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Simcyp

Predicting Dermal Absorption in Diseased or Damaged Skin using PBPK Modelling

Disclaimer

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FDA U.S. FOOD & DRUG ADMINISTRATION

Characterization of key system parameters of mechanistic dermal PBPK models in various skin diseases and performance verification of the model using observed local and systemic concentrations (U01FD006521, 2018 - 2020)

Lead Investigator — CERTARA Simcyp — **James Clarke**

Co-investigator — The University Of Queensland AUSTRALIA — **Michael Roberts**

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Topics

- Brief introduction to the MPML MechDermA model
- Summary of Psoriasis Physiological changes accounted for in the model, Focusing on the Epidermis
- Example simulations with Methoxsalen and Caffeine

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Physiologically Based Pharmacokinetic Modelling

What PBPK modelling is not:

- A means for ‘out of the box’ prediction based only on simple physicochemical properties.

What PBPK modelling is:

- A mechanistic modelling framework to be used in conjunction with *in vitro* and clinical data.
- Many parameters can be predicted, but should be measured where possible, QSAR models are available to fill the gaps.
- Often overlooked, but particularly important, is characterisation of the formulation.
- Once a model has been verified for one population, PBPK can be used to extrapolate to another population and ask ‘what if ?’ questions.

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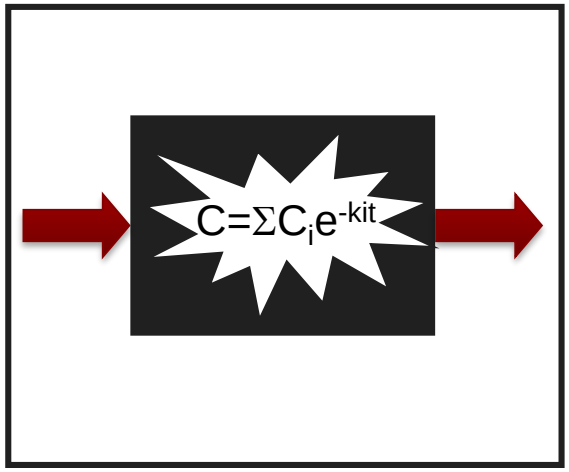
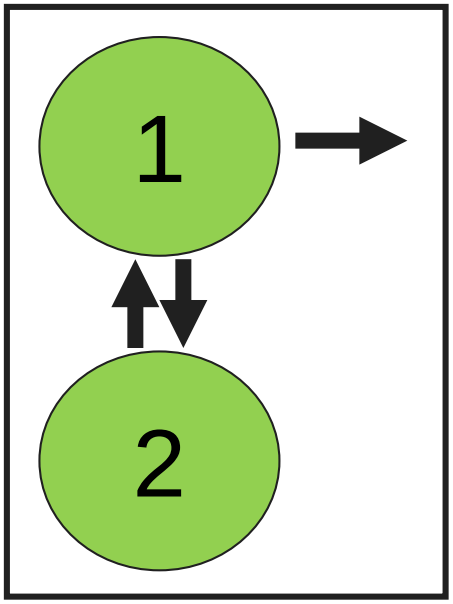
Typical Models Used to Describe Pharmacokinetics

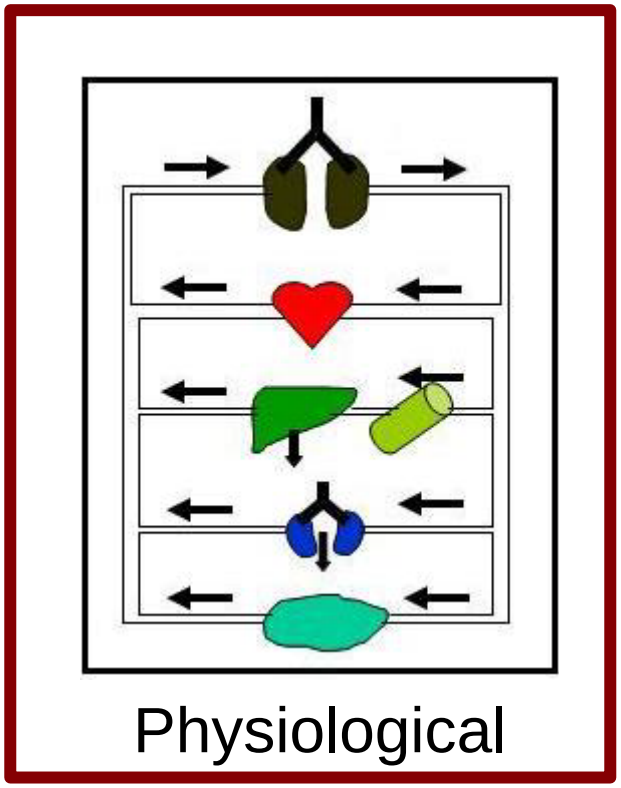
Three types of model can be used to describe concentration time profiles (PK)



Empirical



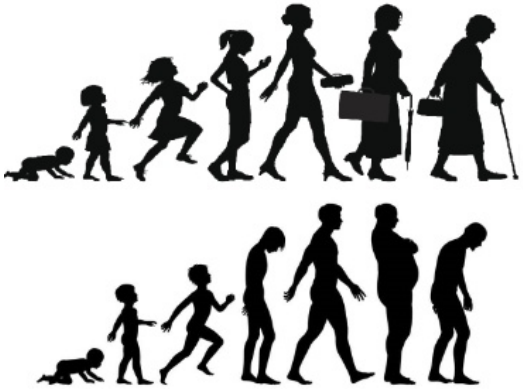
Compartmental



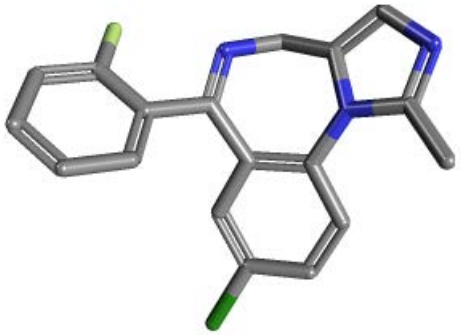
Physiological

Advantage of PBPK: Separating Systems & Drug Information

Systems Data | **Trial Design** | **Drug Data**



Dose
Administration route
Frequency
Co-administered drugs
Populations



Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

(Jamei *et al.*, DMPK, 2009, Rostami-Hodjegan, CPT, 2012)

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Simcyp's Impact on Novel Drug Approvals

Pfizer Revatio (Sildenafil) Pulmonary Arterial Hypertension	**Johnson & Johnson** Xarelto (Rivaroxaban) Deep Vein Thrombosis and Pulmonary Embolism	**Tibotec** Edurant (Rilpivirine) HIV infection	**Ariad** Iclusig (Ponatinib) Chronic Myeloid Leukemia	**GW Pharma** Epidiolex (Cannabidiol) Epilepsy	**Lilly** Olumiant (Baricitinib) Rheumatoid Arthritis
Novartis Odomzo (Sonidegib) Basal Cell Carcinoma	**Janssen** Olysio (Simeprevir) Hepatitis C	**Actelion** Opsumit (Macitentan) Pulmonary Arterial Hypertension	**Pharmacyclics** Imbruvica (Ibrutinib) Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia	**AstraZeneca** Movantik (Naloxegol) Opioid Induced Constipation	**Genentech** Cotellic (Cobimetinib) Metastatic Melanoma
Genzyme Cerdelga (Eliglustat) Gaucher Disease	**Sanofi** Jevtana (Cabazitaxel) Prostate Cancer	**Novartis** Zykadia (Ceritinib) Metastatic Non-small Cell Lung Cancer	**Pfizer** Bosulif (Bosutinib) Chronic Myelogenous Leukemia	**Alkermes** Aristada (Aripiprazole lauroxil) Schizophrenia	**AstraZeneca** Lynparza (Olaparib) Advanced Ovarian Cancer
Novartis Farydak (Panobinostat) Multiple myeloma	**Eisai** Lenvima (Lenvatinib) Thyroid cancer	**Genentech** Alecensa (Alectinib) Non-small Cell Lung Cancer	**AstraZeneca** Tagrisso (Osimertinib) Metastatic NSCLC	**Amgen** Blincyto (Blinatumomab) Acute Lymphoblastic Leukemia	**AstraZeneca** Calquence (Acalabrutinib) Mantle Cell Lymphoma
Eli Lilly Verzenio (Abemaciclib) Metastatic Breast Cancer	**Intercept** Ocaliva (Obeticholic acid) Primary Biliary Cholangitis	**Actelion** Uptravi (Selexipeg) Pulmonary Arterial Hypertension	**Janssen** Invokana (Canagliflozin) Type 2 Diabetes	**Merck** Prevymis (Letermovir) Cytomegalovirus	**Merck** Steglujan (Ertugliflozin) Type 2 Diabetes
Novartis Kisqali (Ribociclib succinate) Metastatic Breast Cancer	**PTC Therapeutics** Emflaza (Deflazacort) Duchenne Muscular Dystrophy	**Shionogi** Symproic (Naldemedine) Opioid Induced Constipation	**Spectrum** Beleodaq (Belinostat) Peripheral T-cell Lymphoma	**UCB** Briviact (Brivaracetam) Epilepsy	**Vertex** Symdeko (Tezacaftor/ivacaftor) Cystic Fibrosis
Novartis Rydapt (Midostaurin) Acute Myeloid Leukemia	**Ariad** Alunbrig (Brigatinib) Metastatic Non-small Cell Lung Cancer	**Janssen** Erleada (Apalutamide) Non-metastatic Prostate Cancer	**Helsinn** Akynzeo (fosnetupitant/palonosetron) Acute and Delayed Nausea	**AkaRx** Doptelet (Avatrombopag maleate) Thrombocytopenia	**GSK** Dectova (Zanamivir) Influenza A and B

PBPK areas of application (FDA/OCP)

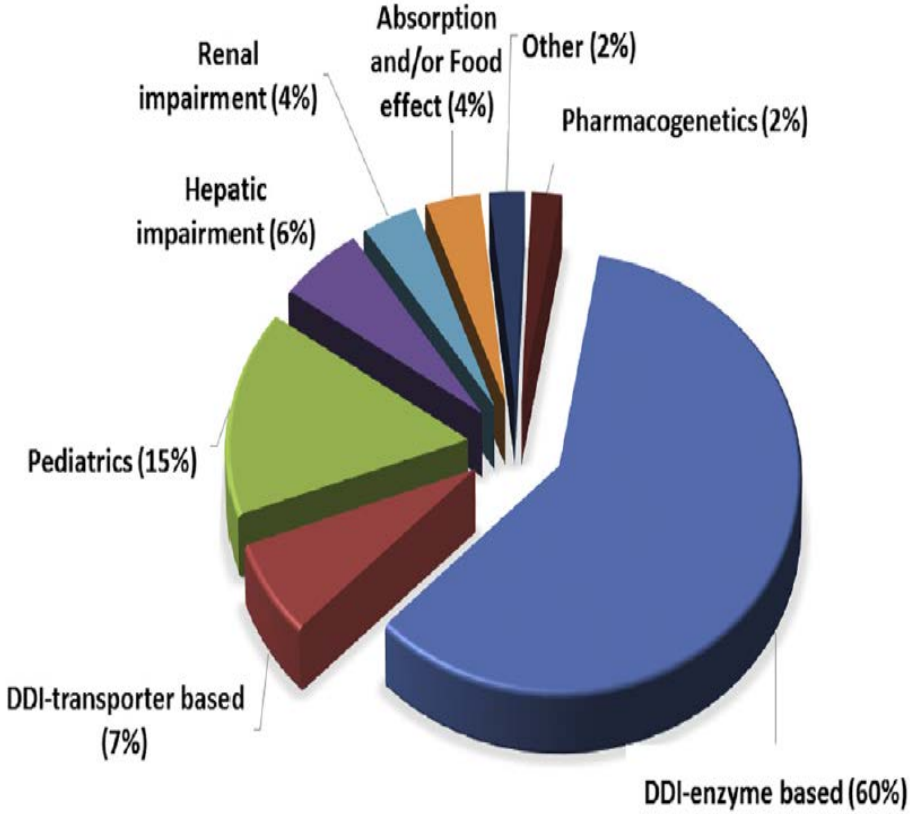
Special Topic Commentary

Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology

Manuela Grimstein, Yuching Yang*, Xinyuan Zhang*, Joseph Grillo, Shiew-Mei Huang, Issam Zineh, Yaning Wang

Journal of Pharmaceutical Sciences 108 (2019) 21-25

PBPK modeling and simulation areas of intended applications in IND/NDA submissions reviewed by the OCP from 2008 to 2017. A total of **254** submissions were reviewed by OCP including **94 NDAs**. Each submission might contain more than 1 area of application.



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Virtual Bioequivalence

Bioequivalence ANDA, FDA accepted PBPK modelling of local skin concentrations in place of a clinical endpoint study for Diclofenac Gel.

Case II (ANDA Review): PBPK Modeling to Support BE Evaluation for a Locally Acting Product

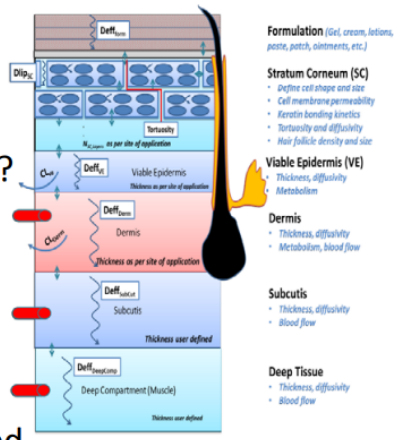
Product Y, Topical Gel for topical treatment

Background: The applicant proposed an alternate approach for the BE evaluation which includes Dermal PBPK as part of support of not conducting a comparative clinical endpoint study with a Q1/Q2 and Q3 similar formulation.

Question: Is the proposed alternate BE approach acceptable?

Impact:

- The PBPK model helped us understand the systemic to local link and supported the proposed alternative approach.
- In vivo PK BE study supported the BE assessment and product approval without conducting a PSG recommended comparative clinical endpoint BE study.



Reference:
Liang Zhao, Office of generic drugs, FDA
GDRSI workshop 2019

www.fda.gov

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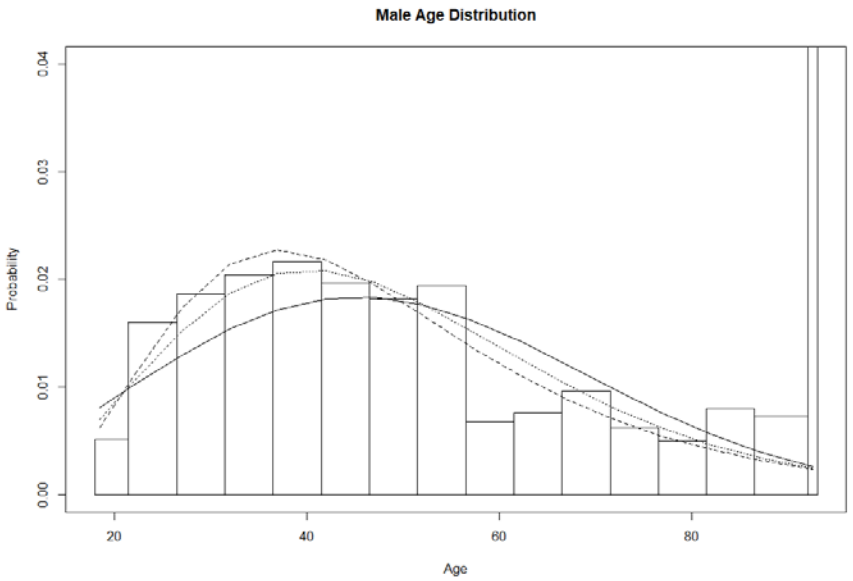
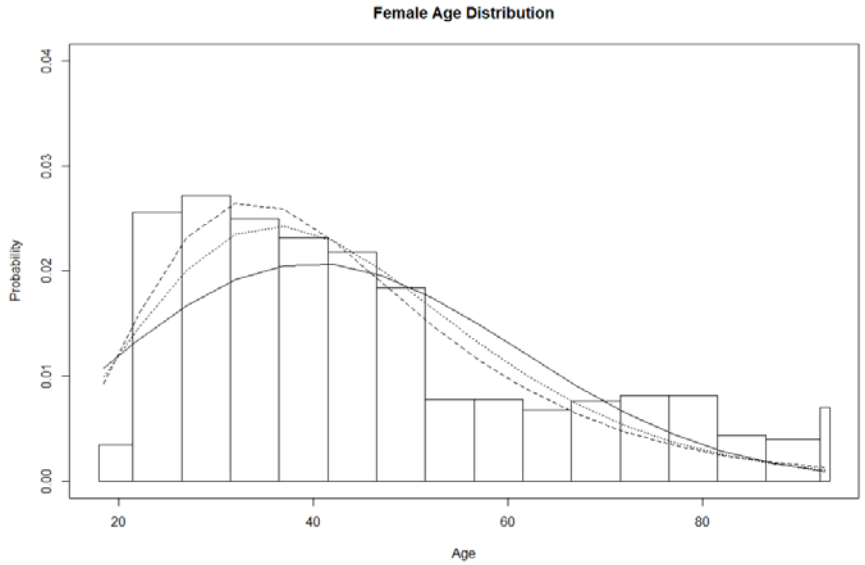
Psoriasis Vulgaris

Plaque Psoriasis Incidence by Age - North European Caucasian





Incidence data was fit to a log-normal distribution.

This Distribution is used to select more relevant individuals in simulations.

Psoriasis Plaque, Important Parameters

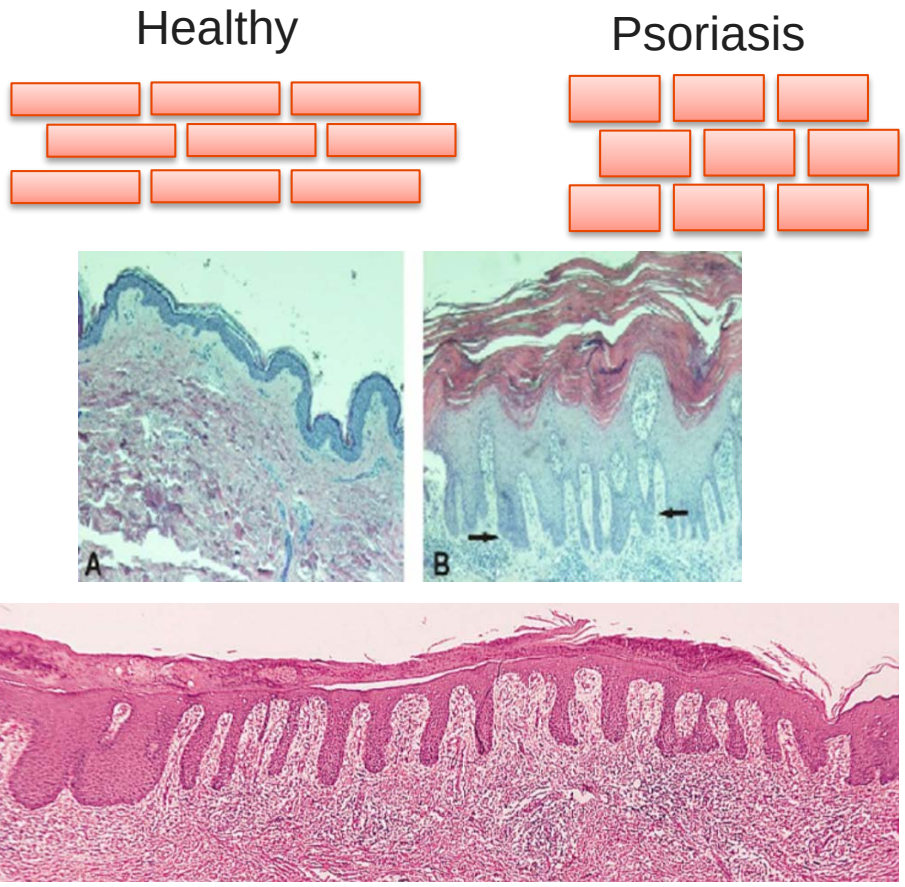
Surface
- pH ↓
- Temperature ↑

Stratum Corneum
- Thickness (number of layers) ↑
- Corneocyte Thickness ↑
- Corneocyte Surface Area ↓
- Hydration ↓
- Cracks/ disorganised structure

Viable Epidermis
- Thickness ↑
- Undulation ↑

Dermis
- Blood Flow ↑
- Capillary Volume Fraction ↑
- Inflammation (> Capillary Leakage > ISF volume > Lymph flow) ↑

Subcutis
- Blood Flow ↑



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Corneocyte Dimensions

Corneocyte thickness ↑ Corneocyte Surface Area ↓

These dimensions can be used to re-calculate intercellular lipid pathway tortuosity

TABLE 3. Parameters of corneocytes from the involved and uninvolved sites of psoriatic patients

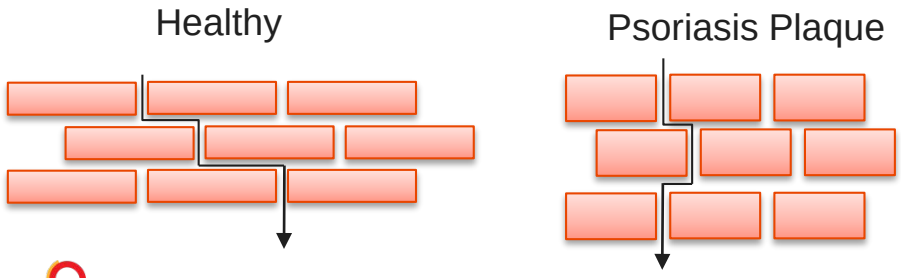
		Subject 9, age 63 (Female)		Subject 10, age 48 (Female)		Subject 11, age 36 (male)	
Parameter	Dimension	Involved	Uninvolved	Involved	Uninvolved	Involved	Uninvolved
Mean thickness	μm	0.389 ± 0.09	0.237 ± 0.04	0.462 ± 0.107	0.235 ± 0.041	0.827 ± 0.186	0.263 ± 0.056
Projected area	μm^2	1113 ± 139	1615 ± 88	1019 ± 135	1448 ± 115	1020 ± 123	1060 ± 89
Surface area	μm^2	1156 ± 139	1649 ± 87	1048 ± 141	1471 ± 113	1060 ± 122	1095 ± 95
Volume	μm^3	426 ± 85	382 ± 64	465 ± 101	339 ± 58	841 ± 204	276 ± 61
Flatness index		3.06 ± 1.08	7.03 ± 1.34	2.33 ± 0.62	6.36 ± 1.33	1.36 ± 0.59	4.27 ± 1.22

Data are reported as mean ± SD, $n = 20$.

Three-dimensional analyses of individual corneocytes with atomic force microscope: norphological changes related to age, location and to the pathologic skin conditions

Nobuo Kashibuchi[1], Yoshikazu Hirai[1], Kenichiro O'Goshi[2] and Hachiro Tagami[2]

ola Laboratories, Pola Chemical, Inc. Yokohama, Japan and [2]Department of Dermatology, Tohoku University School of Medicine, Sendai, Japan



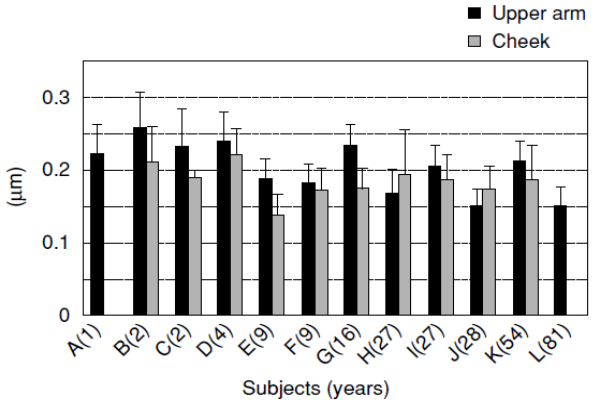


Fig. 1. Mean thickness of the corneocytes of various aged subjects and that at various locations. Mean thickness of the corneocytes obtained from the flexor surface of the upper arm decreased with age. In contrast, the corneocytes from the cheek showed no such a relation because of its great individual differences. Data are reported as mean ± SD (n = 20 corneocytes).

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Corneocyte Dimensions

Corneocyte thickness ↑ Corneocyte Surface Area ↓

These dimensions can be used to re-calculate intercellular lipid pathway tortuosity

Surface Area Measurements of Psoriatic Corneocytes: Effects of Intralesional Steroid Therapy

HERBERT GOLDSCHMIDT, M.D.

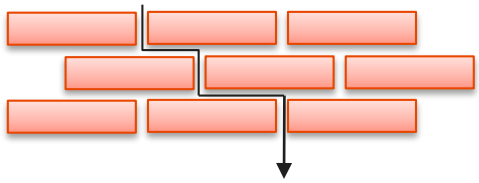
The Department of Dermatology, University of Pennsylvania Medical School (Duhring Laboratories), Philadelphia, Pennsylvania, U.S.A.

Mean corneocytes surface areas (μm^2) and standard deviations in 11 psoriatic patients before and after treatment

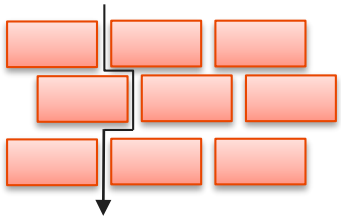
Patient	Age	Sex	Area	Normal (Control)		Psoriasis							
						Before treatment		After treatment					
								2 weeks		4 weeks		6 weeks	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	38	M	Knee	790	102	440	101	580	100	631	84	750	96
2	70	M	Knee	974	146	599	83	632	77	663	89	862	111
3	76	M	Knee	805	111	551	92	568	95	756	80	801	110
4	61	M	Knee	668	116	489	67	577	119	659	123	651	82
5	22	M	Lower leg	604	62	560	90	583	76	612	106	602	81
6	36	F	Lower leg	678	77	618	63	680	80	697	111	687	95
7	49	F	Gluteal	798	58	609	89	747	124	754	129	784	76
8	50	F	Elbow	676	89	564	108	577	61	618	75	654	100
9	38	F	Elbow	713	97	506	68	556	80	662	88	721	58
10	47	F	Elbow	620	101	511	62	568	66	607	76	590	98
11	33	M	Forearm	781	94	442	68	615	101	595	78	712	82

.70 x 10.46 in

Healthy



Psoriasis Plaque



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Corneocyte Dimensions

Corneocyte thickness ↑ Corneocyte Surface Area ↓

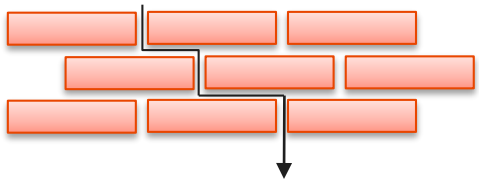
These dimensions can be used to re-calculate intercellular lipid pathway tortuosity (Johnson 1997)

Tortuosity ↓

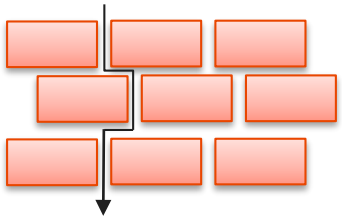
$$\tau^* = 1 + \frac{2g}{h}\ln\left(\frac{d}{2s}\right) + \frac{Ndt}{sh} + \left(\frac{d}{1+\omega}\right)^2\left(\frac{\omega}{hg}\right)(N-1) \qquad (7)$$

	Corneocyte pH		Corneocyte thickness (µm)		Corneocyte width (µm)		Corneocyte length (µm)		Hydration level (% water volume)		Keratin volume fraction	SC lipid viscosity (centipose)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	Mean	CV (%)
Top 25% of SC layers	6.8	0	0.71	36	27.7	9.2	34.2	4.1	35.5	17	0.645	75	0
Upper middle 25% of SC layers	6.8	0			27.7	9.2	34.2	4.1	46.1	11	0.539	75	0
Lower middle 25% of SC layers	6.8	0			27.7	9.2	34.2	4.1	56.75	7	0.4325	75	0
Bottom 25% of SC layers	6.8	0			27.7	9.2	34.2	4.1	67.4	4	0.326	75	0

Healthy



Psoriasis Plaque



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Corneocyte Hydration

Corneocyte Hydration ↓

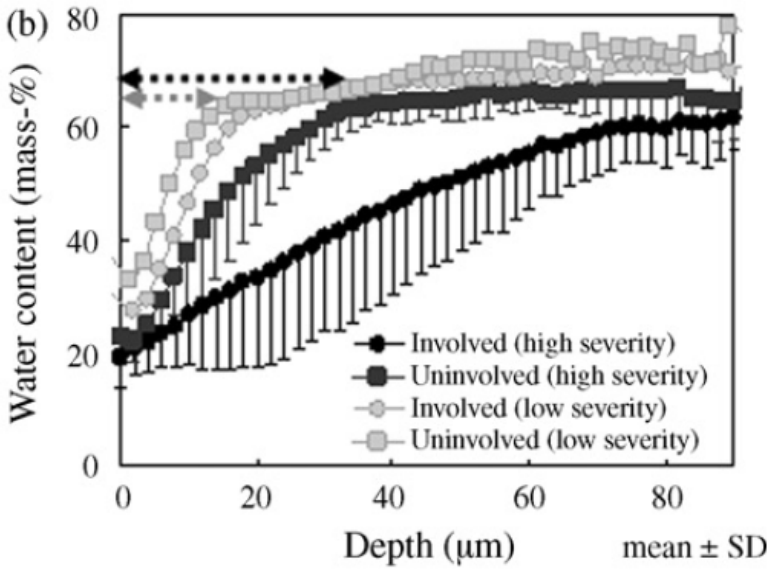
A proton NMR study on the hydration of normal *versus* psoriatic stratum corneum: linking distinguishable reservoirs to anatomical structures

Cornelia Laule[a,b*], Sumia Tahir[a], Charmaine L. L. Chia[a], Irene M. Vavasour[b], Neil Kitson[c] and Alex L. MacKay[a,b]

Table 1. Hydration of the normal and psoriatic stratum corneum (SC) samples

Sample	Hydration (g H_2O/g SC)
Normal	
1a	0.91
1b	0.51
Psoriatic	
1	0.25
2	0.22
3a	0.54
3b	0.54
4a	0.57
4b	0.63
4c	0.80
4d	0.42
5a	0.23
5b	0.35
5c	0.44
5d	0.43

***In vivo* characterization of the structure and components of lesional psoriatic skin from the observation with Raman spectroscopy and optical coherence tomography: A pilot study**



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Number of SC layers

SC N-layers was calculated from the measured thickness of total SC, corneocyte thickness and hydration.

Example hydration for forearm:

	Healthy	Plaque
Bin1	33.9	29.72
BIn2	44.7	33.32
Bin3	55.5	35.81
Bin4	66.4	41.75

Example (male) :

Site	Healthy	Plaque	Healthy	Plaque
	µm	µm	N Layers	N Layers
Forehead	11.68	27.68	12	16
Forearm	18.04	42.76	22	28
Outer Forearm	20.77	49.23	22	28
Upper arm	17.61	41.74	18	23
Face	8.74	20.72	13	17
Lowe Leg	25.68	60.87	22	28
Upper Leg	21.06	49.92	18	23
Back	14	33.18	17	22

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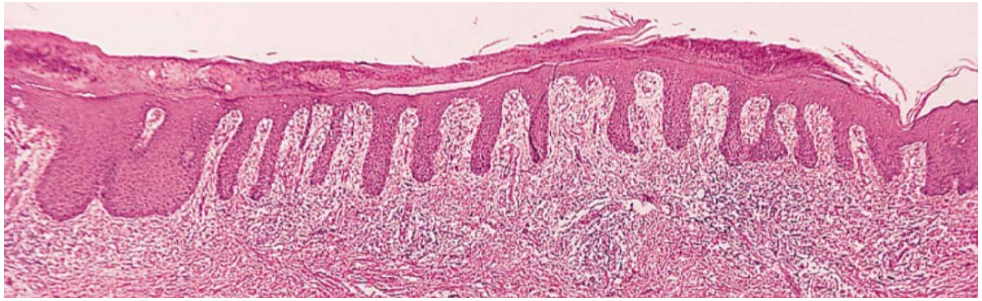
Viable Epidermis

- In Psoriasis the viable epidermis is thicker on average but has deep rete ridges.
- There is good data available for this: (more than shown here)



Original Article

Cellular Features of Psoriatic Skin: Imaging and Quantification Using In Vivo Reflectance Confocal Microscopy

E. A. W. Wolberink,* P. E. J. van Erp, M. M. Teussink, P. C. M. van de Kerkhof, and M. J. P. Gerritsen
Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Table 2
Shape Descriptors of Dermal Papillae in Psoriatic and Uninvolved Skin

	Psoriasis		Uninvolved			
	Mean	SD	Mean	SD	*T*-test	*P*-value
Area (μm^2)	4186.5	1496.9	3095.8	2082.6	1.3	0.23
Mean gray value	41.7	8.2	50.5	13.2	−2.9*	0.02
Mode gray value	34.7	5.9	40.9	9.5	−3.2*	0.02
Perimeter (μm^2)	247.2	48.7	211.0	70.9	1.3	0.25
Feret (μm^2)	80.5	15.7	70.4	24.7	1.1	0.33
MinFeret (μm^2)	63.9	12.8	51.3	15.3	2.0	0.91
Circularity	0.79	0,02	0.75	0.03	3.7**	<0.01

Circularity, mean and mode gray value of dermal papillae are statistically significant RCM parameters in psoriatic and uninvolved skin. (*$P < 0.01$, **$P < 0.001$).

Table 1
Quantification and Correlation of Parameters in Psoriatic and Uninvolved Skin

	RCM				Histology			
	Psoriasis		Uninvolved		Psoriasis		Uninvolved	
Feature	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dermal Papillae (number/mm^2)	293.8**	132.9	238.2*	90.9	100.4**	35.5	83.8*	14.7
Parakeratosis surface %	45.0**	42.8	0	0	50.0**	41.1	0	0
Height SP (µm)	86.8*	30.8	47.5*	10.6	90.0*	24.7	60.0*	12.7
Height SC (µm)	41.6**	28.2	12.4**	6.7	48.5**	26.3	25.4**	7.2
Capillaries (number/mm^2)	8.8	3.4	1.3	1.5	122.3	57.2	51.3	47.9
Inflammatory cells *EF* (number/mm^2)	12.6*	5.0	3.1*	2.4	63.9*	43.0	13.2*	31.8
Inflammatory cells T (number/mm^2)					319.6*	226.6	18.1*	10.9
SG surface %					48.8	32.3	100	0
Laser power SG (mW)	3.2	1.5	2.4	2.3				
Refractivity SG	98.0	28.1	80.5	27.4				
Height PD (µm)			38.8	5,7			28.0	11.4
Height EH (µm)			82.4	16.3			79.4	18.8

Dermal papillae number, parakeratosis, amount of inflammatory cells and SP and SC height are significantly correlated to histology. (SP, suprapapillary plate; SC, stratum corneum; EF, *en face* sections; T, transverse sections; SG, stratum granulosum; PD, papillary dermis; EH, epidermal height, *$P < 0.01$, **$P < 0.001$).

Measurement of epidermal thickness in a patient with psoriasis by computer-supported image analysis

Table 2. Epidermal thickness measurements of psoriasis patients and controls according to biopsy location.

Biopsy location	Full epidermal thickness (µm)	Stratum corneum thickness (µm)	Rete length (µm)	Suprapapillary epidermal thickness (µm)	Dermal papilla distance (µm)
Patient elbow (11)	500	133	361	60	51
Control elbow (9)	326	73	225	88	69
Patient knee (22)	610	87	491	72	40
Control knee (16)	208	36	157	65	37
Patient leg (10)	532	91	447	53	56
Control leg (10)	195	37	159	69	45
Patient trunk (8)	365	64	307	53	46
Control trunk (7)	204	23	180	40	63
Patient palmar region (13)	663	192	388	78	35
Control palmar region (15)	207	45	162	43	46

The number of subjects in each group is given in parentheses. The data are reported as medians in micrometers.

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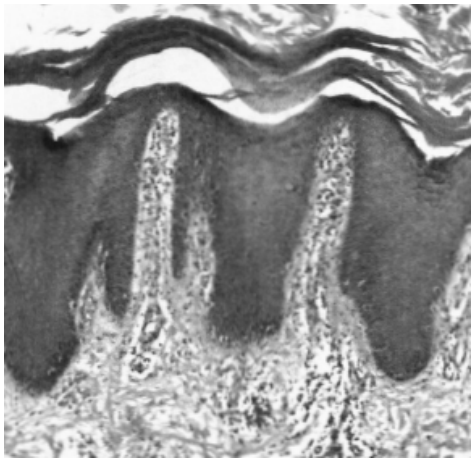
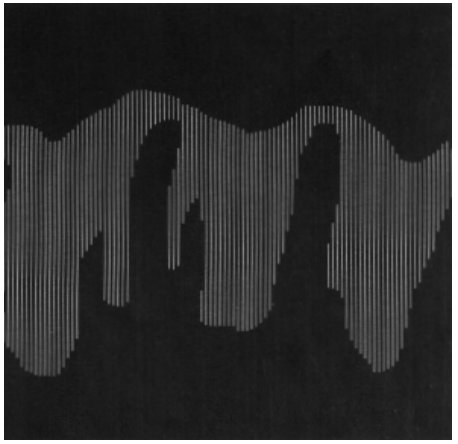
Viable Epidermis Thickness

A Simple Method for the Evaluation of Epidermal Thickness Variations in Psoriasis Vulgaris





Psoriasis Area and Severity Index (PASI) given for each patient

VE thickness assumed to be the average depth between Rete ridge and supra-papillary plate.

Table I *Pretreatment Lesional and Nonlesional, and Post-treatment Lesional Biopsy, the Values of Thickness of Epidermis (micron) and,*

	Min			Max			Mean		
Case no.	Les	Nonl	PL	Les	Nonl	PL	Les	Nonl	PL
1	29	16	13	264	96	73	165.48	45.18	38.66
2	32	20	18	157	64	53	86.59	37.28	34.12
3	27	16	14	235	92	88	131.47	45.45	43.52
4	19	17	14	171	72	64	103.66	35.58	42.10
5	36	22	18	235	72	70	138.46	35.95	32.24
6	35	25	22	204	99	101	102.75	53.15	50.90
7	24	19	15	294	123	151	144.46	67.26	71.91
8	32	27	10	365	61	75	213.92	41.68	34.73
9	32	24	17	254	81	82	122.23	43.68	52.68
10	42	9	11	239	78	80	147.18	31.97	33.45
11	34	17	11	236	86	83	121.14	43.62	42.38
12	19	18	11	218	48	46	138.37	31.65	31.03
13	12	16	14	292	113	88	189.06	50.52	40.25
14	50	19	13	246	66	58	157.52	35.60	28.36
15	24	19	16	184	82	153	109.41	43.72	72.08
16	15	27	14	216	105	65	109.98	51.44	41.90
17	26	25	18	299	67	69	160.37	50.24	46.12
18	38	16	13	335	78	79	160.60	40.10	38.23
19	26	19	16	322	84	83	162.82	48.51	42.32
20	18	18	17	217	101	93	110.00	46.07	45.15
21	32	16	16	342	107	98	174.71	38.02	39.42
22	21	16	15	325	104	98	147.52	47.16	45.30

Les = pretreatment lesional, Nonl = pretreatment nonlesional, PL = post-treatment lesional, CV = coefficient of variation, Pre = pretreatment, Post = post-treatment, PASI = Psoriasis Area and Severity Index.

PASI Scores

	SD			CV			PASI	
Les	Nonl	PL	Les	Nonl	PL	Pre	Post
69.23	19.43	15.18	41.84	43.01	39.27	11.9	0.4
31.47	10.43	9.32	36.34	27.98	27.32	9.6	0.3
58.28	18.83	16.32	44.33	41.43	37.50	11.2	0.7
51.58	15.36	13.50	49.76	43.17	32.07	12.3	0.6
72.01	13.14	14.05	52.01	36.55	43.58	14.7	0.7
60.93	17.94	21.27	59.30	33.75	41.79	8.7	0.1
101.94	28.86	34.30	70.57	42.91	47.70	14.2	0.4
118.27	8.03	15.50	55.29	19.27	44.63	21.7	0.9
78.31	10.86	15.43	64.07	24.86	29.29	8.9	0.4
68.61	14.56	15.85	46.62	45.54	47.38	6.9	0.1
68.07	18.94	17.36	56.19	43.42	40.96	8.9	0.5
59.57	7.44	7.15	43.05	23.51	23.04	14.2	0.6
82.93	28.02	16.72	43.86	55.46	41.54	17.1	1.2
76.85	10.27	10.05	48.79	28.85	35.44	13.2	1.2
54.98	18.38	32.12	50.25	42.04	44.56	21.4	1.7
54.42	19.94	12.10	49.48	38.76	28.88	6.9	0.3
101.05	9.95	13.99	63.01	19.80	30.33	11.2	0.6
100.34	15.48	13.25	62.48	38.60	34.66	12.1	0.2
108.87	17.80	10.67	66.87	36.69	25.21	13.1	1.1
61.98	18.92	16.90	56.35	41.07	37.43	11.7	0.9
106.33	19.11	16.10	60.86	50.26	40.84	12.5	1.4
102.73	21.05	18.50	69.64	44.64	40.84	16.3	1.3

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Dermis Parameters

Parameter Accounted for in the Depth Resolved Dermis Model (not presented further here).

- ↑ Capillary Volume Fraction
- ↑ Capillary Diameter (Vasodilation)
- ↑ Blood Flow

Quantification of microvascular changes in the skin in patients with psoriasis

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**Boots Pharmaceuticals Division, Nottingham NG2 3AA, U.K.*

Accepted for publication 29 January 1992

Assessment of dermal papillary and microvascular parameters in psoriasis vulgaris using *in vivo* reflectance confocal microscopy

ALEXANDRA BATANI[1*], DACIANA ELENA BRĂNIŞTEANU[2*], MIHAELA ADRIANA ILIE[1*], DANIEL BODA[1*], SIMONA IANOSI[3*], GABRIEL IANOSI[4*] and CONSTANTIN CARUNTU[5,6*]

- ↑ Transvascular Leakage & Lymph Flow

Exchange of Macromolecules between Plasma and Skin Interstitium in Extensive Skin Disease

ANNE-MARIE WORM, M.D.

Departments of Clinical Physiology and Dermatology, The Finsen Institute, Copenhagen, Denmark

Increased vessel density in psoriasis: involvement of lymphatic vessels in the papillary dermis

Lymphatic albumin clearance from psoriatic skin

Bent Staberg, M.D., Per Klemp, M.D., Michael Aasted, M.D., Anne-Marie Worm, and Per Lund, M.D.
Copenhagen, Denmark

Transvascular transport and distribution of fluid and protein in psoriasis

Bent Staberg, M.D., Anne-Marie Worm, M.D., Per Klemp, M.D., and Niels Rossing, M.D.
Copenhagen, Denmark

- ↑ ISF Volume

Indian Dermatology Online Journal
Wolters Kluwer -- Medknow Publications

Comparison of levels of serum copper, zinc, albumin, globulin and alkaline phosphatase in psoriatic patients and controls: A hospital based casecontrol study

Gousia Sheikh, Qazi Masood, [...], and Iffat Hassan

Additional article information

- ↓ Albumin in ISF and Plasma

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Dermis Parameters

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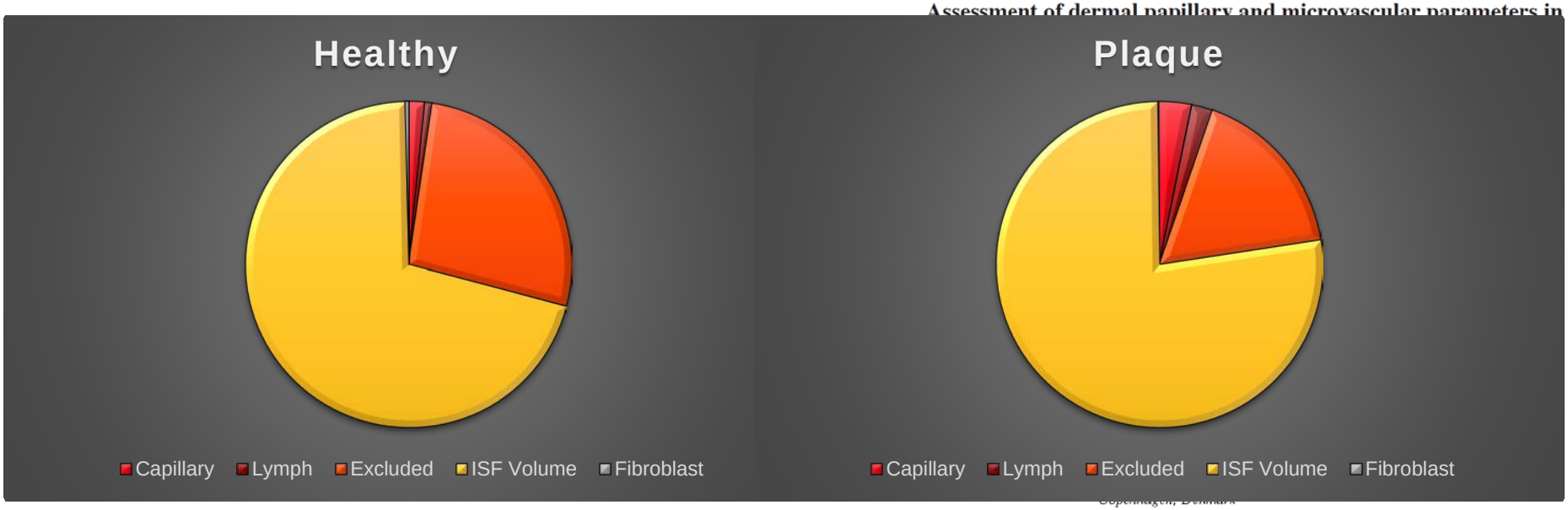
Assessment of dermal papillary and microvascular parameters in

- ↑ Capillary Volume Fraction



in

- ↑ ISF Volume

Gaps and Limitations

- Are corneocytes more/less permeable in psoriatic plaque?
- Some evidence that intercellular regions in SC are larger, but not quantifiable currently.
- Undulation of the Viable Epidermis is not accounted for currently.
- There may be metabolic changes

Example Simulations

Example simulations were run for two model compounds:

- Methoxsalen as a moderately lipophilic example
- Caffeine as a hydrophilic example

A simple solution formulation was used for all simulations

Simulations were run in both healthy and psoriatic population representatives.

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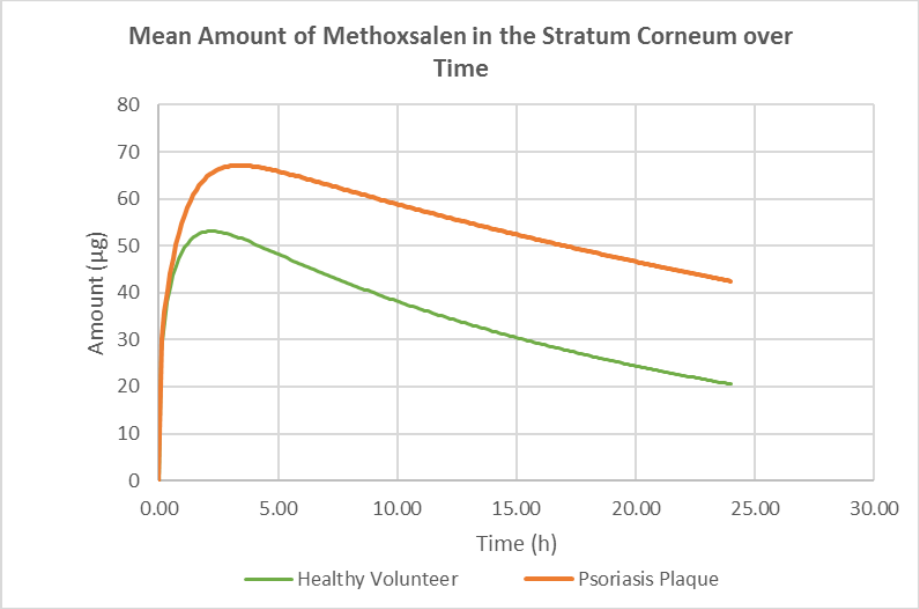
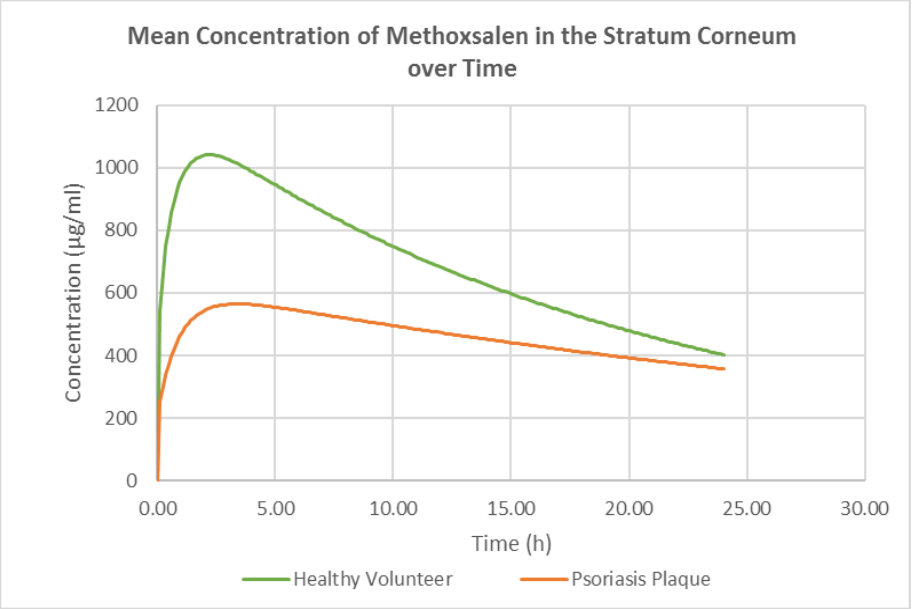
Methoxsalen Simulations

Stratum Corneum __ Psoriasis __ Healthy

Amount



Concentration



> Amount due to thicker SC

< Concentration

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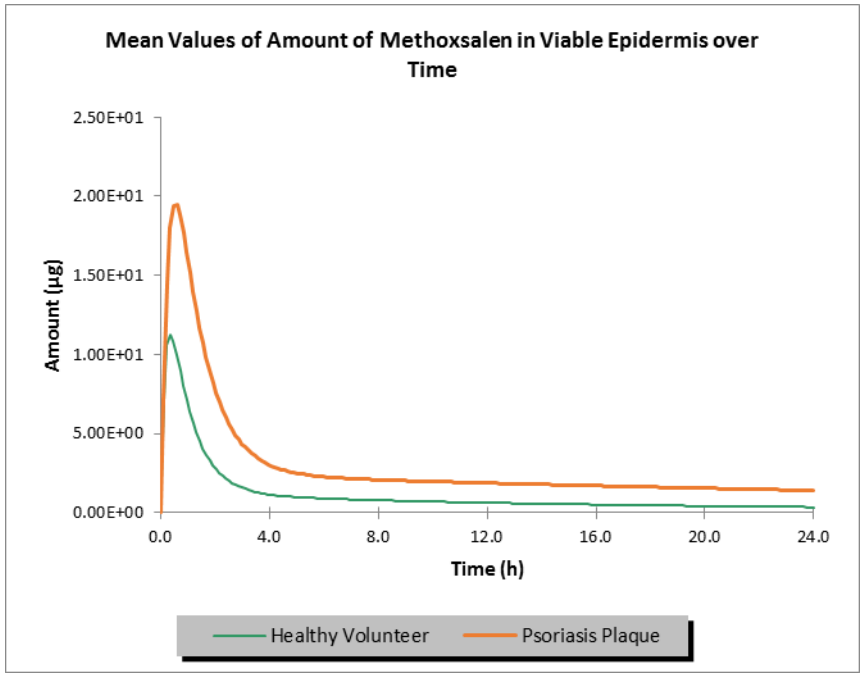
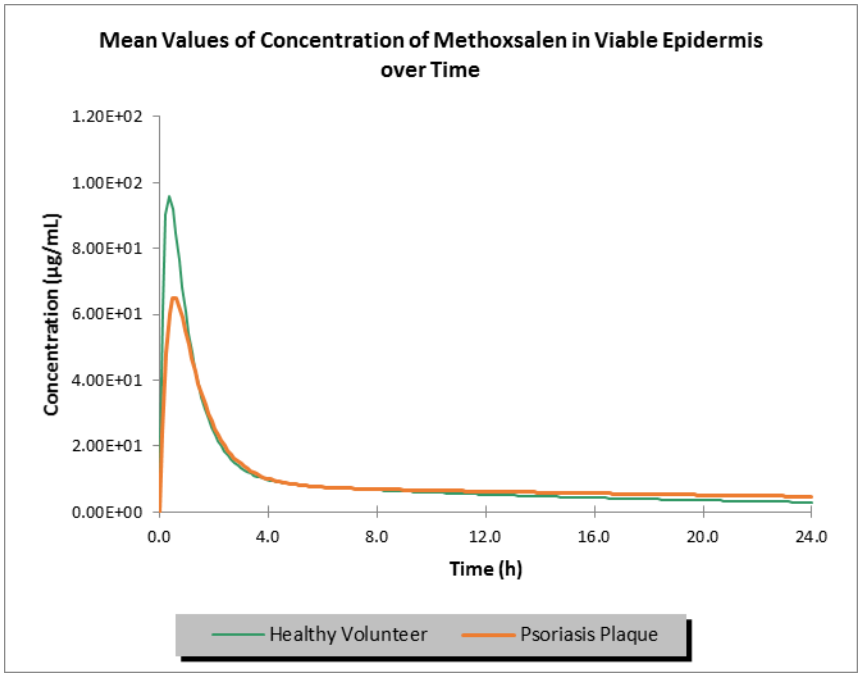
Methoxsalen Simulations

Viable Epidermis __ Psoriasis __ Healthy

Amount



Concentration

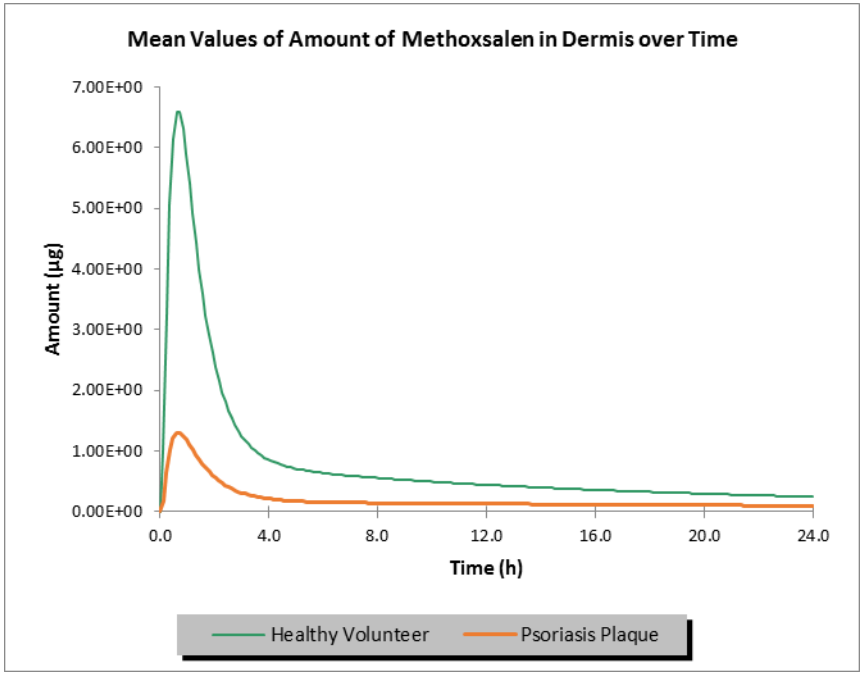


> Amount in Psoriasis but < Concentration

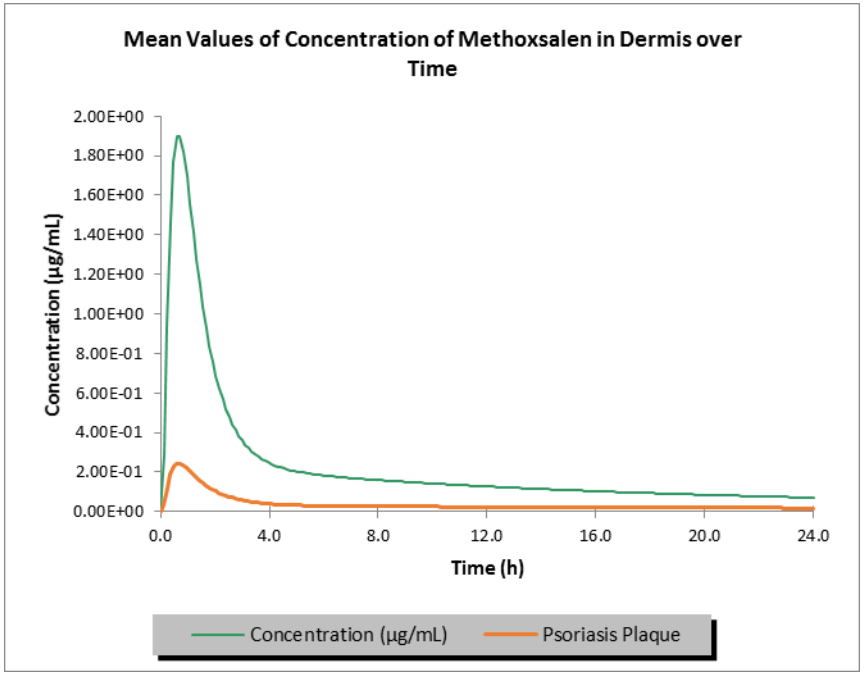
Methoxsalen Simulations

Dermis __ Psoriasis __ Healthy

Amount



Concentration



< Amount and Concentration due to >> Blood Flow

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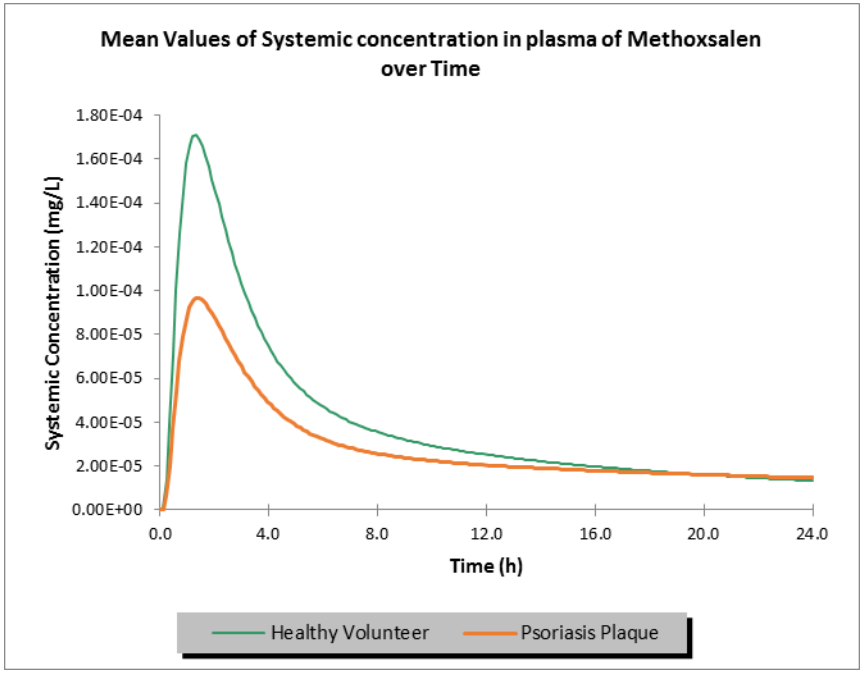
Methoxsalen Simulations

Systemic Concentration __ Psoriasis __ Healthy

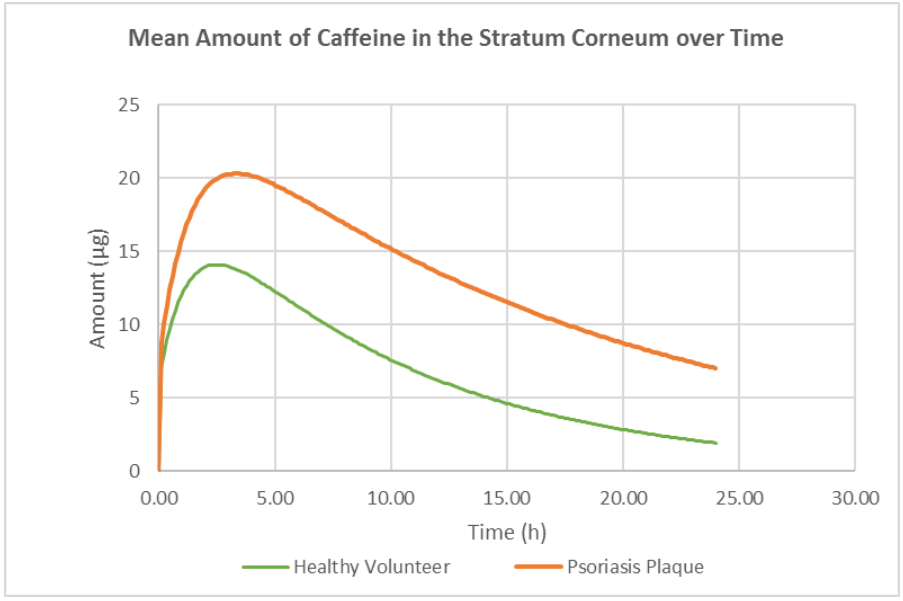


< Methoxsalen permeates to the systemic circulation

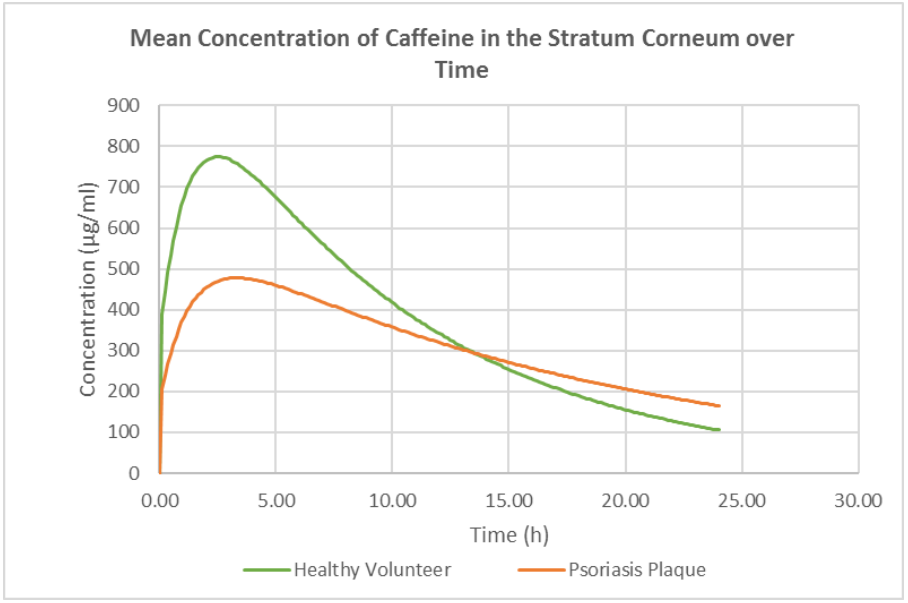
Caffeine Simulations

Stratum Corneum __ Psoriasis __ Healthy

Amount



Concentration



> Amount due to thicker SC

< Concentration

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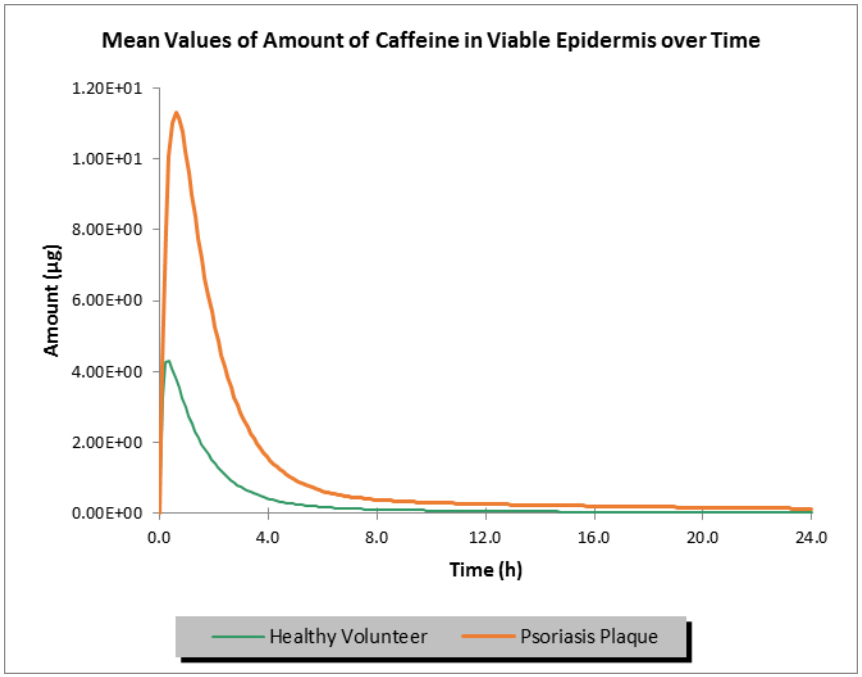
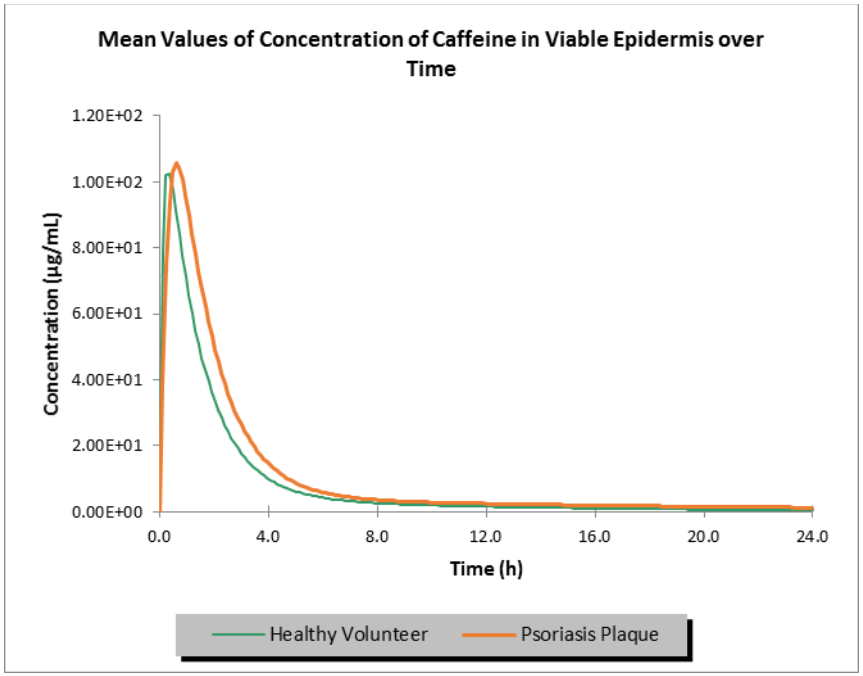
Caffeine Simulations

Viable Epidermis __ Psoriasis __ Healthy

Amount



Concentration

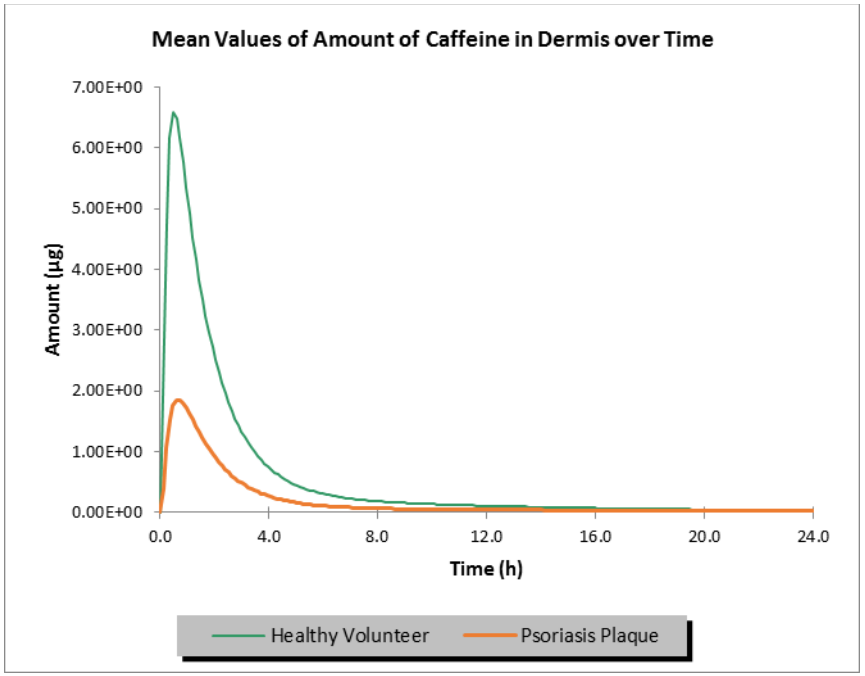


> Amount ~= Concentration

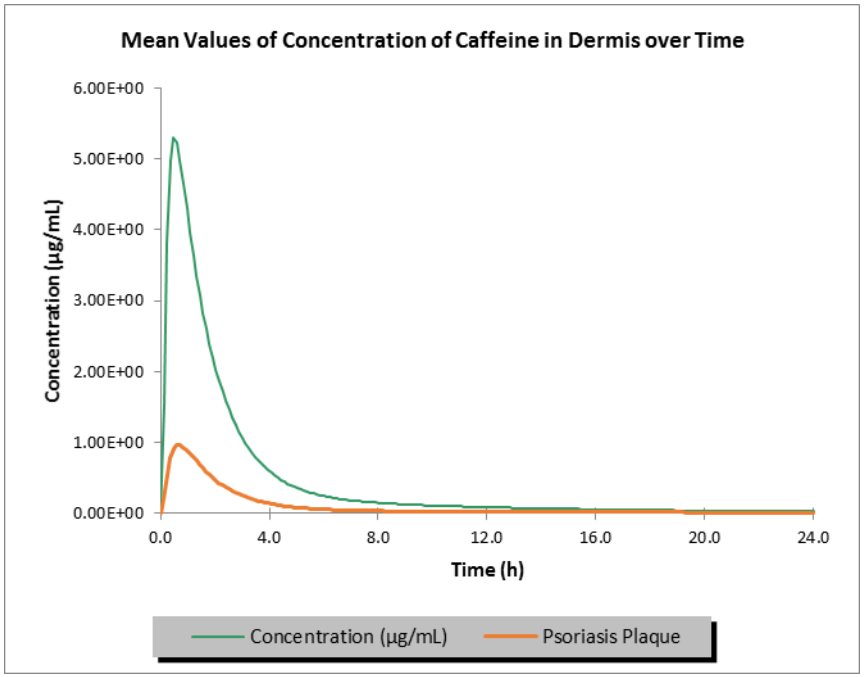
Caffeine Simulations

Dermis __ Psoriasis __ Healthy

Amount



Concentration



< Amount and Concentration due to >> Blood Flow

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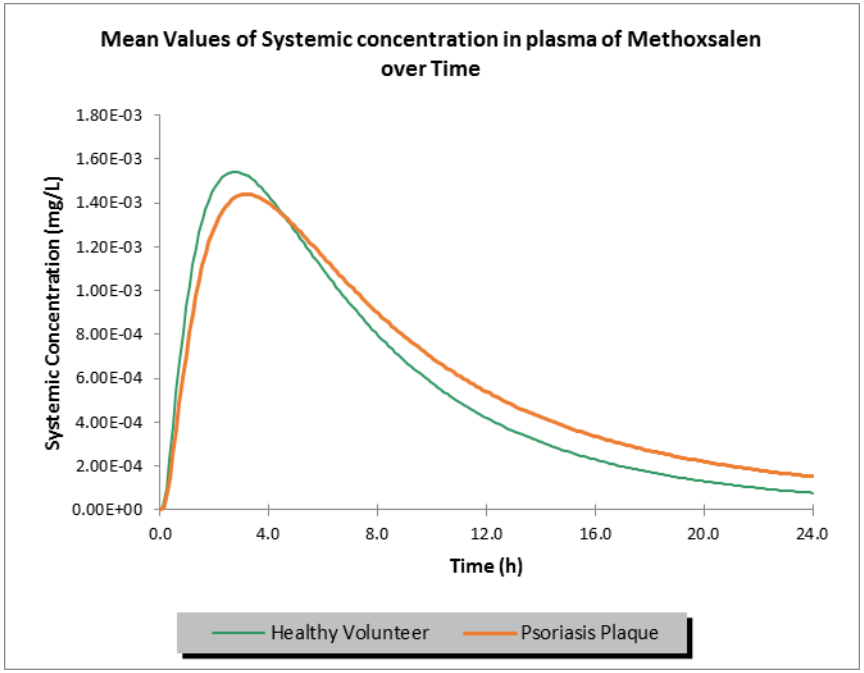
Caffeine Simulations

Systemic Concentration __ Psoriasis __ Healthy



~= amount permeates to the systemic circulation

Conclusions

- More drug accumulates in the Stratum Corneum and Viable Epidermis for both drugs
- Drug is removed faster from the dermis due to > blood flow resulting in lower local dermis concentrations
- Differences in absorption in the diseased skin are not universal but dependent on physicochemical properties of the drug.

Upcoming Research

- Ex vivo imaging studies using scrape biopsies of psoriatic plaques
- In vivo imaging studies
- Investigating other diseases such as:
  - Atopic Dermatitis
  - Acne
  - Rosacea

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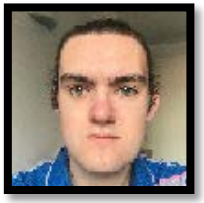

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