



IVPT Studies with Topical and Transdermal Products

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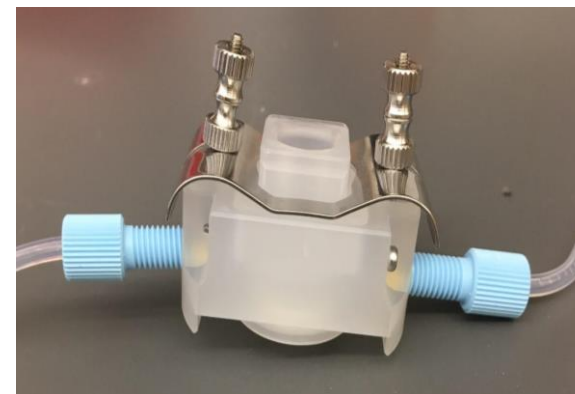
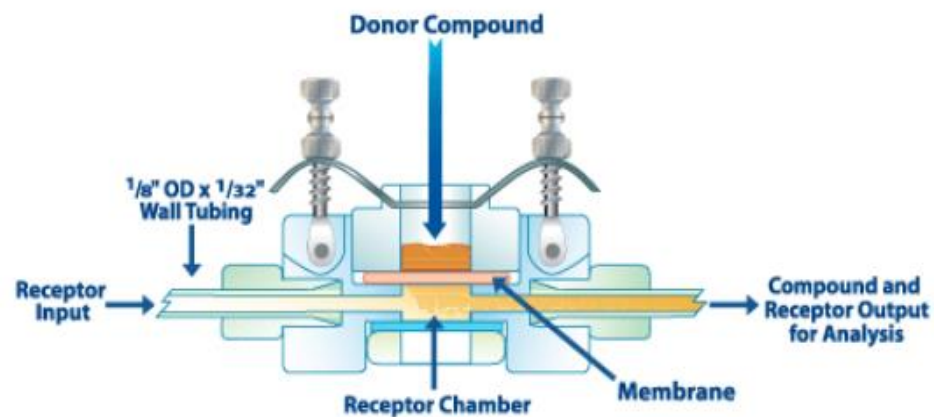
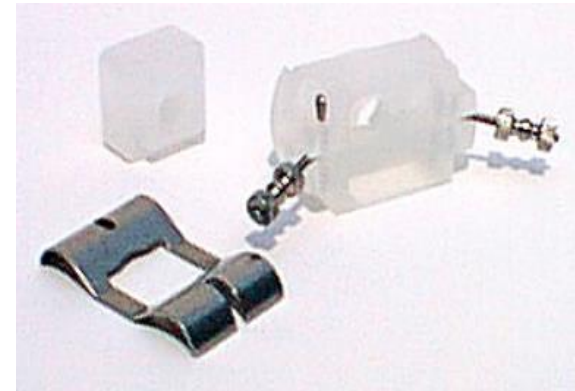
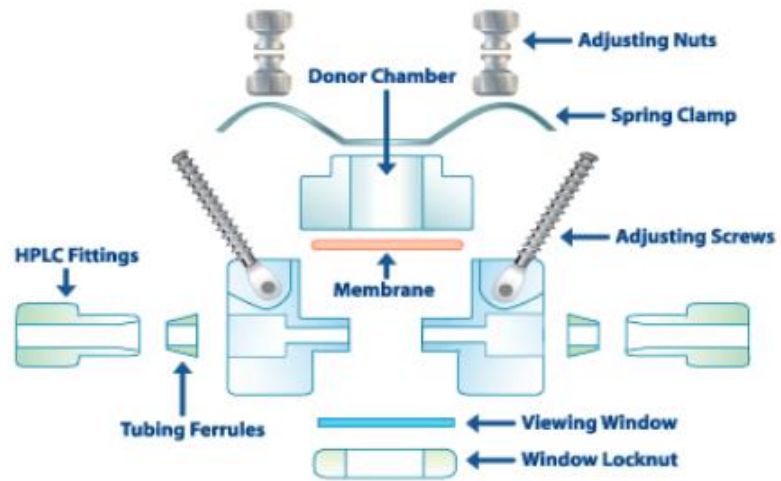
- Chief Scientific Officer and Co-Founder of



- A company developing and testing complex drug products



In-Line Diffusion Cells



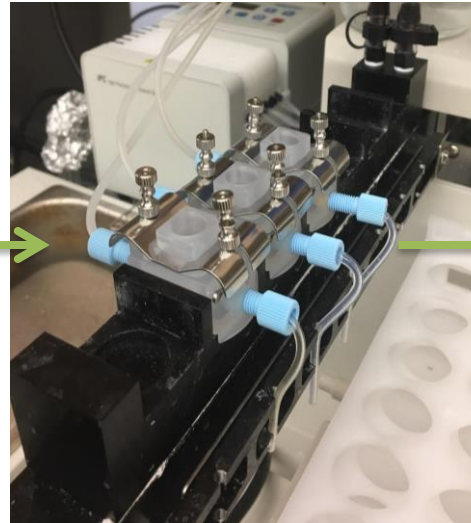


IVPT (In vitro permeation test)

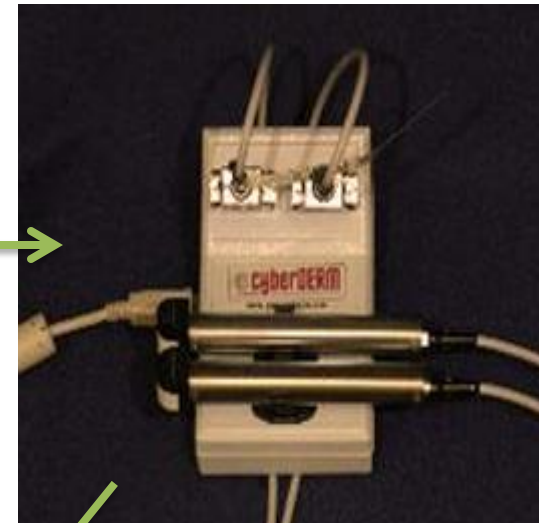
1. Dermatome



2. Assemble setup



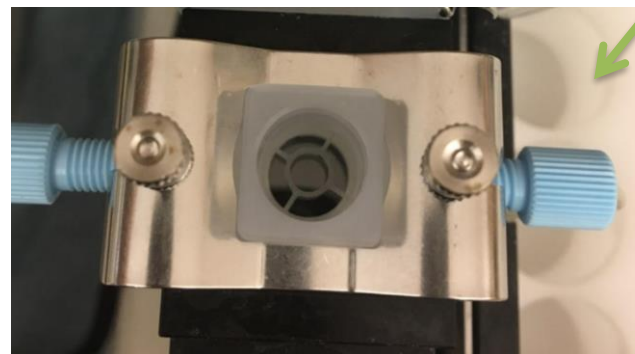
3. Record TEWL



4. Dose Product





Inverted HPLC vial



Positive displacement
pipette

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 post-approval changes
- Minimize/Reduce in vivo clinical studies
(Save  & )
- However, if no full IVIVC for the product/API

Discriminating IVPT studies done with standardized methods in human skin may also be surrogates for some bioequivalence studies, scale-up and post-approval changes



Heat Exposure from Many Sources

Including the Sun



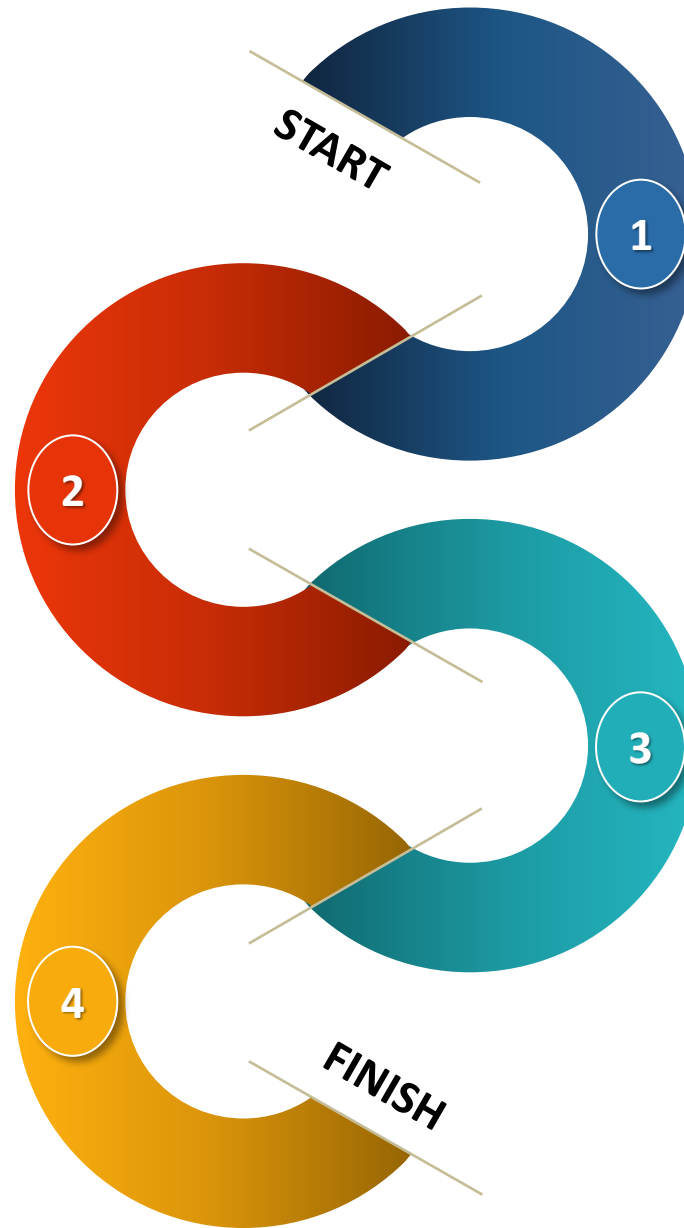


General Approach

In Vivo Studies in Humans

Does the drug show
increased permeation
in vivo?

Explore IVIVC
Can in vitro data be
used to predict in vivo
results under the
influence of heat?



Exploratory IVPT Studies

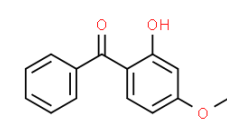
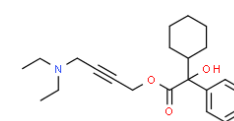
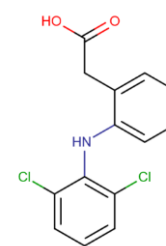
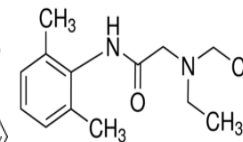
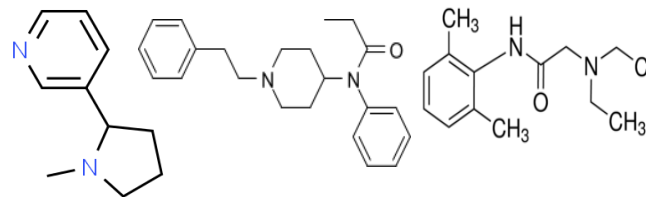
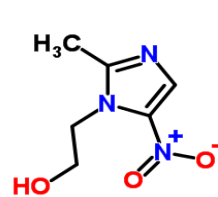
Does the drug show
increased permeation
in vitro?

Pivotal IVPT Studies

Is the effect of heat
similar in vitro and in
vivo under
harmonized study
conditions?

Compound Properties

	Metronidazole	Nicotine	Fentanyl	Lidocaine	Diclofenac	Oxybutynin	Oxybenzone
Molecular wt (g/mol)	171.15	162.23	336.50	234.34	296.10	357.50	228.24
Water solubility (mg/L)	11,000 (@ 25°C)	1 x 10 ⁶ (@ 25°C) [miscible]	200 (@ 25°C)	410 (@ 30°C)	2.37 (@ 25°C)	50 (@ 25°C)	3.7 (@ 25°C)
LogP	-0.02	1.17	4.05	2.44	4.51	4.30	3.79
pKa	2.57, 15.42	8.50	8.99	8.01	4.15	8.04	7.60



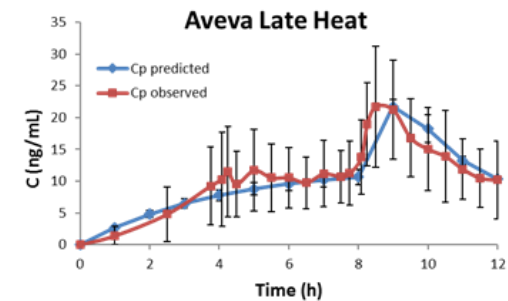
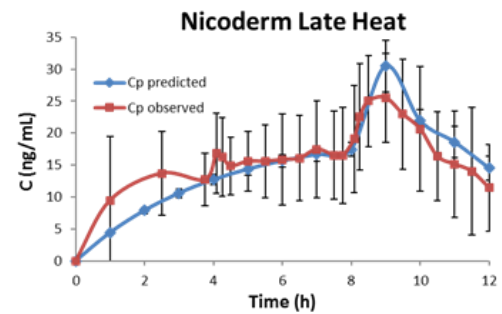
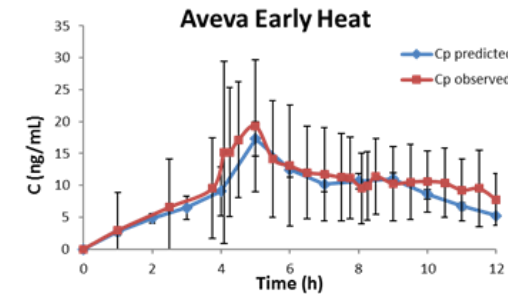
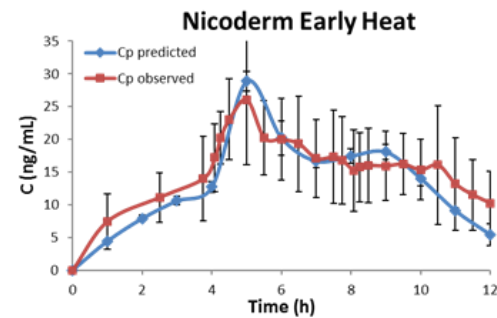
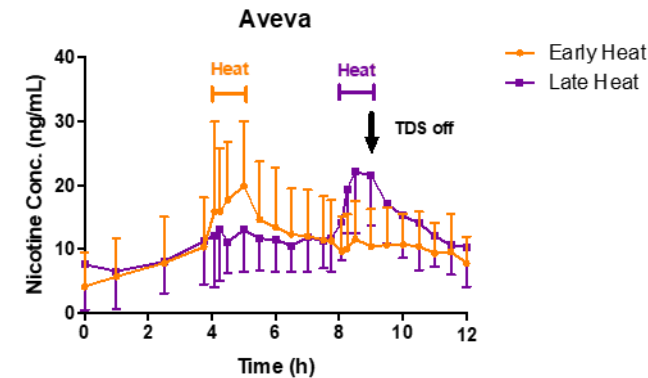
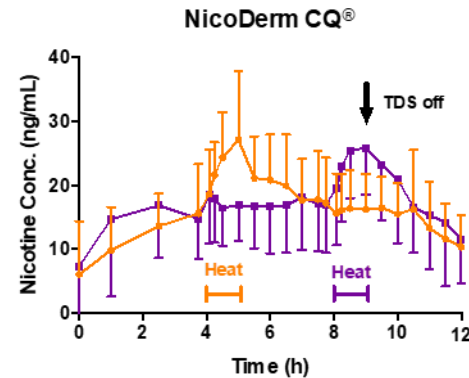
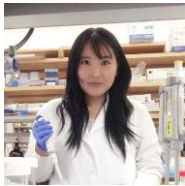
<https://pubchem.ncbi.nlm.nih.gov/>

Strong IVIVC observed for nicotine TDS, including heat effects

Humans

Mean \pm SD
n=10 volunteers

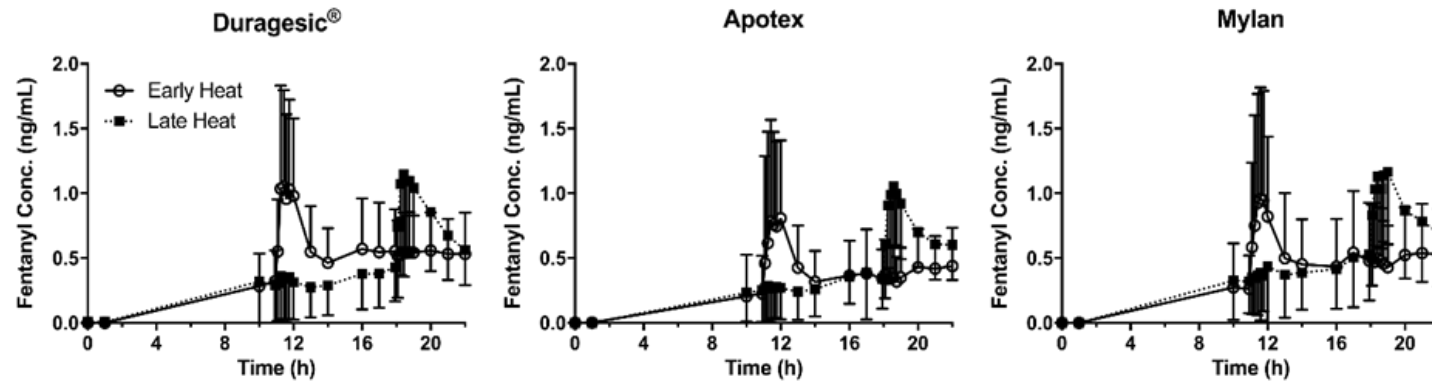
Predicted
from IVPT



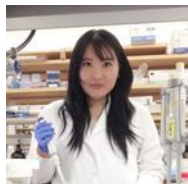
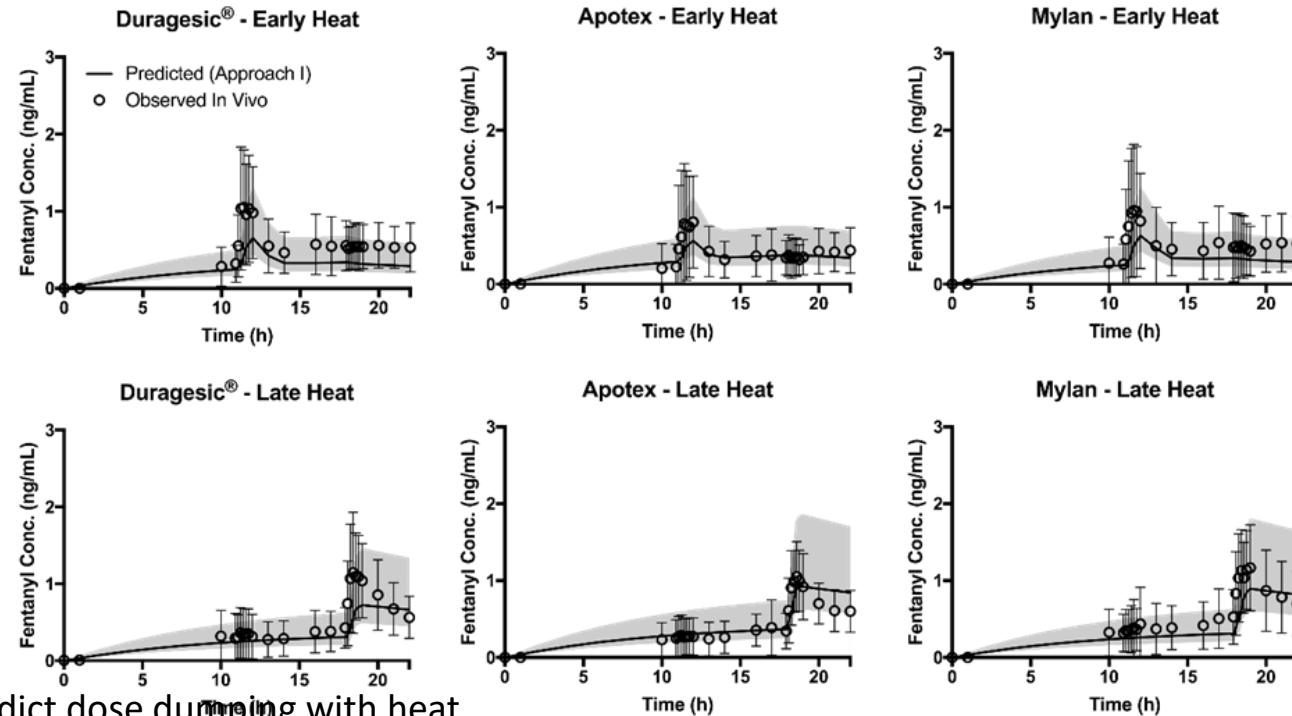
Weaker IVIVC observed for fentanyl TDS

Humans

Mean \pm SD
n=10 volunteers

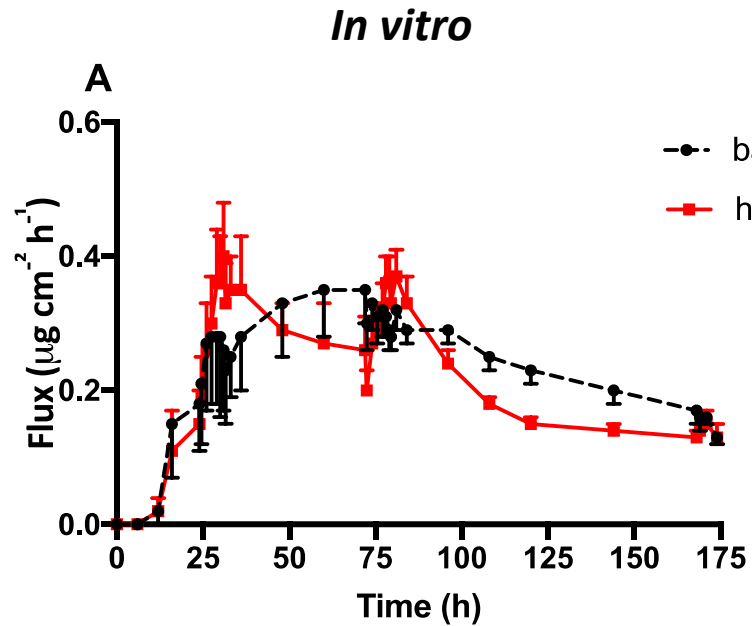


Predicted from IVPT



- Can still predict dose dumping with heat
- Soo Hyeon Shin, Mingming Yu, Dana C. Hammell, Priyanka Ghosh, Sam G. Raney, Hazem E. Hassan, Audra L. Stinchcomb. J. Cont. Release (under review) 2021

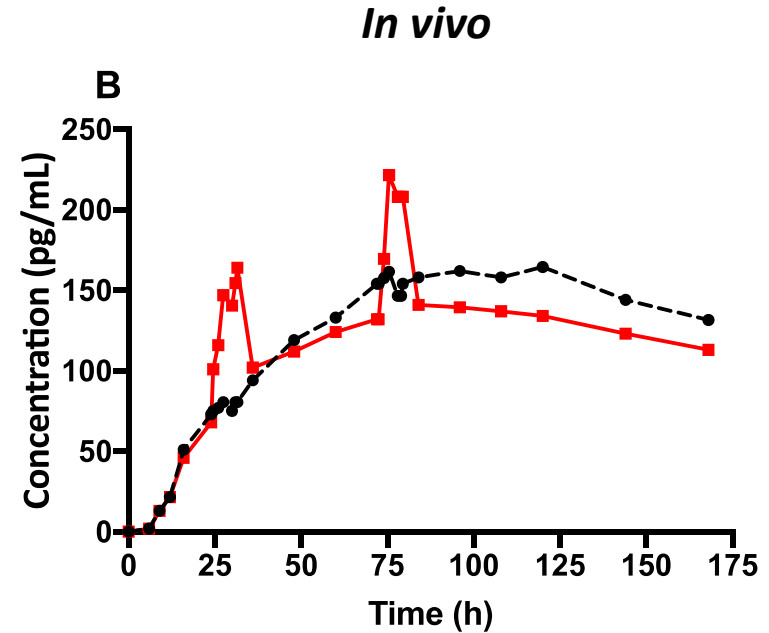
IVPT and PK Data for BuTrans[®]



Flux profile for Butrans[®] (mean \pm SEM) (n=4 human skin donor, 4 replicates/donor) from IVPT data.

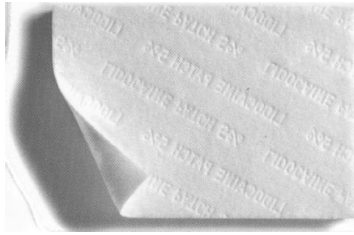


Sherin Thomas thesis, manuscript pending



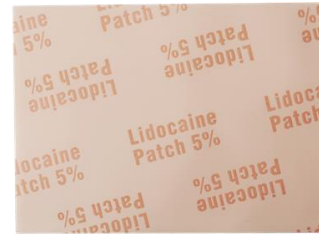
Clinical Pharmacology and Biopharmaceutics Review document for BUTRANS[®] available at Drugs@FDA

IVPT Data for Lidocaine



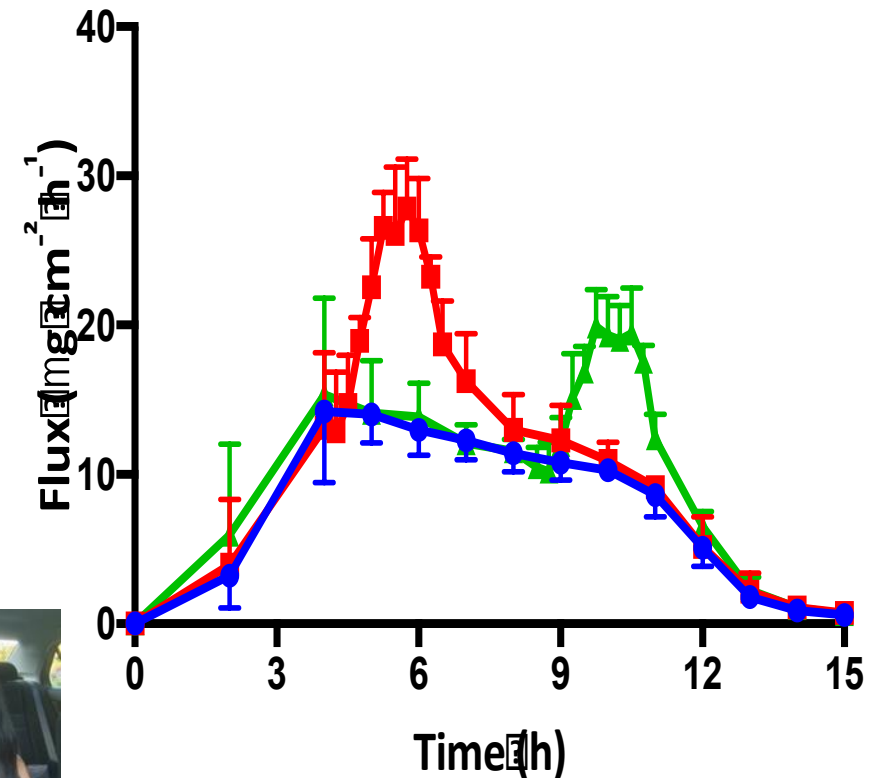
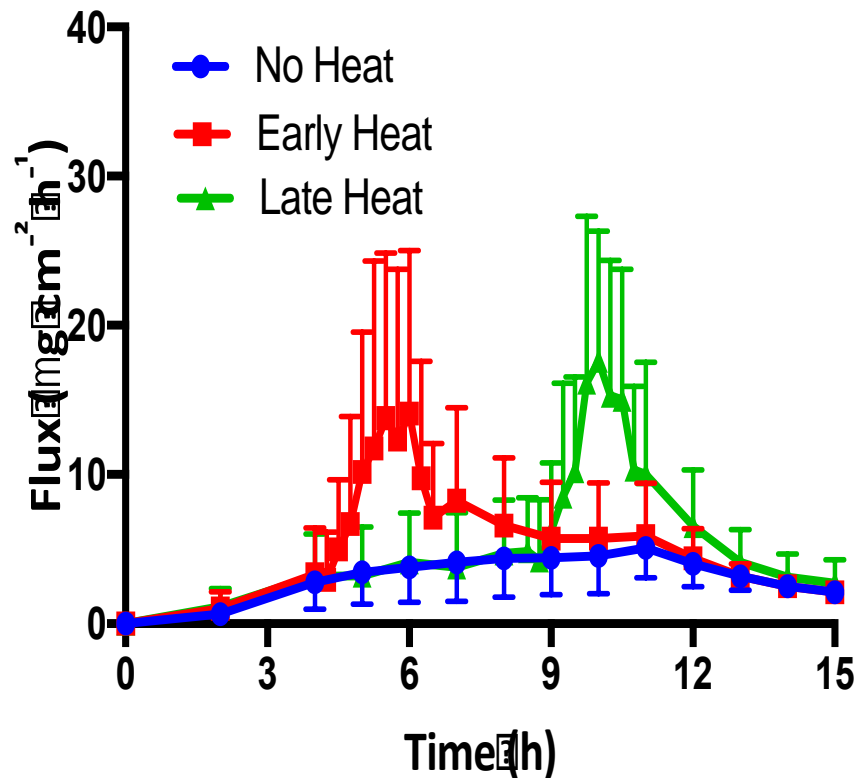
RLD--hydrogel

Product A (n=5)

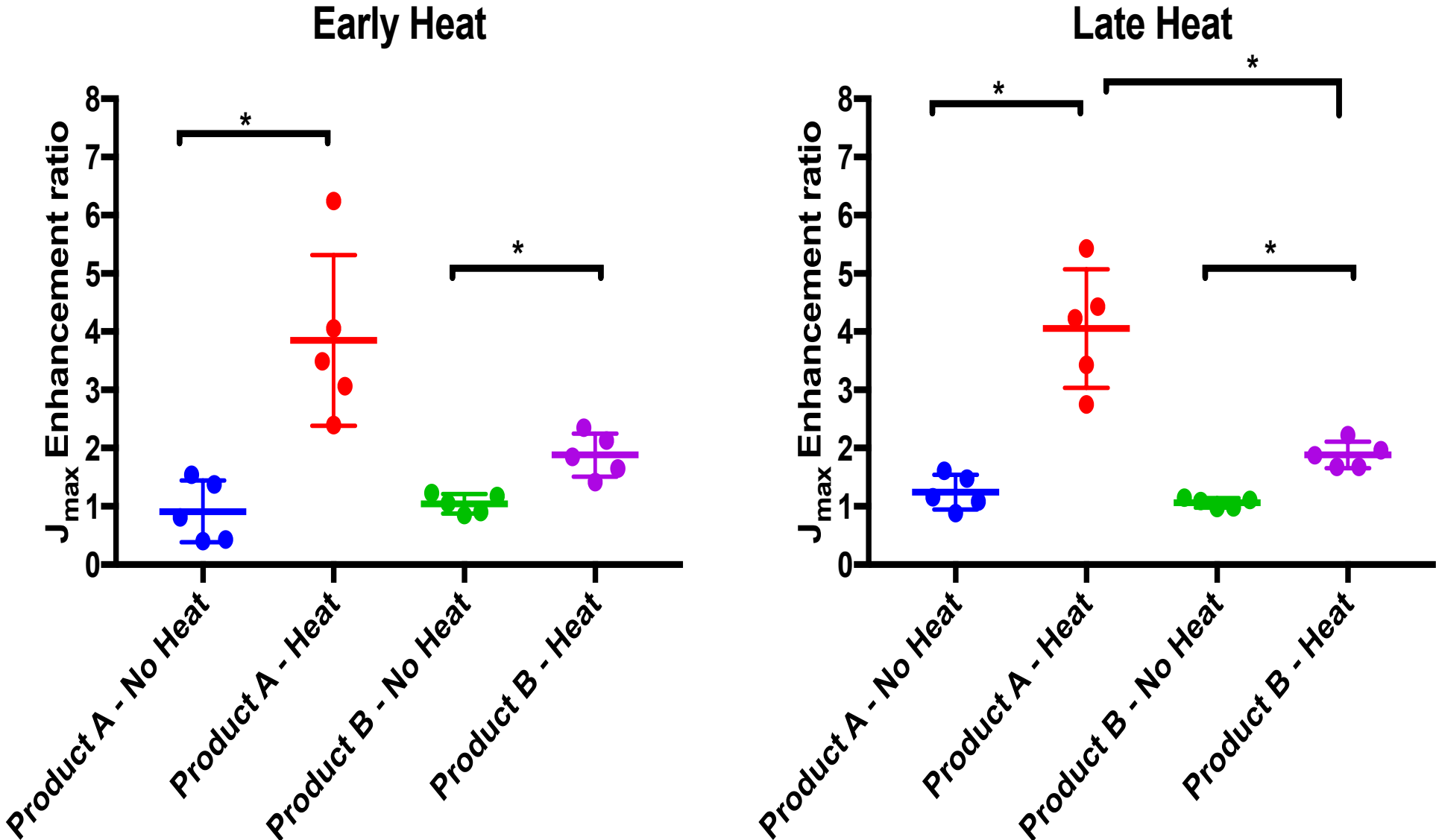


Generic--PIB

Product B (n=5)



IVPT Data for Lidocaine





Diclofenac Products

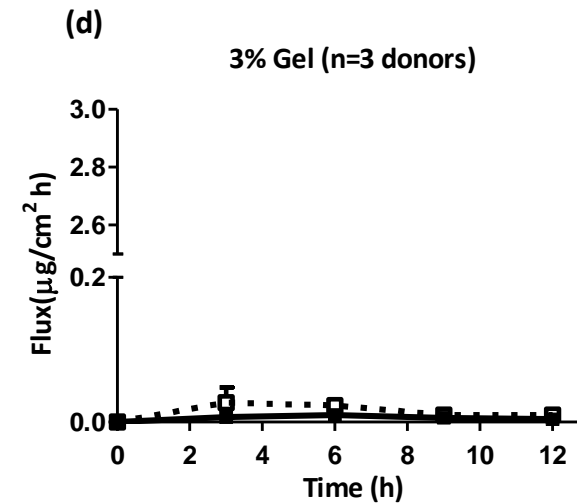
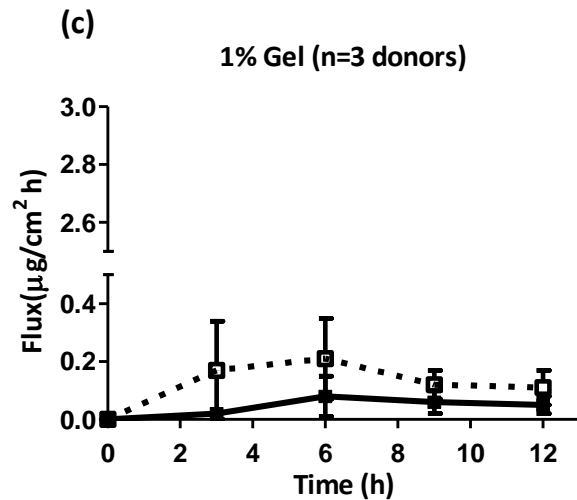
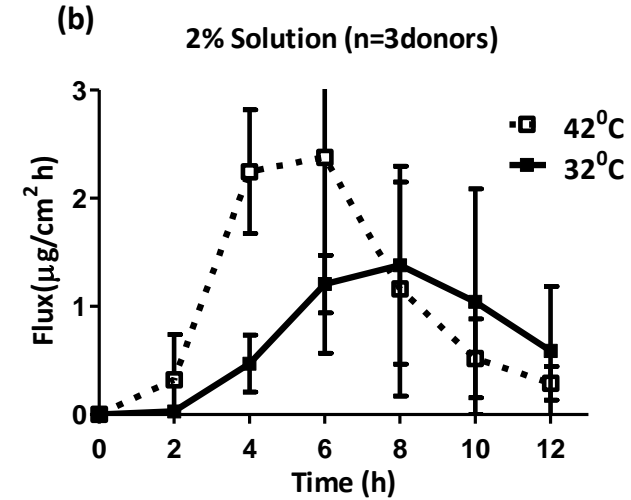
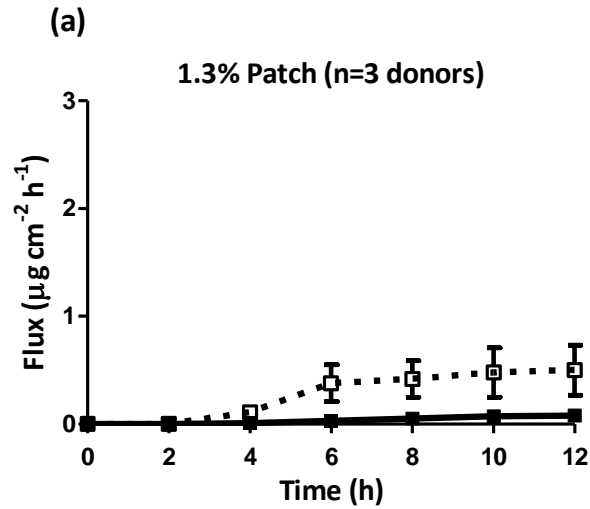
	1.3 % Patch	2% Solution	1% Gel	3% Gel
Inactive ingredients	Adhesive in aqueous base containing sodium polyacrylate, sodium carboxymethylcellulose	DMSO, ethanol, purified water, propylene glycol, hydroxypropyl cellulose	Carbomer homopolymer Type C, cocoyl caprylcaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, strong ammonia solution	Hyaluronate sodium, benzyl alcohol, polyethylene glycol monomethyl ether, purified water
Dose applied	-	5 mg/cm ²	10 mg/cm ²	20 mg/cm ²
(Equivalent amount of diclofenac)	(878 mg/cm ²)	(approx. 100 µg/cm ²)	(approx. 100 µg/cm ²)	(approx. 300 µg/cm ²)

S. Thomas, S.H. Shin, D.C. Hammell, H.E. Hassan, A.L. Stinchcomb, Effect of controlled heat application on topical diclofenac formulations evaluated by in vitro permeation tests (IVPT) using porcine and human skin, Pharm. Res., 37 (2020) 49.





Diclofenac Product IVPT Results on Human Skin— Continuous Heat



Tested Metronidazole Products

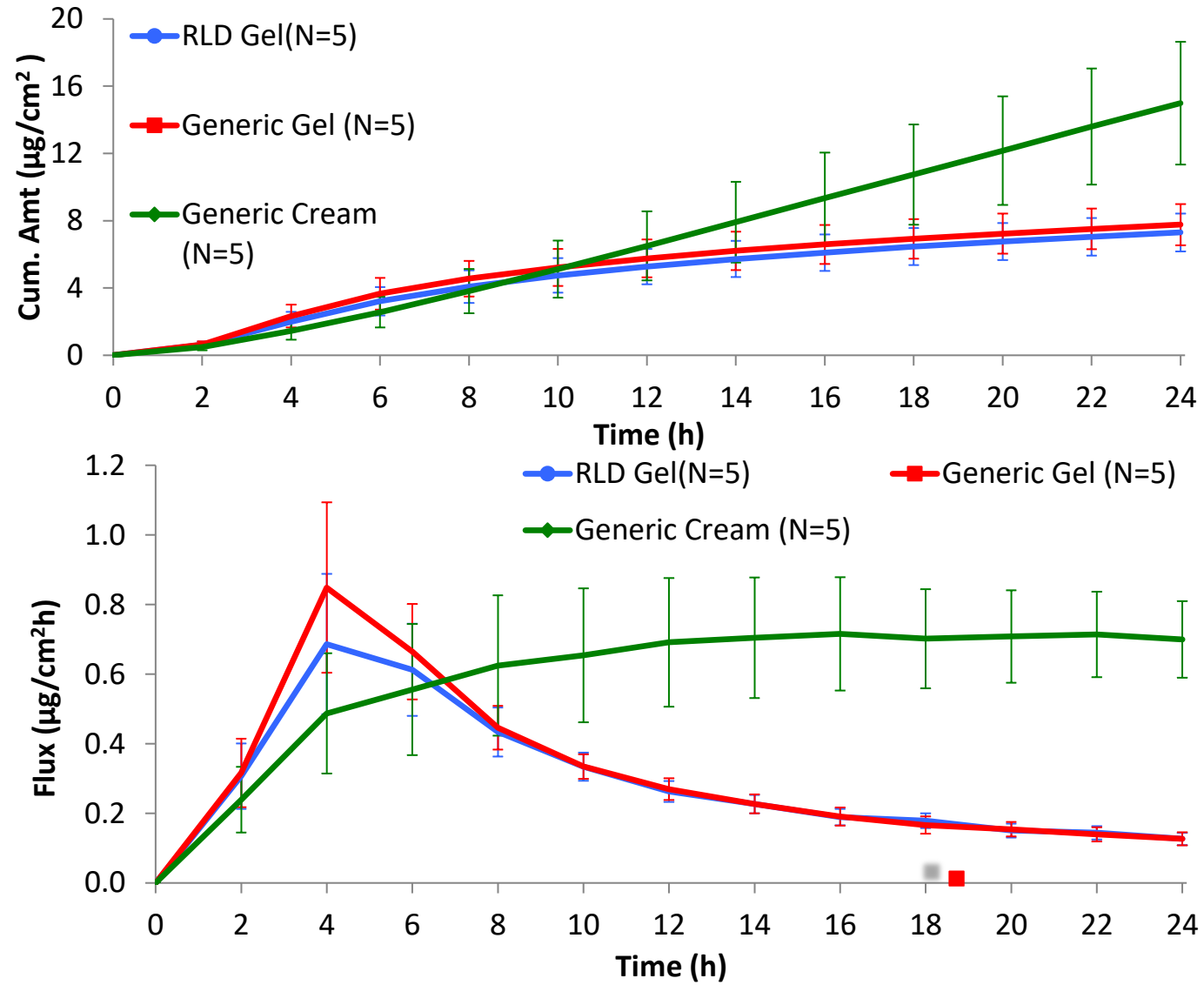
	Metronidazole gel, 0.75% (RLD) NDC: 66993-962-45	Metronidazole gel, 0.75% (generic) NDC: 0115-1474-46	Metronidazole cream, 0.75% (generic) NDC: 0168-0323-46
Inactive ingredients	0.8 mg of methylparaben and 0.2 mg of propylparaben as preservatives in a gel consisting of carbomer 940, edetate disodium, propylene glycol, purified water and sodium hydroxide	Carbopol 980, edetate disodium, methylparaben, propylene glycol, propylparaben, purified water and sodium hydroxide	Emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid, sodium hydroxide and purified water
Formulation	topical gel	topical gel	topical cream
Manufacturer	Prasco Laboratories	Tolmar Inc	Fougera Laboratories
Distributor		Impax Generics	



Qingzhao Zhang thesis, 2021

Metronidazole

Formulation comparison (IVPT Human skin, Mean \pm SEM; N=5 donors)





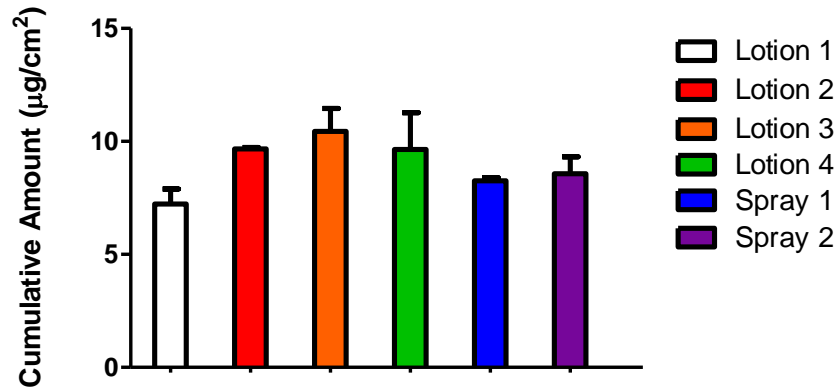
Sunscreen Products



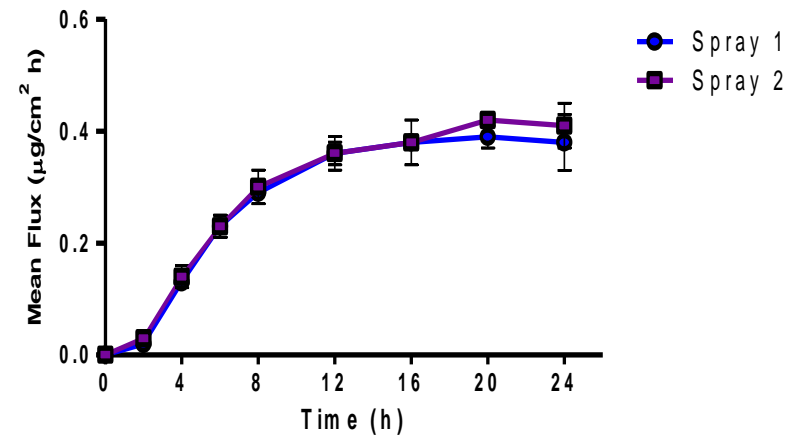
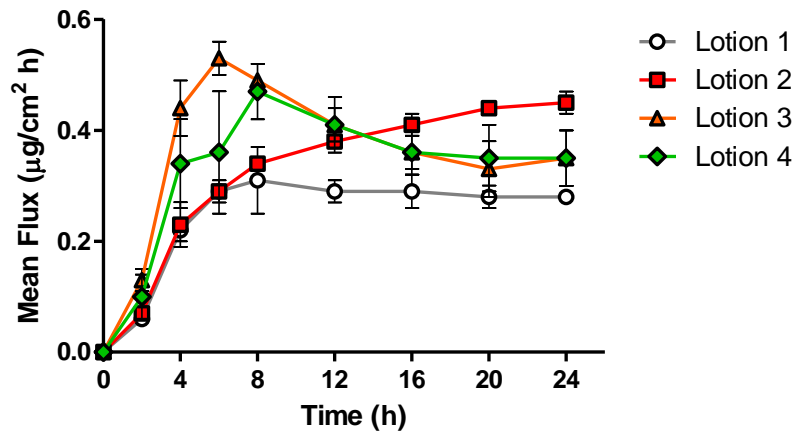
Paige Zambrana thesis
project 2021



Product Comparison with Single Application



Formulation	J_{max}		Cum. Amt.
Lotion 1	8 h	0.31	7.23 ± 0.66
Lotion 2	24 h	0.45	9.67 ± 0.06
Lotion 3	6 h	0.53	10.45 ± 1.01
Lotion 4	8 h	0.47	9.64 ± 1.63
Spray 1	20 h	0.39	8.25 ± 0.14
Spray 2	20 h	0.42	8.57 ± 0.74



Mean ± SD, 1 donor, 3 replicates per product

- Highest cumulative permeation and J_{max} from Lotion 3
- Sprays and lotions follow different flux patterns

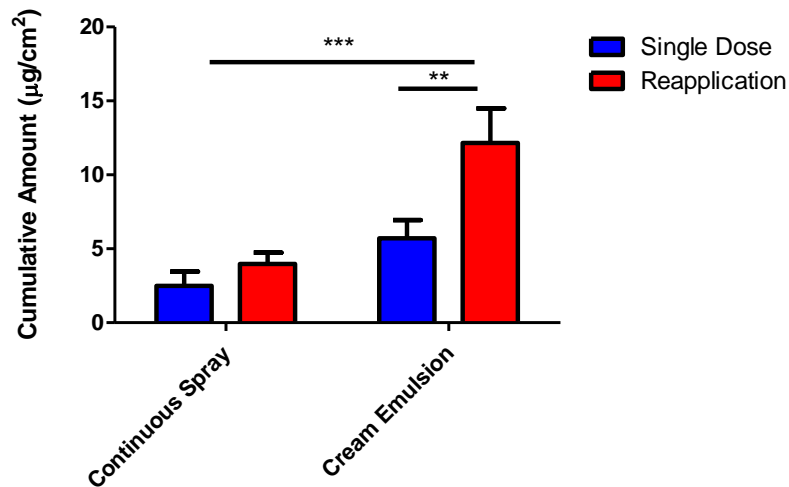


Multiple Dosing

- 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
 - Dose 0, 80, 160 min consistent with product labeling

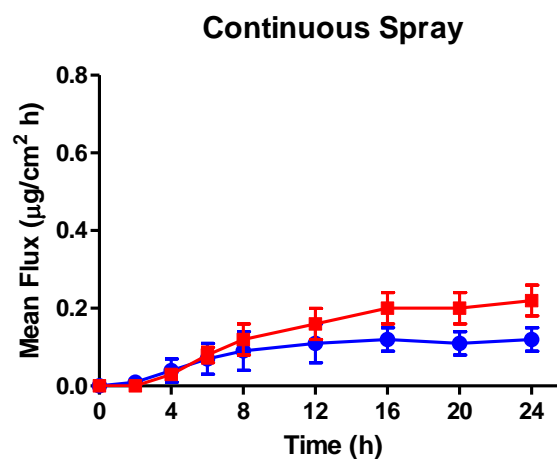
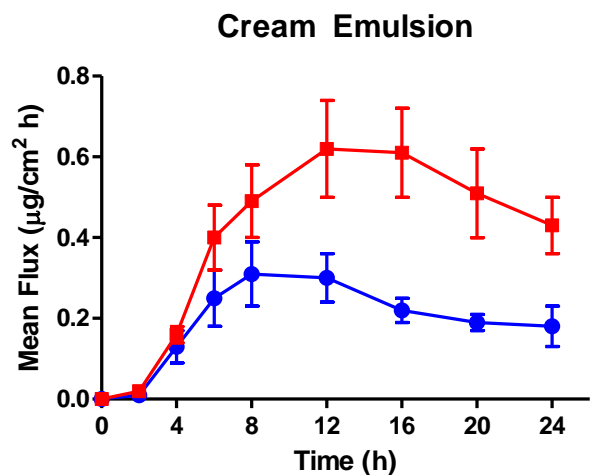


Reapplication on *Ex Vivo* Human Skin



Formulation	Reapplication Enhancement Ratio (Reapplication /Single dose)		*p value (Reapplication vs No Reapplication)	
	J_{\max}	Cum. Amt.	J_{\max}	Cum. Amt.
Cream Emulsion	2.00	2.13	* 0.017	* 0.013
Continuous Spray	1.83	1.60	* 0.031	0.100

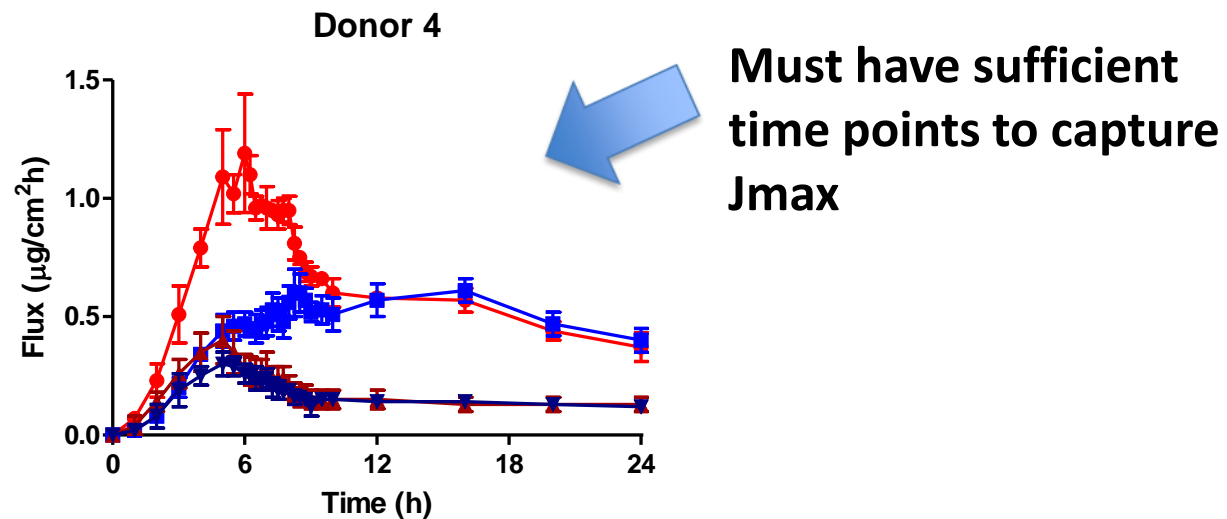
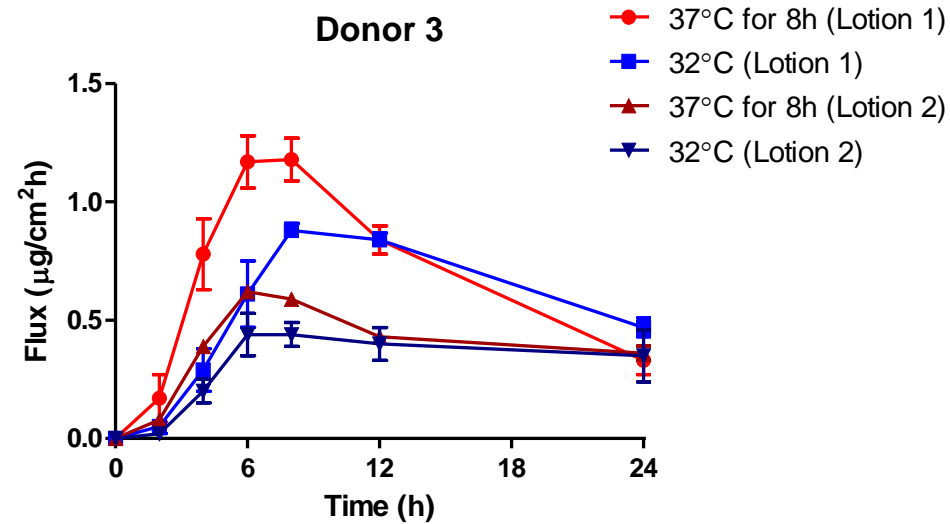
*p values were obtained from unpaired t test



Mean \pm SD, 1 donor, 3 replicates

- Shift in T_{\max} from 8 h for single application to 12 h with reapplication
- No shift in T_{\max} for spray formulation
- Reapplication statistically increased cumulative oxybenzone for cream emulsion formulation
- Formulations are statistically different from each other in cumulative permeation

Flux profile comparison of Lotion 1 vs Lotion 2 for two human skin donors (mean \pm SD) 8 h heat



Sunscreen Selection

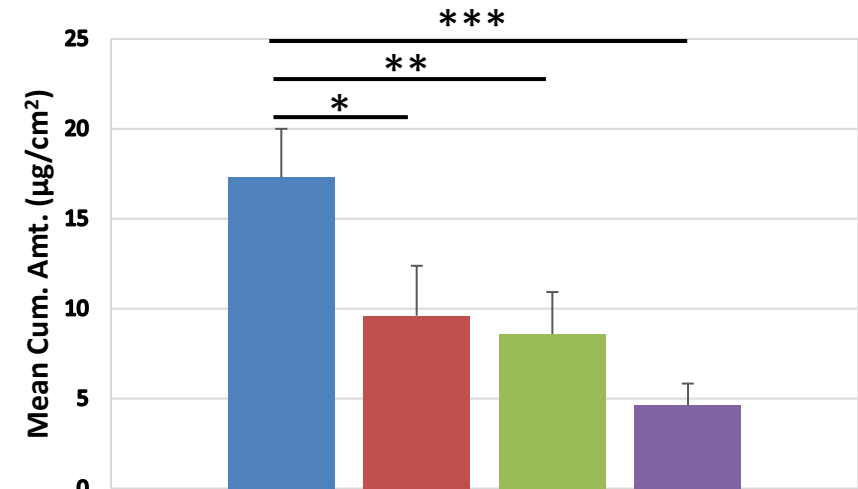
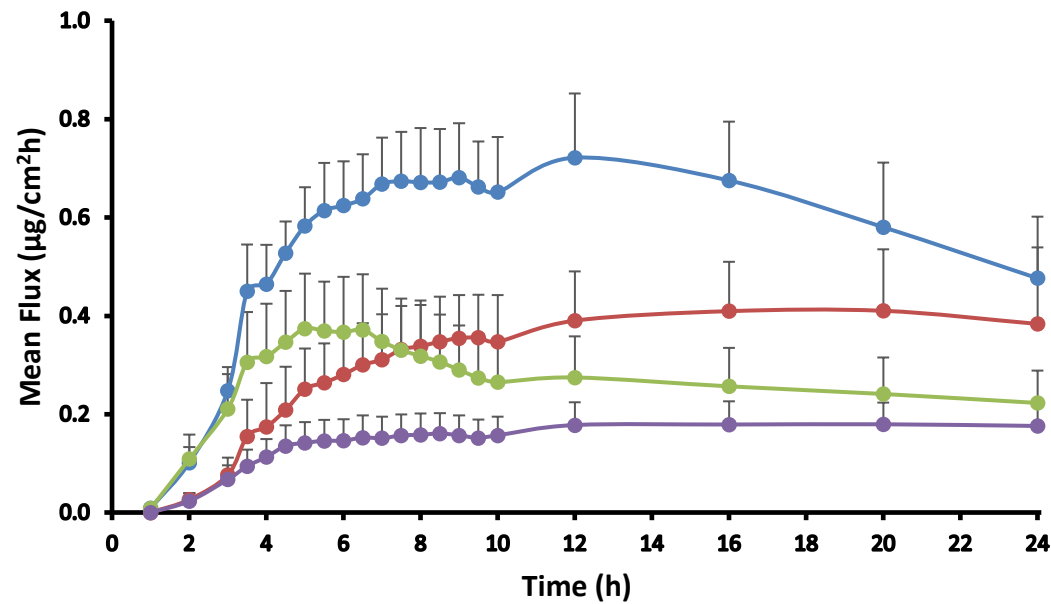


	Cream Emulsion	Solid Stick	Lotion	Continuous Spray
Active Ingredients	Oxybenzone 6% Avobenzzone 3% Homosalate 15% Octisalate 5% Octocrylene 10%	Oxybenzone 6% Avobenzzone 3% Homosalate 15% Octisalate 5% Octocrylene 10%	Oxybenzone 6% Avobenzzone 3% Homosalate 15% Octisalate 5% Octocrylene 10%	Oxybenzone 6% Avobenzzone 3% Homosalate 10% Octisalate 5% Octocrylene 10%
Inactive Ingredients	Water, butylene glycol, microcrystalline cellulose, glyceryl stearate, behenyl alcohol, benzyl alcohol, diethylhexyl syringylidenemalonate, tocopherol (vitamin E), retinyl palmitate (vitamin A), sodium ascorbyl phosphate, stearic acid, palmitic acid, lauryl alcohol, myristyl alcohol, cetyl alcohol, lecithin, caprylic/capric triglyceride, chlorphenesin, cellulose gum, butylated PVP, disodium EDTA	Ozokerite, caprylic/capric triglyceride, C12-15 alkyl benzoate, lauryl laurate, behenyl alcohol, bis-PEG-12 dimethicone beeswax, isopropyl myristate, C20-40 alkyl stearate, synthetic beeswax, tocopherol (vitamin E), polyethylene, sorbitan oleate, VP/hexadecene copolymer, aloe barbadensis leaf extract, stearoxy dimethicone, helianthus annuus (sunflower) seed oil	Water, styrene/acrylates copolymer, silica, beeswax, cyclopentasiloxane, ethylhexylglycerin, glyceryl stearate, PEG-100 stearate, acrylates/dimethicone copolymer, acrylates/c10-30 alkyl acrylate crosspolymer, chlorphenesin, disodium EDTA, triethanolamine, dipotassium glycyrrhizate, BHT, methylisothiazolinone, diethylhexyl 2,6-naphthalate, fragrance	Alcohol denatured, isobutane, acrylates/octylacrylamide copolymer, diethylhexyl syringylidenemalonate, caprylic/capric triglyceride, caprylyl glycol, tocopheryl acetate, mineral oil, aloe barbadensis leaf extract, fragrance

Pivotal IVPT on *Ex Vivo* Human Skin

Application at 0, 80, and 160 min

Skin temperature at 32°C



—●— Cream Emulsion —●— Solid Stick —●— Lotion —●— Continuous Spray

(* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)
Mean \pm SD, 4 donors, 3 replicates per donor

Human Pharmacokinetic (miniMUsT) Study

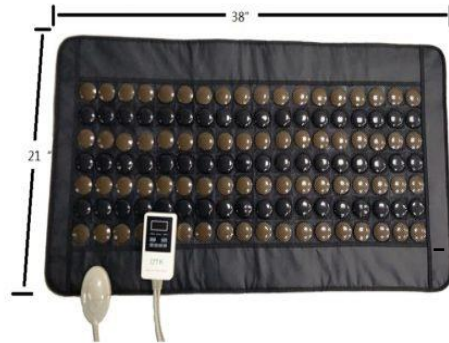
- 12 h open-label, randomized, four-way crossover pharmacokinetic study in healthy human volunteers with minimum one week washout period between sessions
- Controlled skin temperature of 30-34°C and RH 35-55%
- Serum samples analyzed for oxybenzone using a validated LC-MS/MS method
- 2 mg/cm² application → 800 cm² applied 3 times per session

		Temp 30-34°C (86-93.2°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

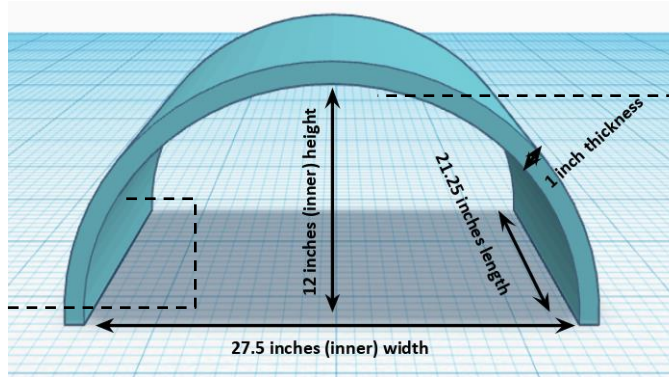


Development of Environmental Control Chamber

IR Heating Pad



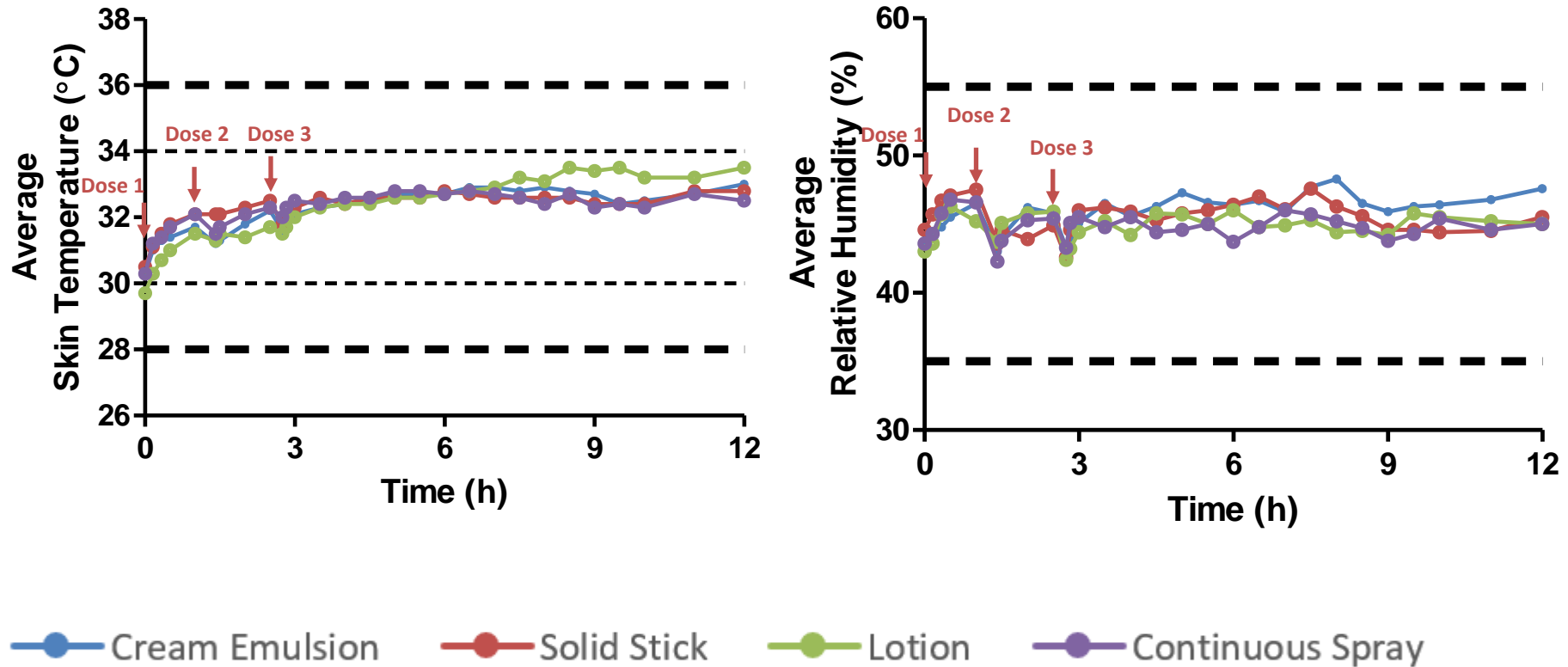
3D Printed Dome



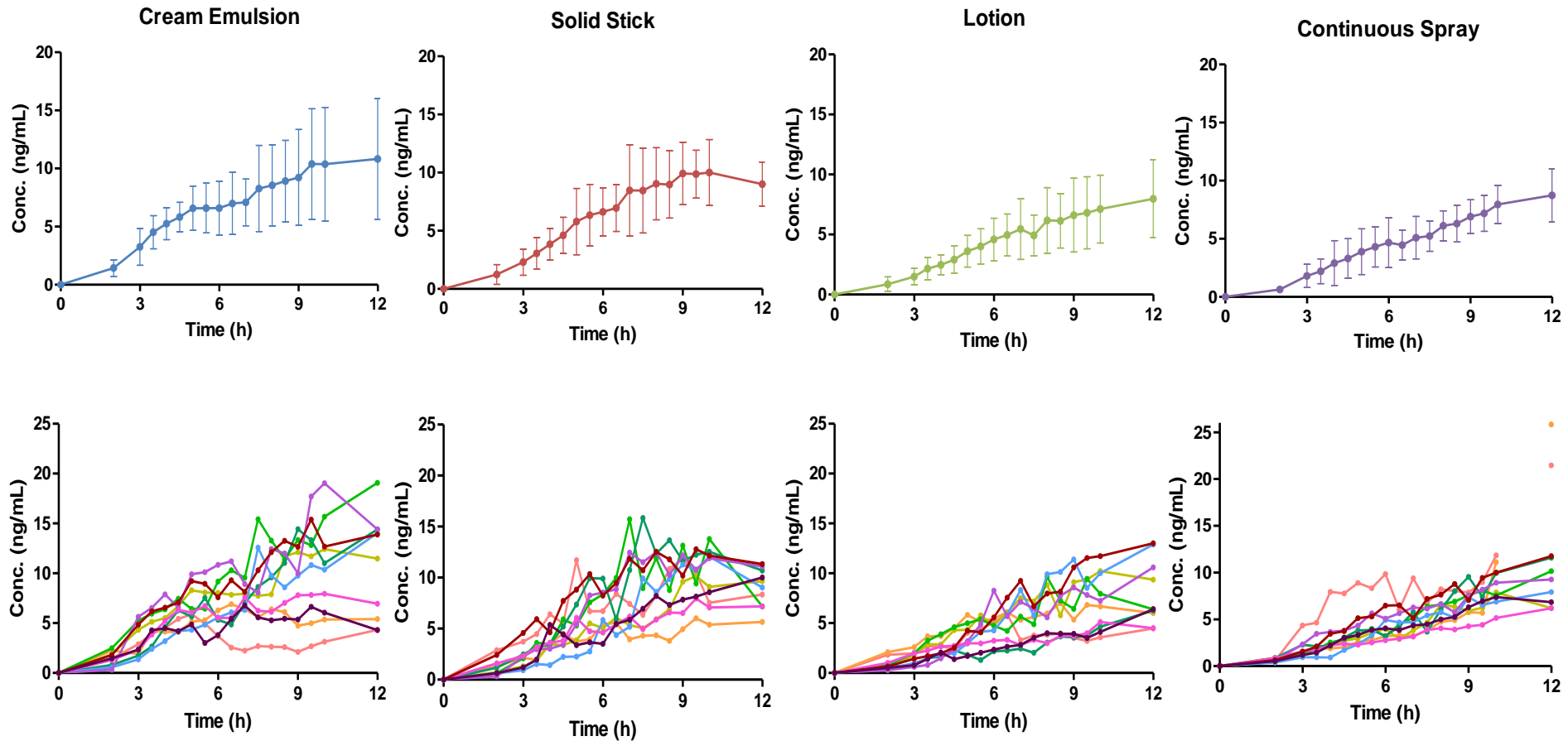
Ultrasonic Humidifier



Clinical & Environmental Conditions Under 3D Dome

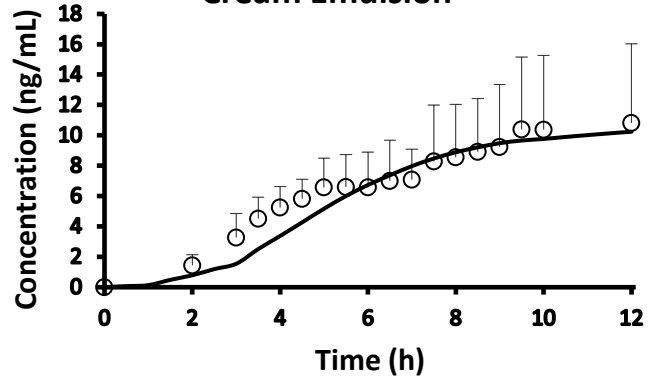


In Vivo Results (N=10 Volunteers; Mean \pm SD)



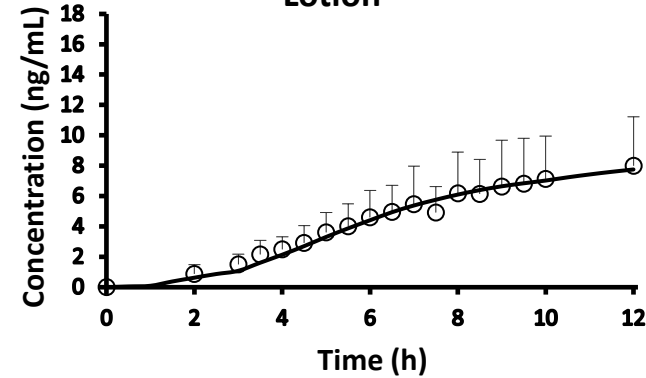
Level A IVIVC – UMB Study

Cream Emulsion



	C_{max} (ng/mL)	AUC_{0-12h} (ng*h/mL)
Observed	10.82	75.79
Predicted	10.25	69.19
%PE	5.27	8.71

Lotion

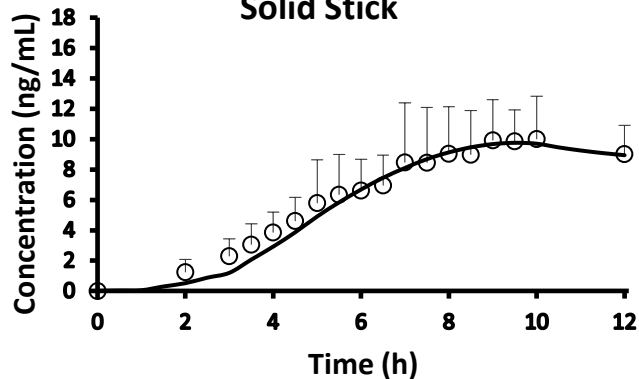


	C_{max} (ng/mL)	AUC_{0-12h} (ng*h/mL)
Observed	7.98	49.71
Predicted	7.75	48.18
%PE	2.88	3.08

○ Observed Conc.

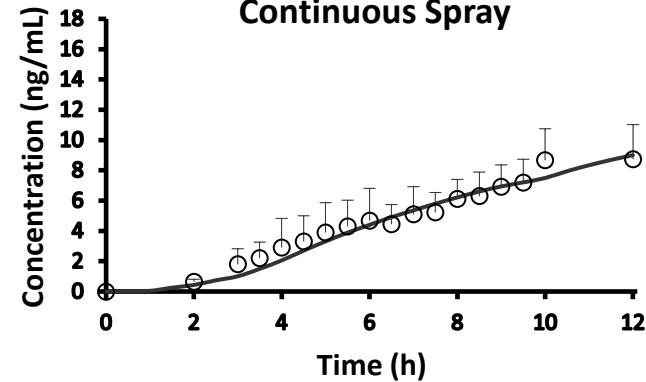
— Predicted Conc.

Solid Stick



	C_{max} (ng/mL)	AUC_{0-12h} (ng*h/mL)
Observed	8.74	53.2
Predicted	9.01	50.19
%PE	-3.09	5.66

Continuous Spray



	C_{max} (ng/mL)	AUC_{0-12h} (ng*h/mL)
Observed	10.01	71.07
Predicted	9.76	66.69
%PE	2.50	6.16



- IVIVC: In Vitro In Vivo Correlation may be the ultimate goal
 - Facilitate testing of drug candidates and optimization of formulation
 - Assist in quality control
 - Serve as a surrogate for bioequivalence studies, scale-up and post-approval changes
- No full IVIVC for the product/API
 - Discriminating IVPT studies done with standardized methods in human skin may also be surrogates for some types of bioequivalence studies, scale-up and post-approval changes

Acknowledgments

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Dr. Annette L. Bunge
Dr. Richard H. Guy
Dr. Tom Franz

Clinical Study Team

Dr. Jeff Fink
Dr. James Campbell
UMB GCRC nurses
Clinical Study Participants

UMB Mass Spec Center

Dr. Vijaya Kumari Karra
(Metronidazole, oxybutynin
& rivastigmine)

Recent Lab Members

Contributors to the work presented:

- 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, oxybutynin & rivastigmine)

Sunscreen Funding

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These projects have been approved by the UMB Institutional Review Board for human subject research