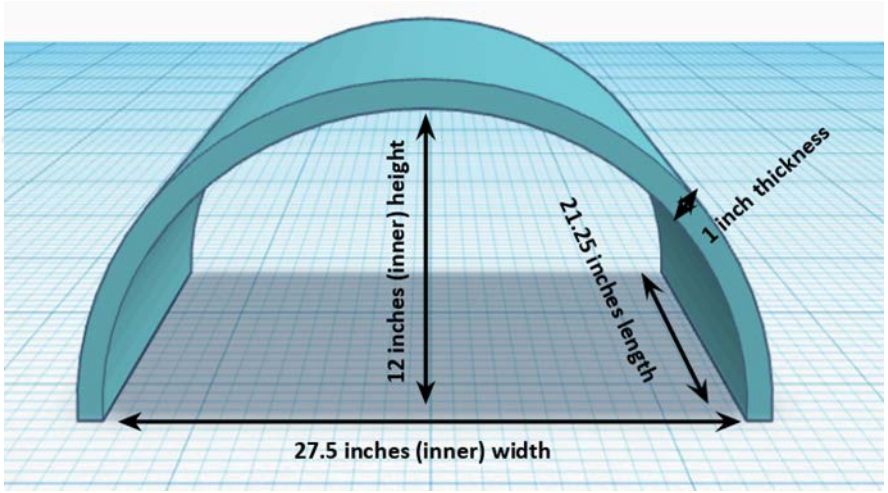
Human Pharmacokinetic Study

- 12 h open-label, randomized, four-way crossover pharmacokinetic study in healthy human volunteers
- Harmonized to the previously mentioned IVPT parameters
- During heat application, skin temperature of 37 ± 2°C was achieved by placing a heating pad adhered to the underside of a 3D printed dome over the top of the volunteers' thighs
- Serum samples were analyzed for oxybenzone using a validated LC-MS/MS method
- 2 mg/cm^2 application ➡ 800 cm^2



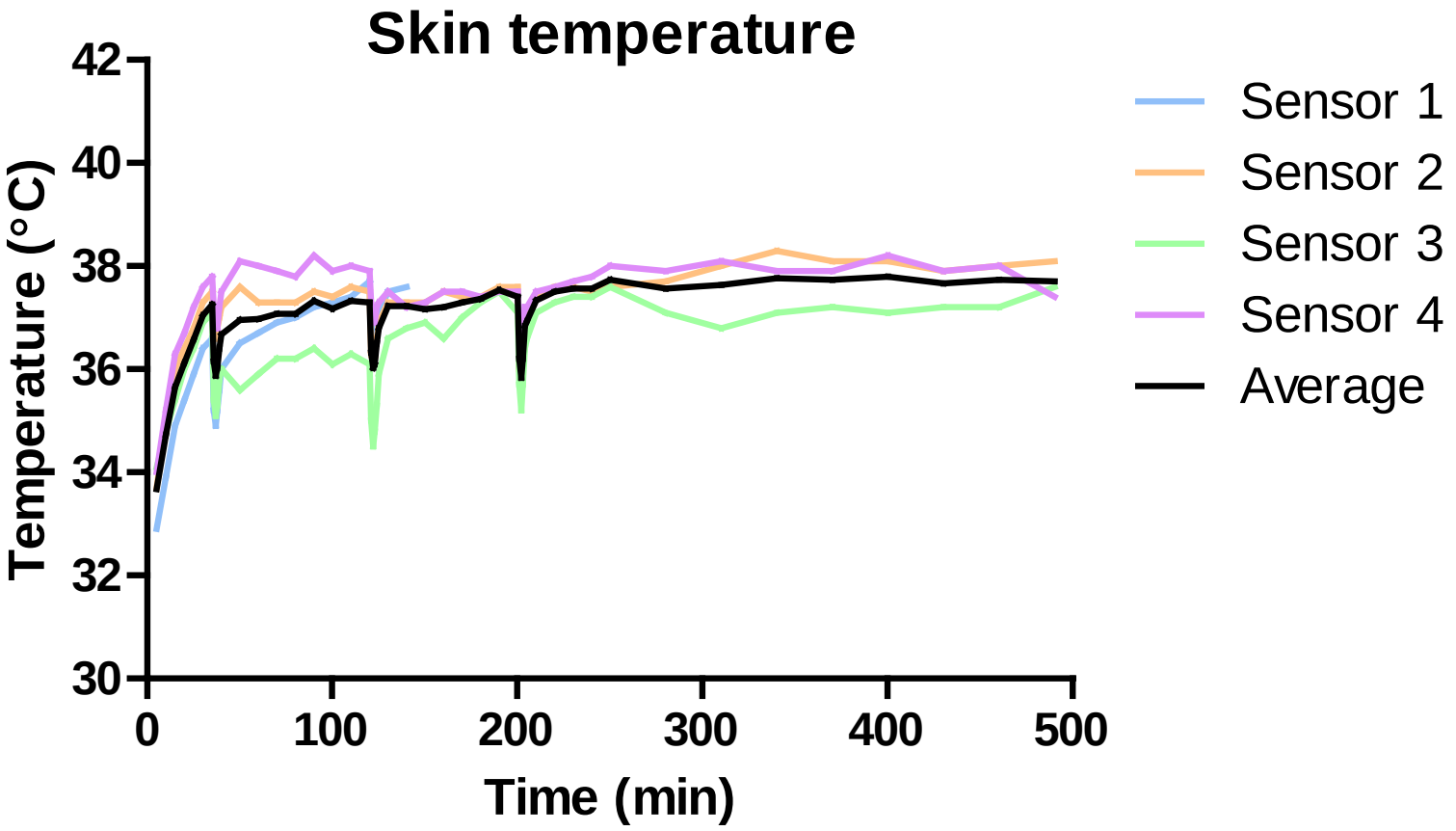
Design of Standardized Heat Dome





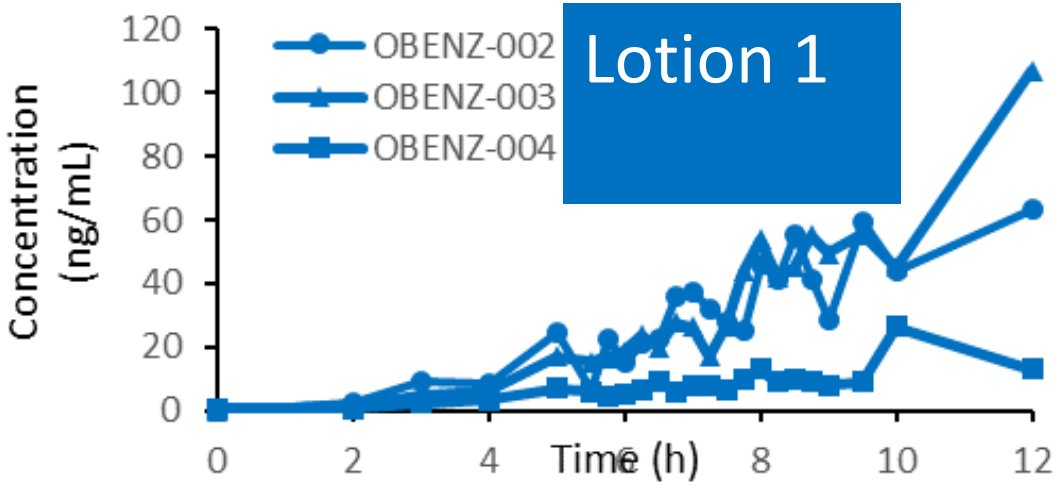
Setup during clinical trial heat procedure days

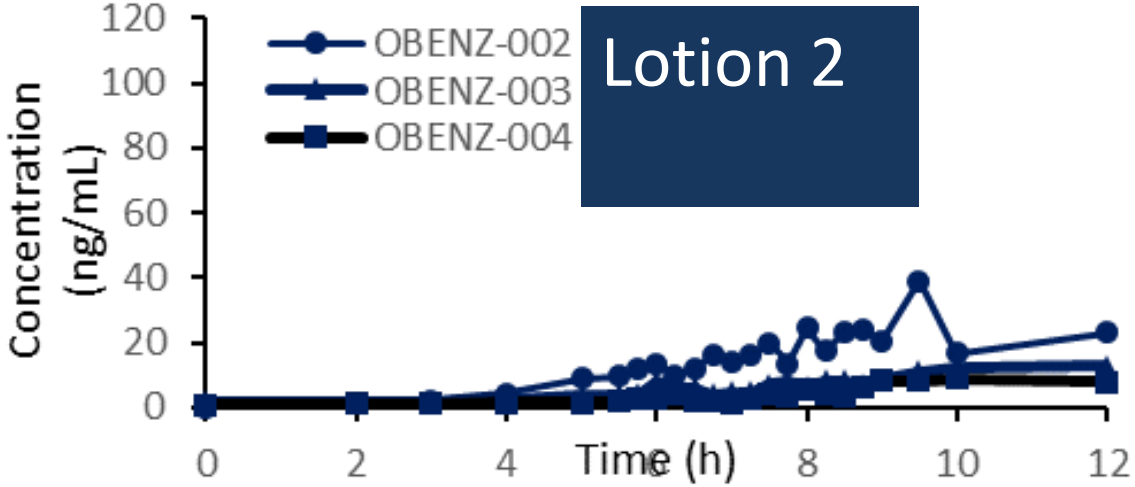
Record of average skin temperature recorded from four separate skin sensors placed on the thighs covering an area of 800 cm^2



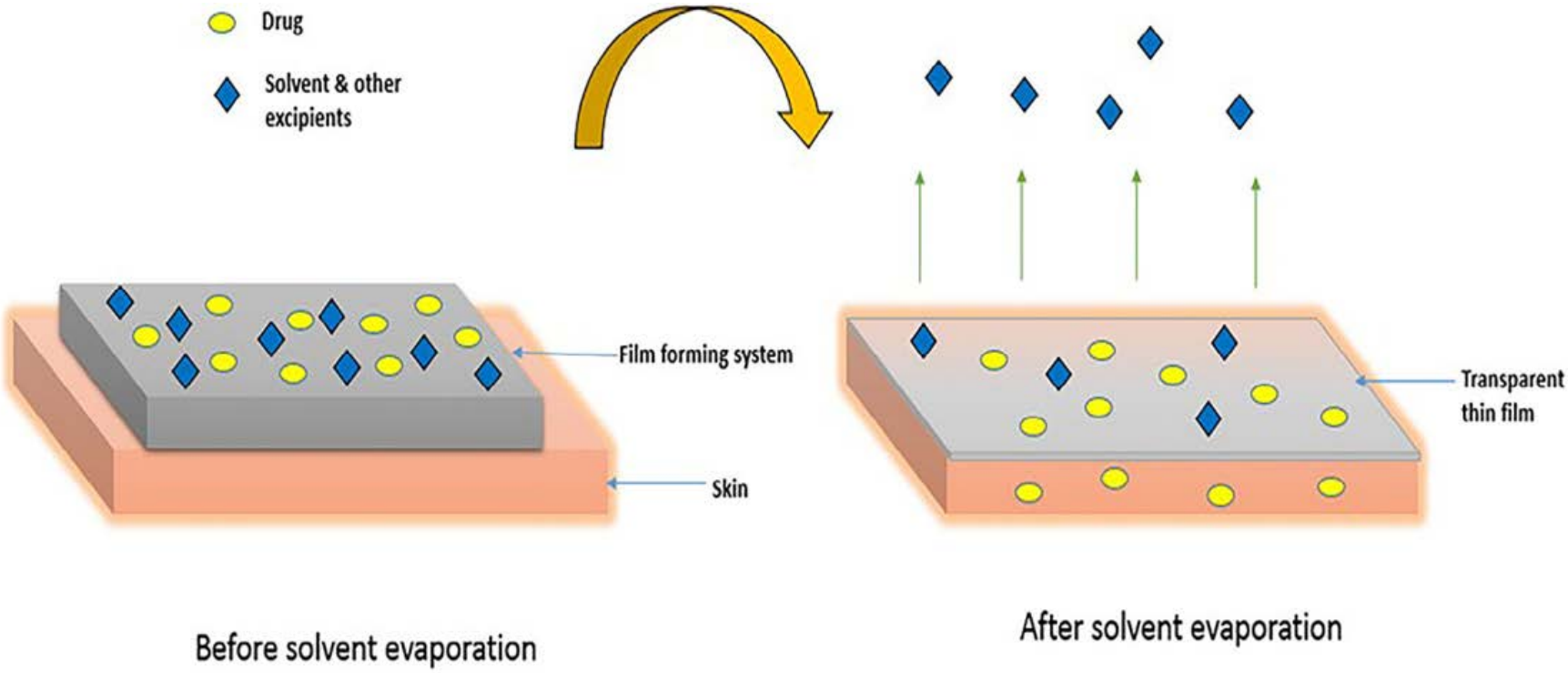
Serum PK profiles for volunteers treated with **Lotion 1** sunscreen and **Lotion 2** sunscreen

0, 80, and 160 min application



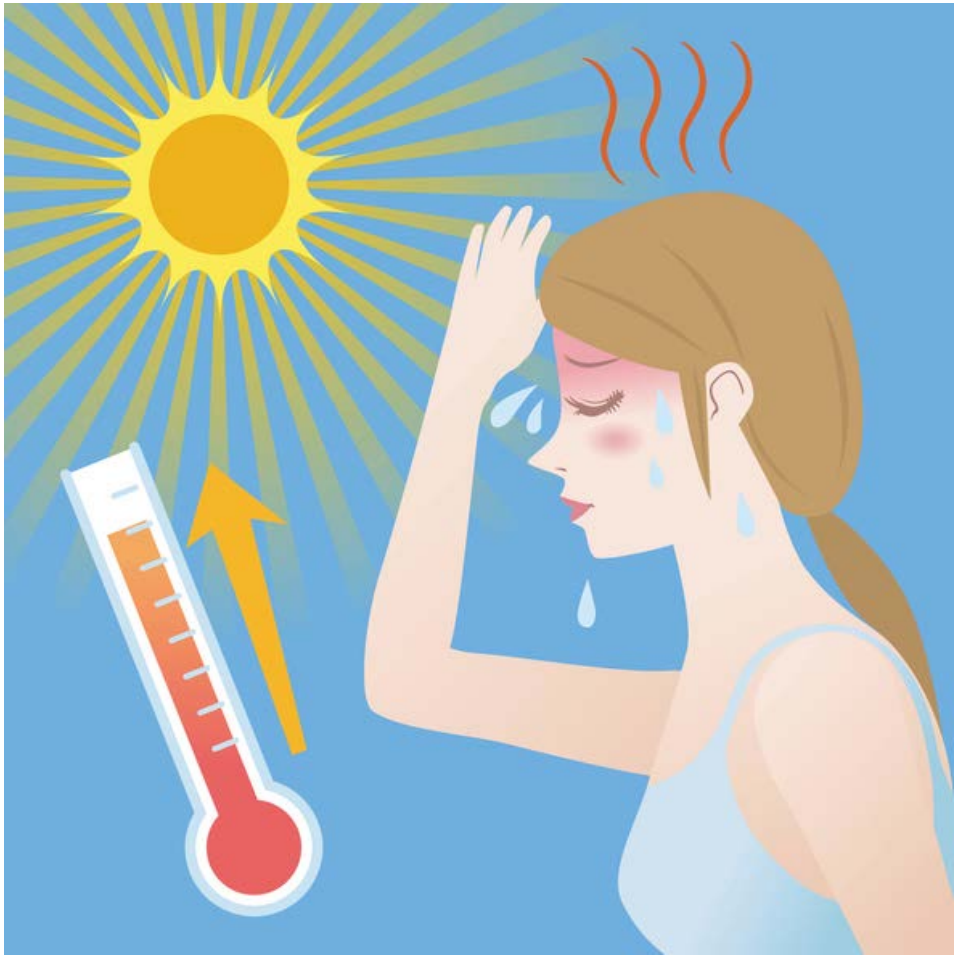


Evaporation Rate of Excipients Influences Percutaneous Absorption



https://innovareacademics.in/journals/index.php/ijcpr/article/download/25886/14261/119954

Temperature and Relative Humidity Influence Formulation Evaporation Rate



https://qph.fs.quoracdn.net/main-qimg-1d3774bfe2610597783cda119b8c1233

Temperature Control
(31-33°C (87.8-91.4°F)
Humidity Control

(humidifier set at 45% RH)

miniMUsT Clinical Design

Temp 31-33°C (87.8-91.4°F)
Humidity 45% RH

(0, 80 and 160 min) Sunscreen Application

Procedure Day (hour)	zero	1	2	3	4	5	6	7	8	9	10	11	12
Sampling time points 18 total	predosing		2:00	3:00	3:30 4:00	4:30 5:00	5:30 6:00	6:30 7:00	7:30 8:00	8:30 9:00	9:30 10:00		12:00

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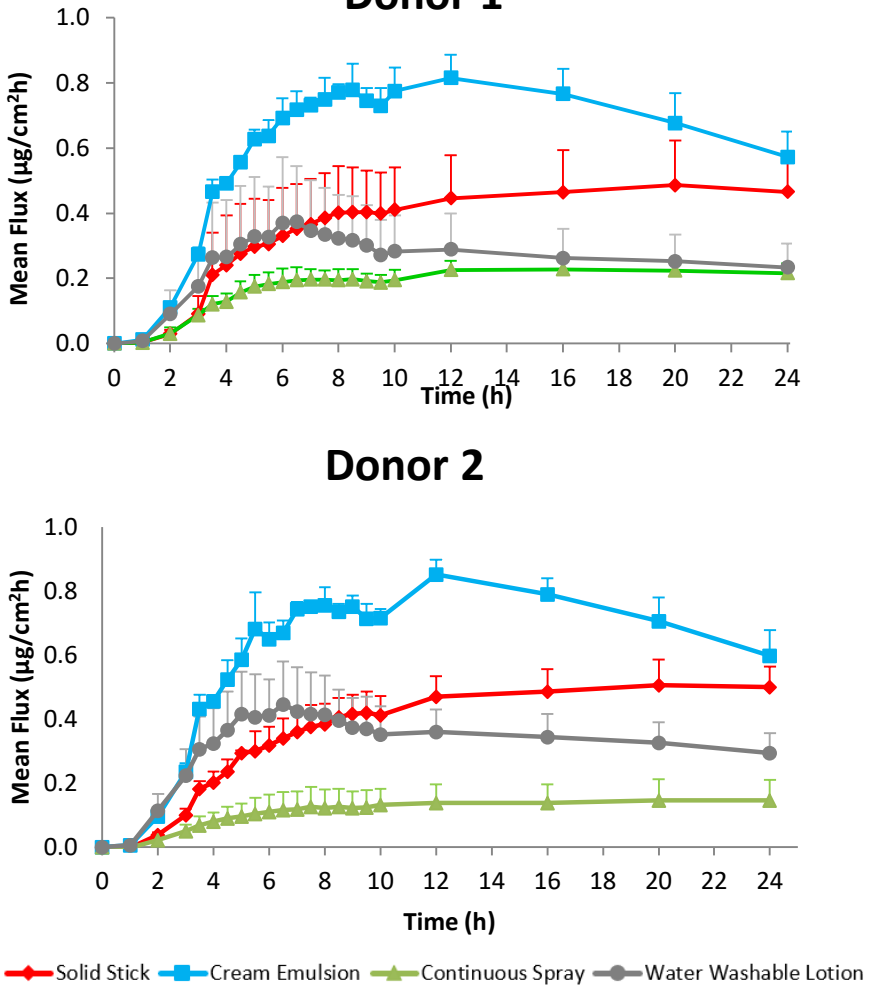
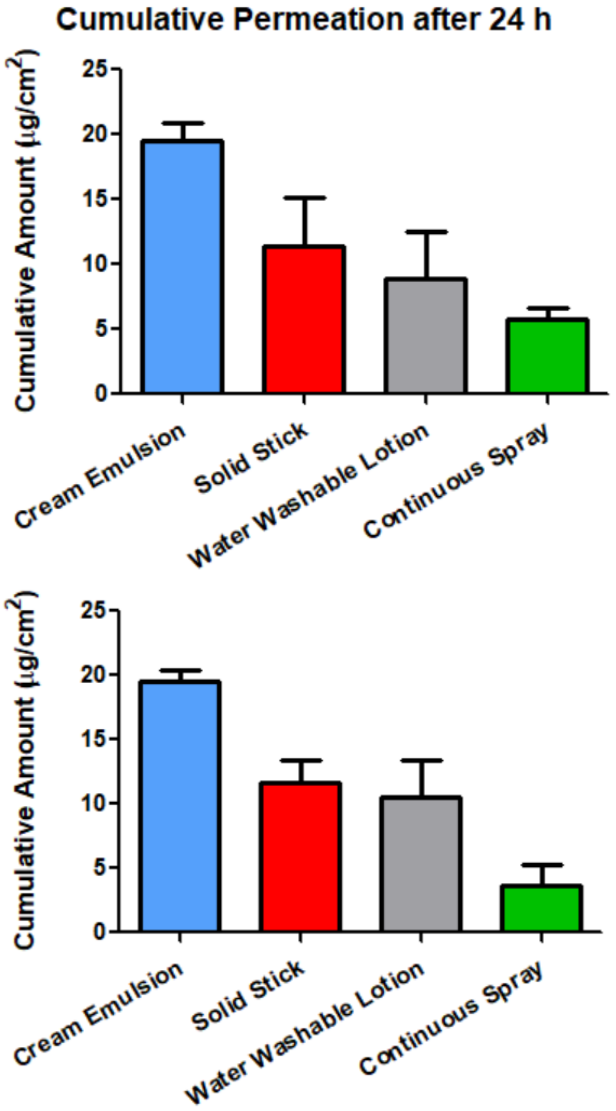
In Vitro Results

Human Skin Profile for All Products to be Tested In Vivo (Mean ± SD) (3 replicates/donor)





Goals

- Develop a streamlined testing method that is more clinically and environmentally harmonized for quantifying sunscreen UV filter safety levels
  - Extrapolate full body exposure data from surrogate 800 cm^2 thigh study
  - Make sure that skin surface temperature and relative humidity are controlled so that products can be compared to each other
- Generate more accurate information as to the potential total permeation of oxybenzone in worst-case scenarios
- Show the difference that formulation makes advocating for final formulation testing for permeation
- Optimized in vitro study protocols may help to decrease the number of clinical trials required for UV filter product testing

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Dr. Tom Franz

Clinical Study Team
Dr. Jeff Fink
UMB GCRC nurses
Clinical Study Participants

Current Lab Members
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- Sherin Thomas (Lidocaine, buprenorphine, diclofenac)
- Dana Hammell, MS (Lab Manager and Document Control)
- Dani Fox (Clinical Coordinator)
- Sagar Shukla (Lidocaine)
- Paige Zambrana (Sunscreens & glucose monitoring, fentanyl)
- Qingzhao Zhang (Metronidazole & rivastigmine)

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  TDS Heat Effects & OGD IVIVC

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- U01FD004955

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This project has been approved by the UMB Institutional Review Board for human subject research