

Heat Effects on Multi-Application Sunscreen Use: IVPT 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



A company developing and testing topical drug products



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Lab Members

- Sagar Shukla, PharmD
- Sherin Thomas
- QingZhao Zhang
- Paige Zambrana
- Dana Hammell, M.S.
- Danielle Fox

Paige Zambrana PhD thesis project





Methods of Assessment of Bioavailability

IVPT



Microdialysis



Tape stripping



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Pharmacodynamic assay (vasoconstriction)



Urine levels



7

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY In-Line Diffusion Cells











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
- design an in vivo study, under harmonized conditions, to evaluate the pharmacokinetics of oxybenzone absorption in healthy human volunteers for two sunscreen lotion products each containing 6% oxybenzone

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
- \rightarrow Minimize/Reduce in vivo clinical studies





Influence of Heat



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





1) **↑** Diffusivity of Drug from its Vehicle







Influence of Heat on Percutaneous Absorption

2) 个 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



Study Design





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

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





6

12

Time (h)

18

24

1.5-

1.0-

0.5

0.0

0

Flux (μg/cm²h)



IVPT Data: Lotion 1

| Formulation | Donor (human skin) | Heat Enhancement Ratio (Heat/No Heat) | | ^{**} p value (Heat vs No Heat) | |
|-------------|--------------------------|---|--------------|--|--------------|
| | | J _{max} | Cum. Amt. | J _{max} | Cum. Amt. |
| Lotion 1 | 1a | 2.10 | 2.05 | 0.0036 | 0.0036 |
| | 2a | 2.22 | 2.20 | 0.0126 | 0.0140 |
| | 3 | 1.91 | 2.23 | 0.0353 | 0.0241 |
| | 4 | 2.54 | 2.56 | 0.0091 | 0.0019 |
| | Mean (n=4 donors) | 2.18 | 2.32 | 0.0413 | 0.0605 |

*Heat enhancement in Jmax and Cum. Amt. at 6 h was calculated **p values were obtained from unpaired t test for individual donors and paired t test for mean of four donors

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











IVPT Data: Lotion 2

| Formulation | Donor (human skin) | Heat Enhancement Ratio (Heat/No Heat) | | ^{**} p value (Heat vs No Heat) | |
|-------------|--------------------------|---|--------------|--|--------------|
| | | J _{max} | Cum. Amt. | J _{max} | Cum. Amt. |
| Lotion 2 | 1b | 1.35 | 1.43 | 0.018 | 0.0082 |
| | 2b | 1.79 | 1.97 | 0.0417 | 0.0227 |
| | 3 | 1.34 | 1.62 | 0.2545 | 0.1265 |
| | 4 | 1.10 | 1.36 | 0.5953 | 0.2131 |
| | Mean (n=4 donors) | 1.42 | 1.59 | 0.0934 | 0.0322 |

*Heat enhancement in Jmax and Cum. Amt. at 6 h was calculated

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

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



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 will be analyzed for oxybenzone using a validated LC-MS/MS method
- 2 mg/cm² application → 800 cm²





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 cm²



Serum Concentration vs Time Profile oxybenzone absorption under non-heated conditions for two healthy human volunteers







Goals

- Develop a streamlined testing method that is more clinically and environmentally harmonized for sunscreen UV filter safety levels
 - Extrapolate full body exposure data from 800 cm² thigh study
 - Make sure 37 degrees C or higher temp does not significantly influence the product's absorption
- Generate more accurate information as to the 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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<u>Clinical Study Team</u>

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Current Lab Members

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- Dana Hammell, MS (Lab Manager and Document Control)
- Dani Fox (Clinical Coordinator)
- Sagar Shukla (Lidocaine)
- Paige Zambrana (Sunscreens & glucose monitoring, fentanyl)
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This project has been approved by the UMB Institutional Review Board for human subject research