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Simcyp Version 19 Release Webinar:

Dermal Developments

Version 19 Release Webinars

Date	Webinar
Monday 21st October	Updating and Verification of Compounds
Tuesday 22nd October	Qualification of Compounds
Thursday 24th October	Dermal Developments
Tuesday 29th October	Parent to Metabolite Inter-conversion
Thursday 31st October	ADAM Developments Under FDA Grant
Monday 4th November	Verification of Populations
Thursday 7th November	Transporters IVIVE
Tuesday 12th November	Enhancement/Expansion of PE and ASA

10th Annual Simcyp Virtual Seminar

The 10th Annual Simcyp Virtual Seminar on the Applications of Population-based IVIVE and PBPK provides the chance to join Consortium members, academic and regulatory Simcyp licence holders to discuss usage of the latest applications of the Simulator and recent advances in the field.

Wednesday 13th November (15:00 GMT)	**Simcyp Virtual Seminar – Part I**
Integration of PBPK modelling into protocol design to understand nuances in variability in drug exposure	Flinders University, Australia
The use of PBPK modelling across the pediatric age range using propofol as a case	Freie Universitaet Berlin, Germany
Bottom-up PBPK modelling using expression- and activity-based IVIVE to predict plasma and tissue xenobiotic concentrations	Skin Research Institute of Singapore

Wednesday 20th November (15:00 GMT)	**Simcyp Virtual Seminar – Part II**
Striving for a neonatal PBPK model of morphine using patients' information: Knowledge gaps and next challenges	Cincinnati Children's Hospital, OH, USA
Application of PBPK modelling to predict the pharmacokinetics of drugs in the special populations	NIPER, India
PBPK modelling and in vitro biorelevant dissolution testing for prediction of oral budesonide pharmacokinetics in Crohn's disease	University of Bath, UK

Registration is available via the Simcyp members' area: https://members.simcyp.com

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Upcoming Events

Choose between the 5-day “all-in-one” workshop or various 2-day “focused” workshops covering specific topics

2020 Simcyp Workshops

2d **Washington DC, USA** • Sheraton Silver Spring Hotel
March 23-24: Best Practice, Biologics, FIH, Pediatrics, Absorption I,
March 25-26: Absorption II, Transporters, DDI, PE/PD, or Special Populations

5d **London, UK** • Holiday Inn London Kensington Forum
May 11–15: Full 1 week workshop

2d **Sheffield, UK** • Certara Simcyp Offices
June 23-24: Best Practice, Biologics, FIH, Pediatrics, Absorption I,
June 25-26: Absorption II, Transporters, DDI, PE/PD, or Special Populations

5d **Cambridge, MA, Boston** • Boston Marriott Cambridge
July 6–10: Full 1 week workshop

5d **Tokyo, Japan** • TKP Conference centre
August 17–21: Full 1 week workshop

2d **Sheffield, UK** • Mercure St Paul's Hotel & Spa
September 21–22: Best Practice, Biologics, Transporters, Pediatrics, Absorption I, Absorption II, FIH, DDI, PE/PD, or Special Populations

3d **Sheffield, UK** • Mercure St Paul's Hotel & Spa
September 22–24: Annual Consortium Meeting

5d **Princeton, NJ, USA** • Nassau Inn
October 19–23: Full 1 week workshop

5d **Shanghai, China** • Radisson Blu Hotel Shanghai New World
November 16–20: Full 1 week workshop

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On-Site Education

- Tailored to suit education needs at your site
- Co-ordinated by Scientists who will work with you to plan the education programme and team

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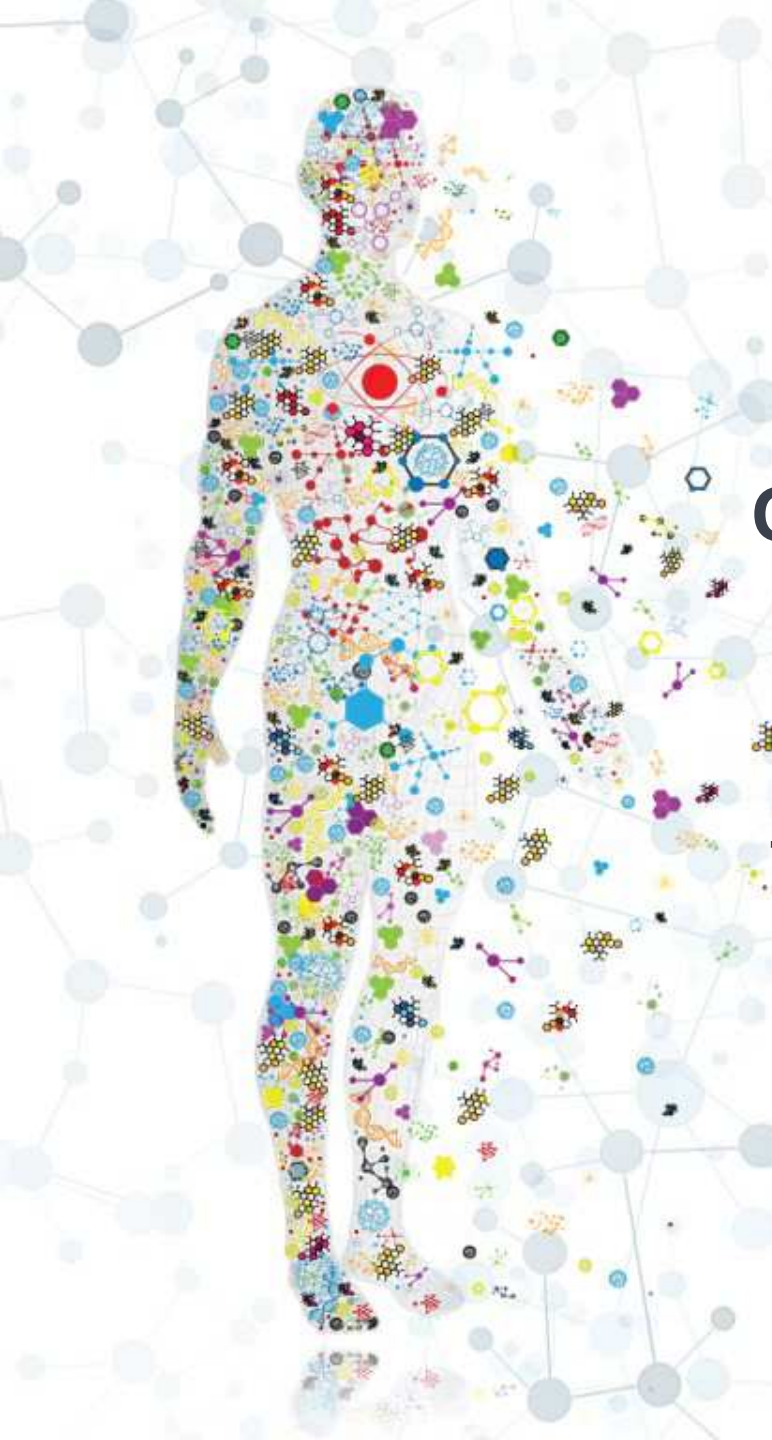
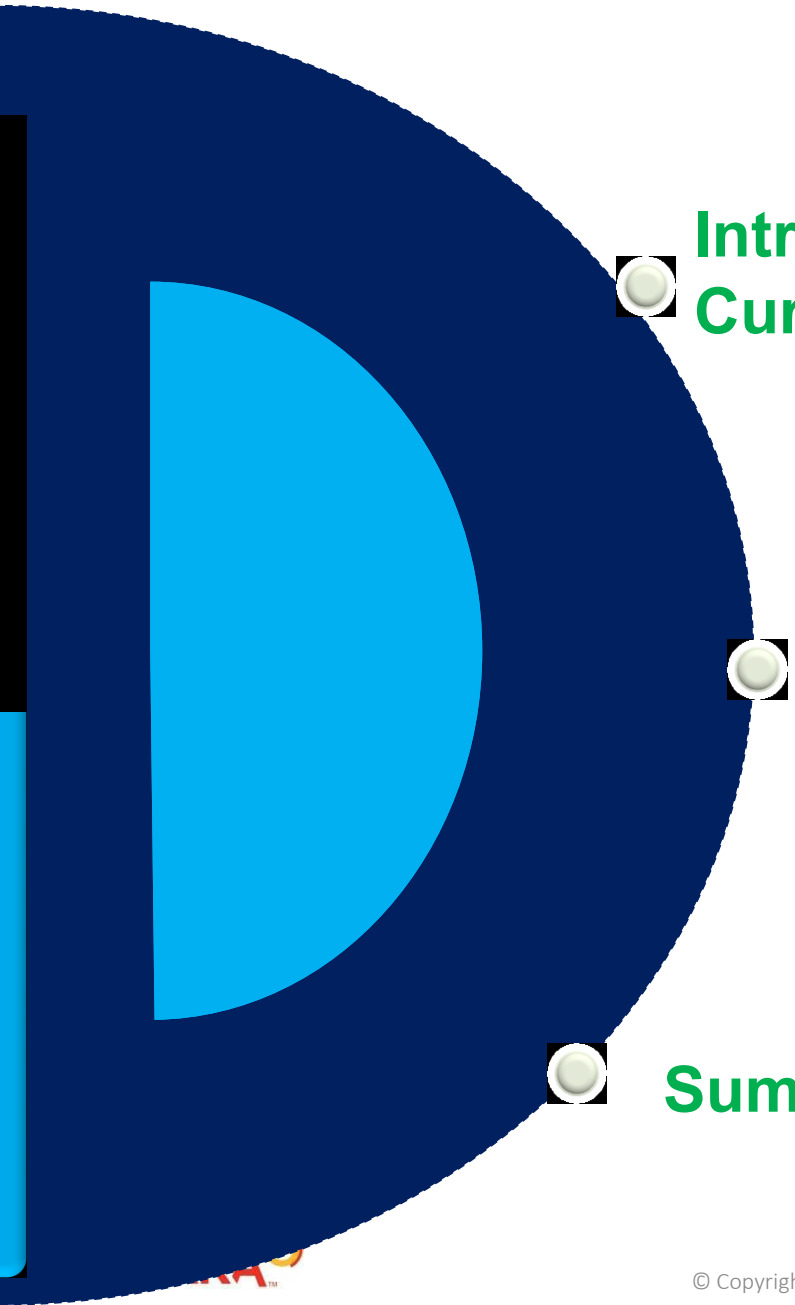


Formulation Drug Product Quality Attributes Additions in Dermal PBPK Model

The work is supported as a part of FDA funded Grant 1U01FD006522-01

Outline of First Part of Presentation



Introduction and Background of the Current Work

Updates in Formulation Input Parameters in Dermal Module V19

- Evaporation Profile Input
- Supersaturation and Precipitation
- Particle Size Distribution
- Introduction of Formulation Toolbox
- Updates to Prediction Toolbox

Summary and Questions

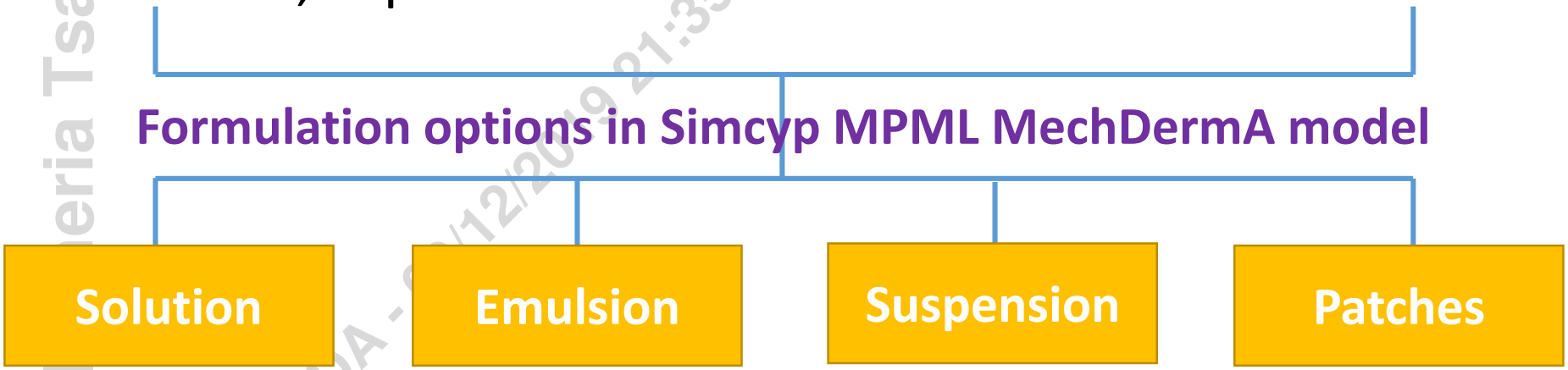
Topical and Transdermal Products – Complex Products

Topical

- Solutions and Sprays
- Creams and Lotions
- Ointments and Oils
- Gels and Jellies
- Shampoos
- Aerosol Foams
- Patches, Tapes and Films

Transdermal

- Transdermal Delivery Systems – Patches
- Ointments
- Gels



Slide Adapted from Dr. Sam Raney Presentation at Complex Generic Drug Product Development Workshop held in September 25-25, 2019

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Shifting Paradigms in BE evaluation of Topical Products

Evaluation of BE for Topical Products

- A Modular Framework for In Vitro BE Evaluation
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness
  - **Physical and Structural (Q3)** Sameness
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- Multiple Approaches for BE Evaluation
  - **In Vivo Pharmacokinetic** Studies
  - **In Vivo Pharmacodynamic** (Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

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Slide taken from Dr. Sam Raney Presentation at Complex Generic Drug Product Development Workshop held in September 25-25, 2019

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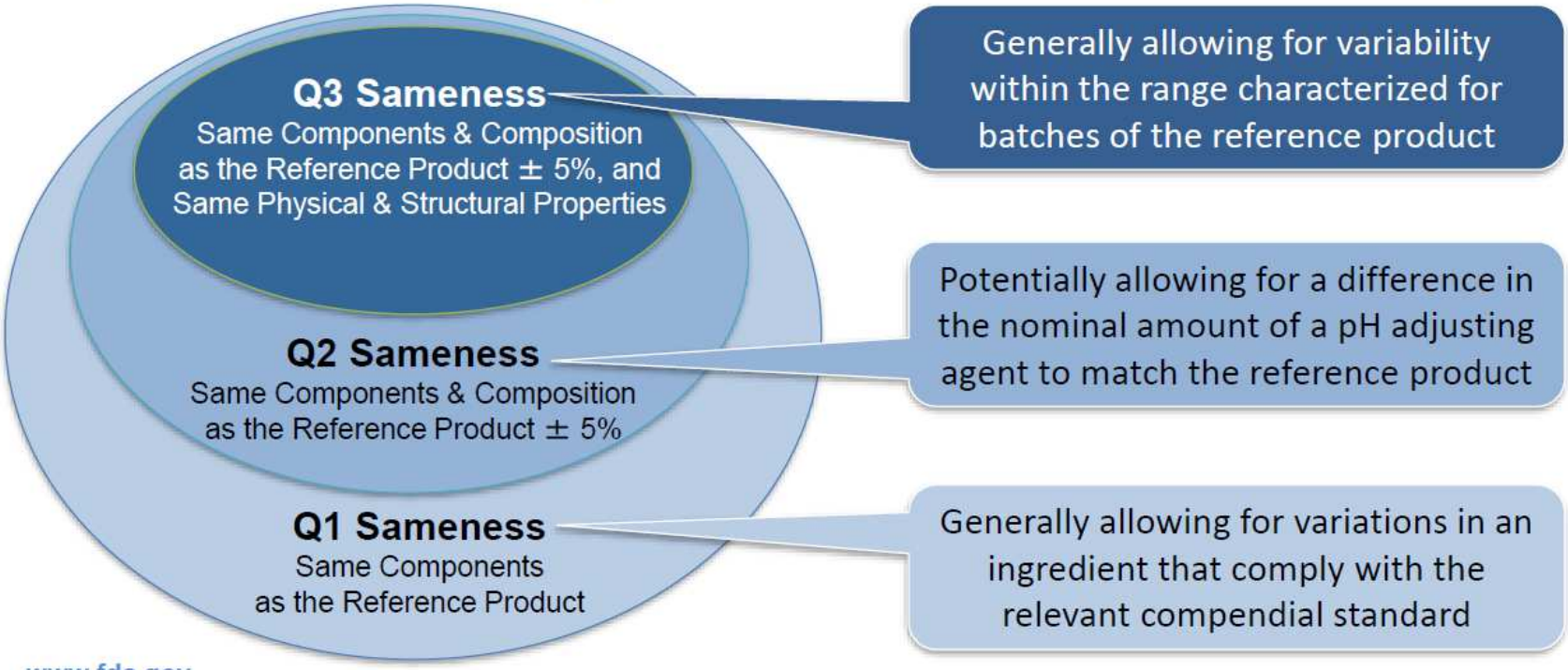
PSGs for Complex Topical/Transdermal Products

Q3 Sameness for Topical Products

- An evolving concept *for topical dermatological products*



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PSG – Product Specific Guidelines

Slide taken from Dr. Sam Raney Presentation at Complex Generic Drug Product Development Workshop held in September 25-25, 2019

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Major Questions -

1. How can we can relate these Q3 properties of the test formulation to its clinical performance?

2. Can we identify critical Q3 properties which are likely to exert significant effects on the bioavailability of the API from the formulation?

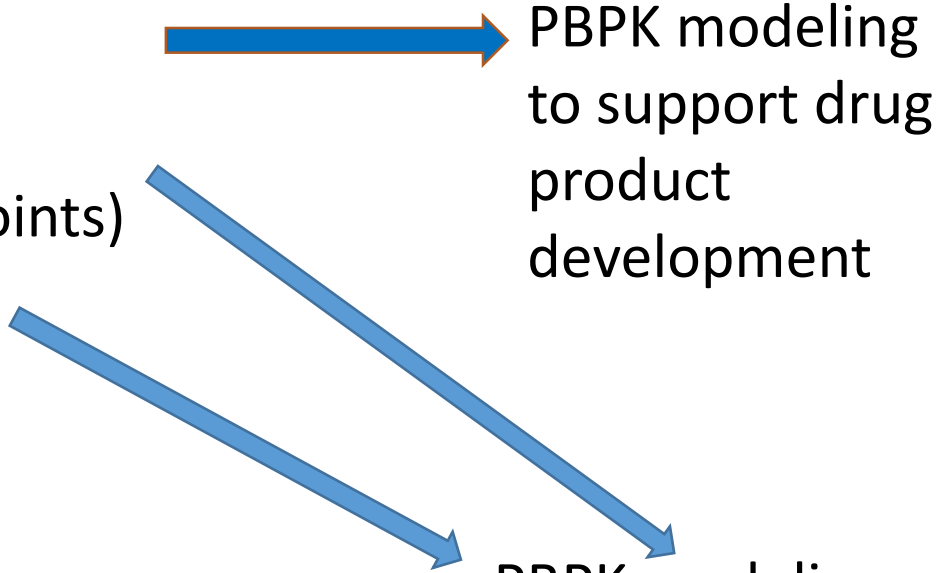
3. Can we come up with a safe space where we can widen the range of these critical Q3 properties ?

PBPK Modelling can play a very important role in answering all these questions

PSGs for Complex Topical/Transdermal Products

Option 1: R and T are Q1/2

- *In vitro* characterization (Q3 similarity+ IVRT + IVPT)
- (+ *In vivo* BE study with PK endpoints)
- (+ *In vivo* comparative clinical end point BE study)



Option 2: R and T are not Q1/2

- *In vivo* comparative clinical end point BE study

R: Reference, T: Test
IVRT – In vitro Release Testing
IVPT – In vitro Permeation Testing

Slide taken from Dr. Eleftheria Tsakalozou Presentation at Complex Generic Drug Product Development Workshop held in September 25-25, 2019

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Q3 properties

Q3 properties for single/multiple phase systems

- Appearance
- Microscopy
- Particle Size
- Polymorphic form
- Drying rate (weight loss)
- Specific gravity
- Rheology
- pH
- Water activity
- Globule Size
- Solubility of drug in different phases
- Supersaturation and Precipitation potential
- Impact of container closure system

Slide adapted from Dr. Priyanka Ghosh's Presentation at Complex Generic Drug Product Development Workshop held in September 25-25, 2019

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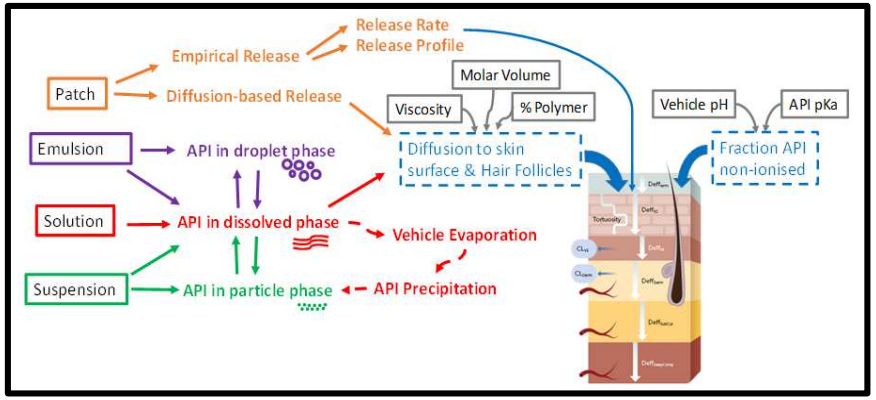
Formulation Q3 inputs in MPML-MechDermA model

Q3 properties for single/multiple phase systems

- Appearance
- Microscopy
- **Particle Size**
- Polymorphic form
- **Drying rate (weight loss)**
- **Specific gravity**
- **Rheology**
- **pH**
- Water activity
- **Globule Size**
- **Solubility of drug in different phases**
- **Supersaturation and Precipitation potential**
- Impact of container closure system



Formulation Inputs in MPML MechDermA Model

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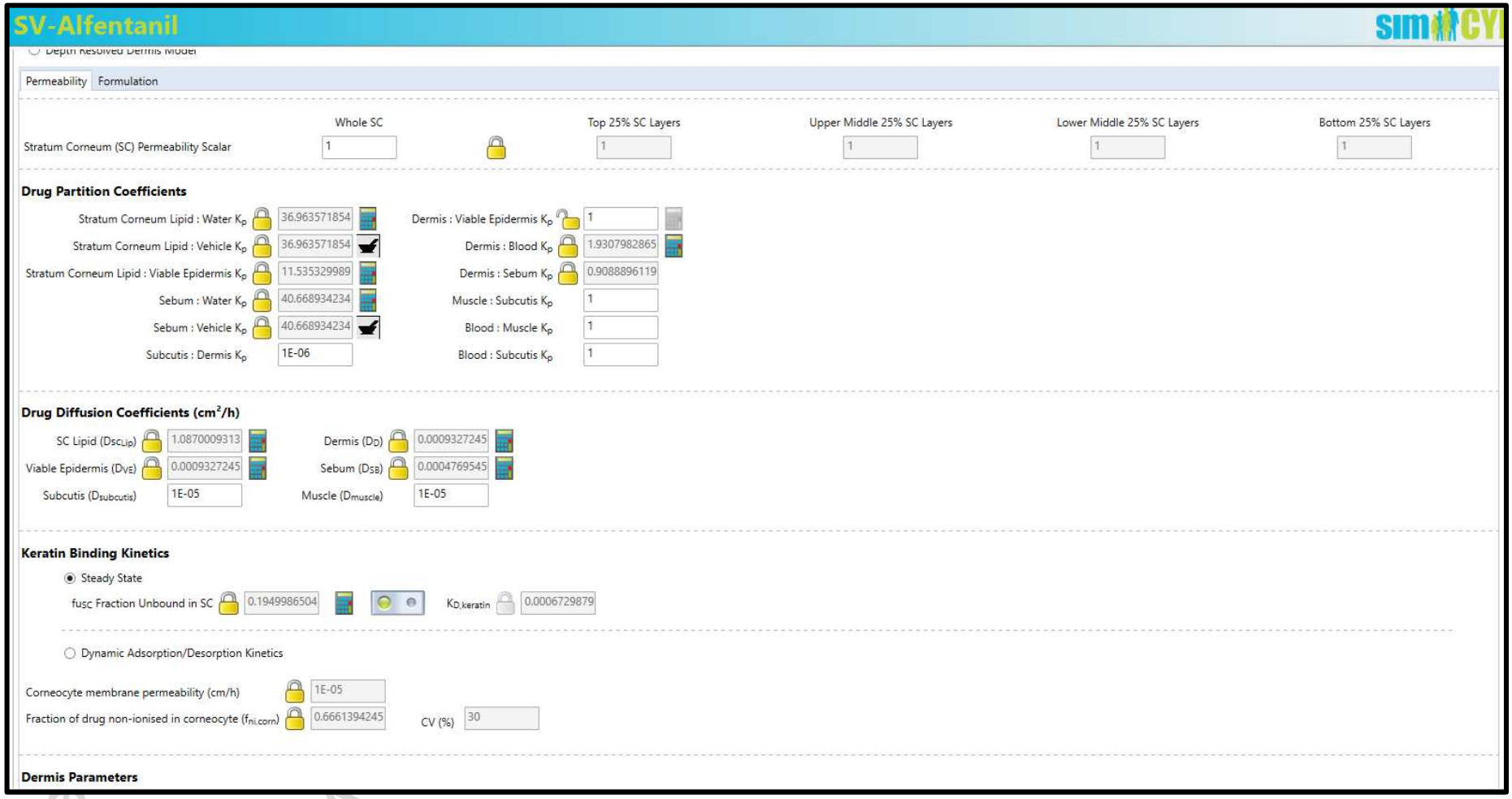
Major Screen Change in V19 (Permeability)

Split of Permeability and Formulation Sections



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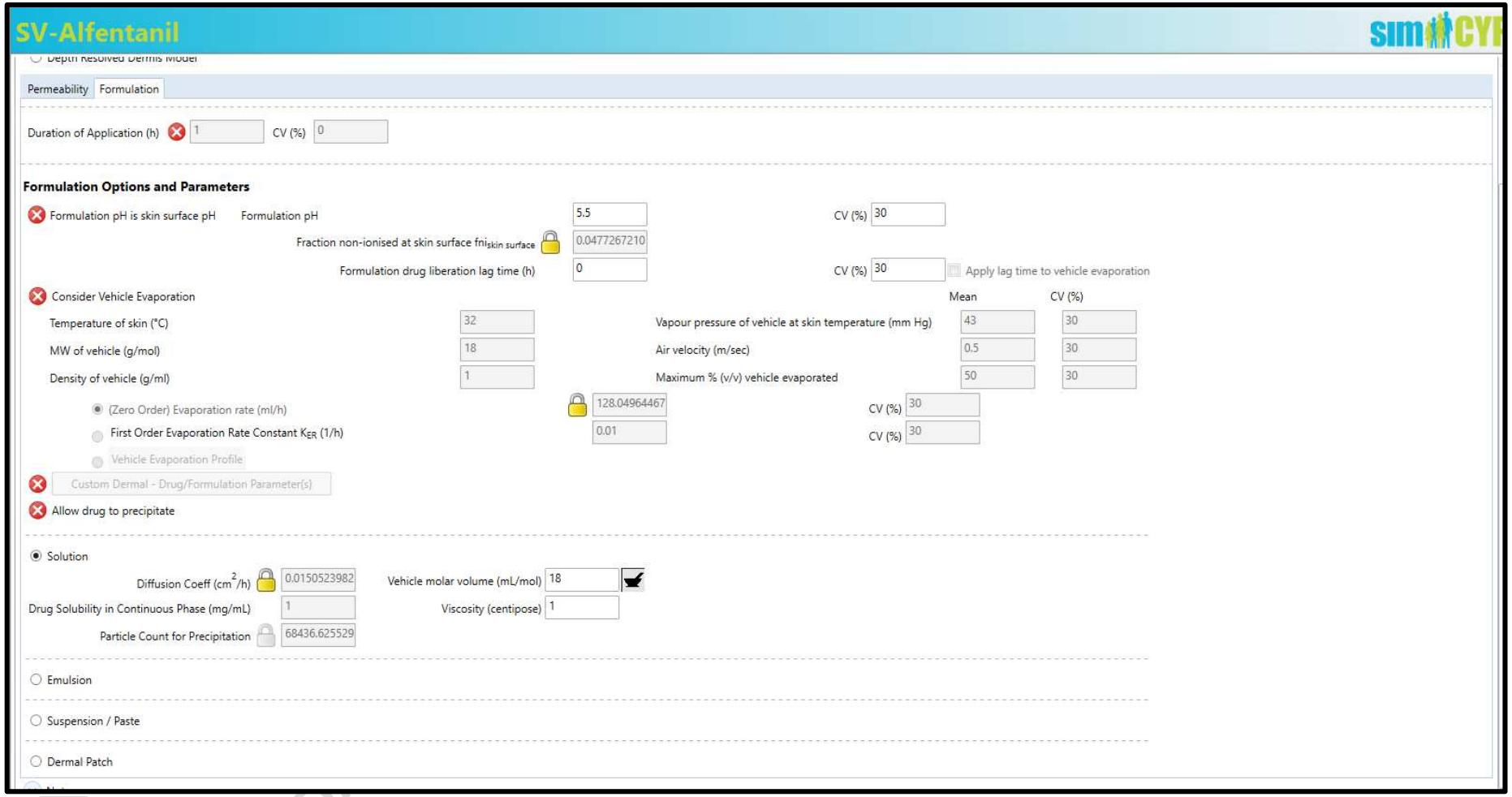
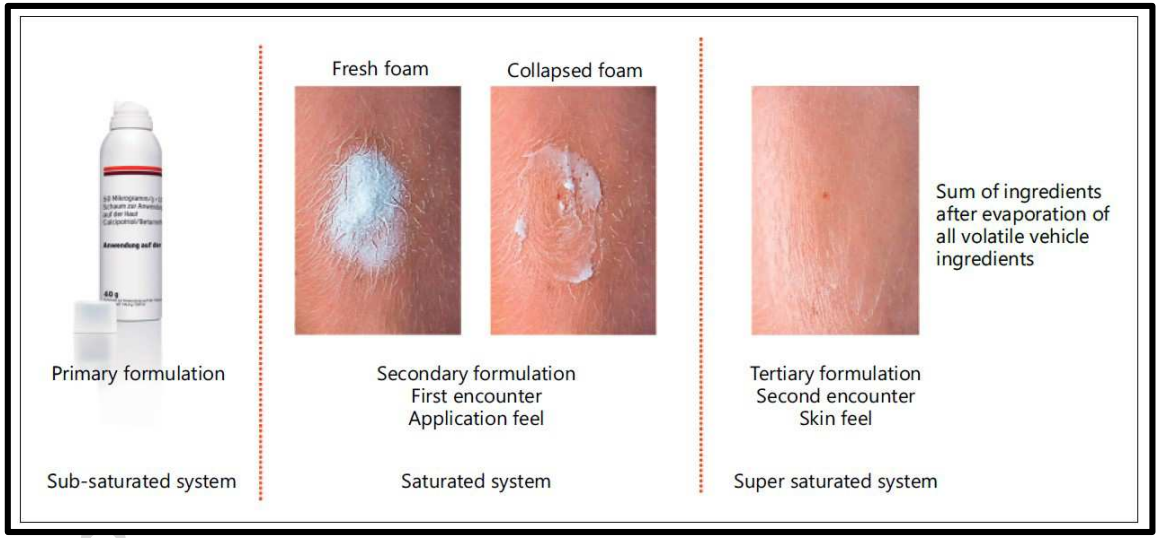


Metamorphosis of Topical Formulations

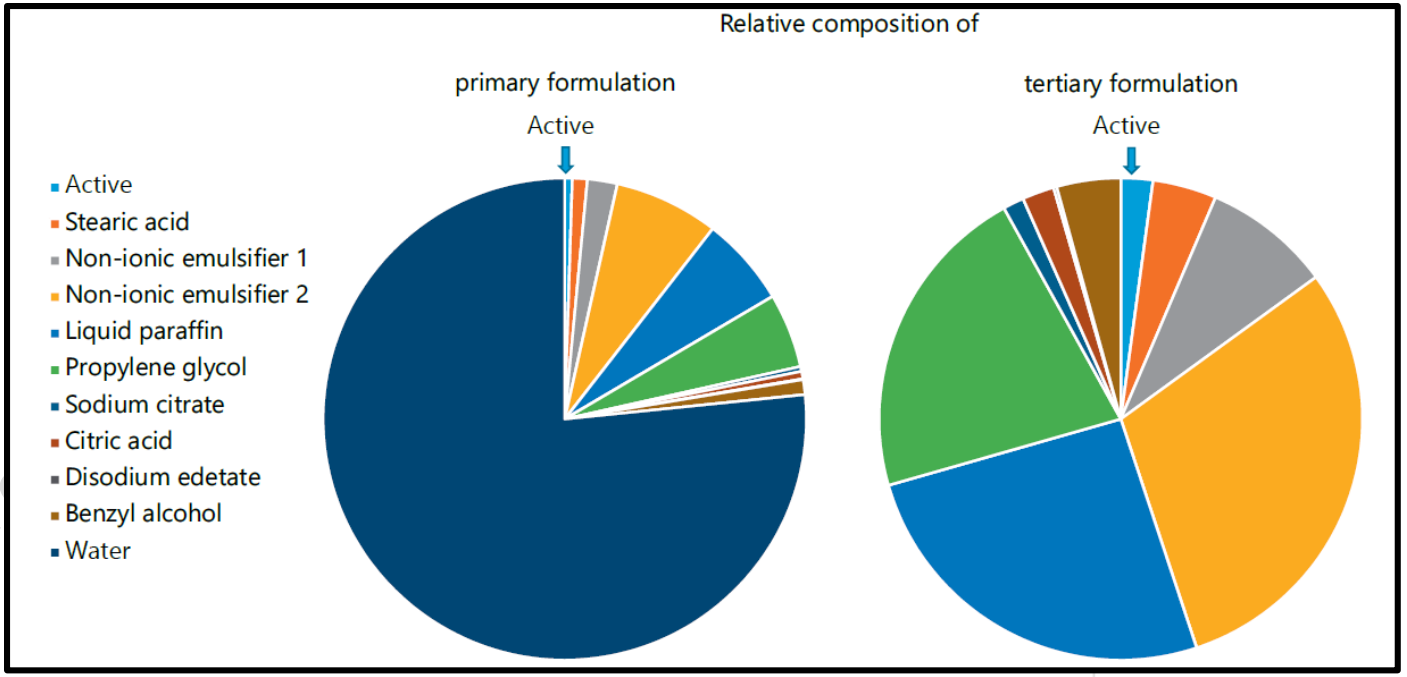


Metamorphosis of the vehicle: primary, secondary and tertiary formulation before, during and after the application procedure of a pressurized product.

Image adapted from Lind et al, Dermatol Ther (Heidelb) 2016; 6: 413–425.

Metamorphosis of the vehicle: relative composition of a commercial topical formulation before (as present in a tube) and after application onto the skin (as present on the skin).

Image adapted from Suber et al, Curr Probl Dermatol. Basel, Karger, 2018, vol 54, pp 152–165



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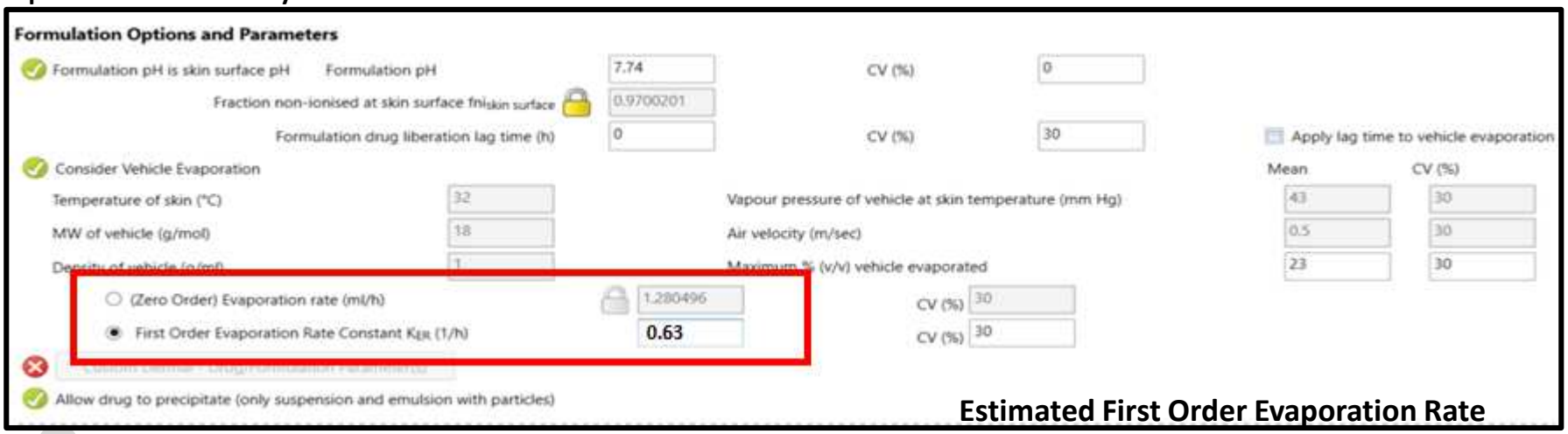
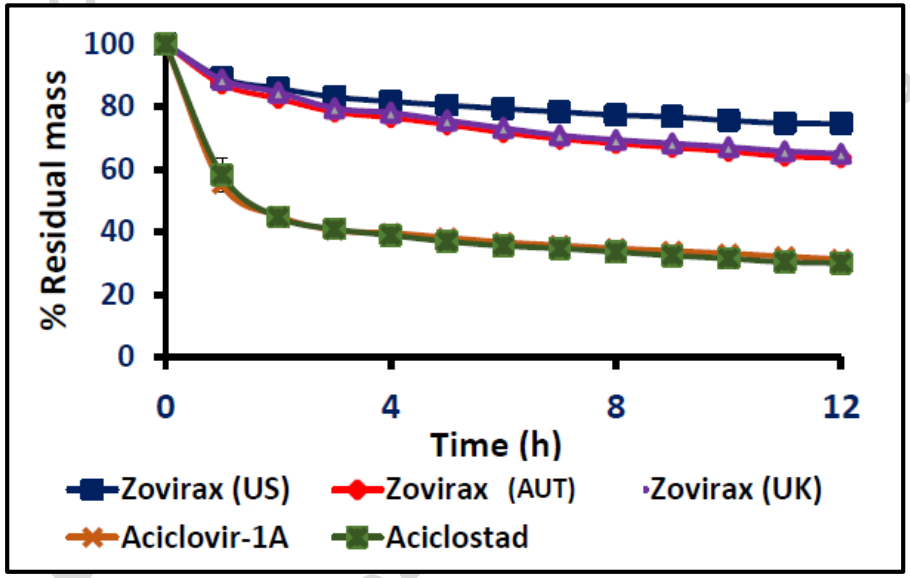
Vehicle Evaporation in MPML MechDermA Model

Options currently available in V18

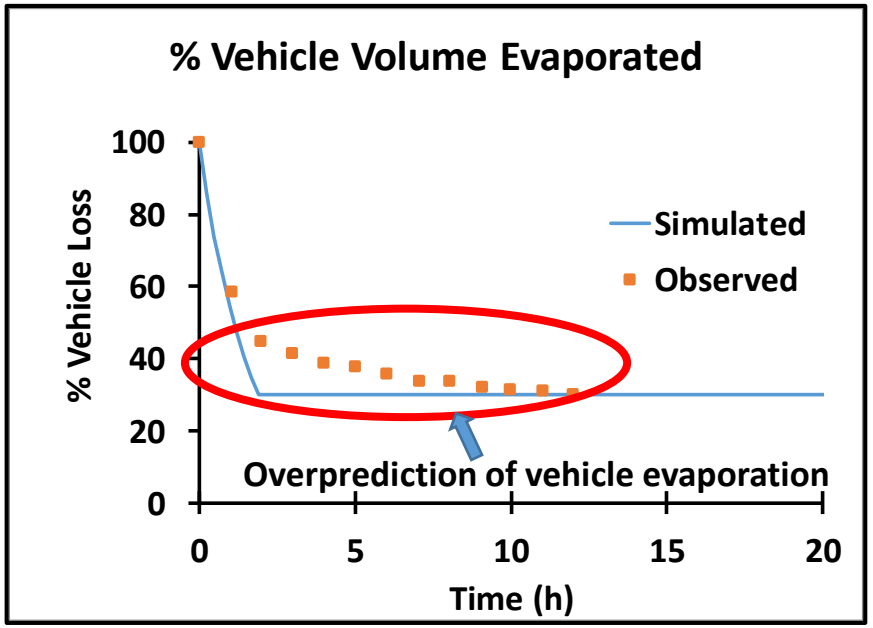


Estimated First Order Evaporation Rate



Vehicle Evaporation Profile of Acyclovir Commercial Products

Data obtained from Prof. Narasimha Murthy (University of Mississippi) Presentation



Observed and Simulated Vehicle Evaporation Profile of Aciclostad

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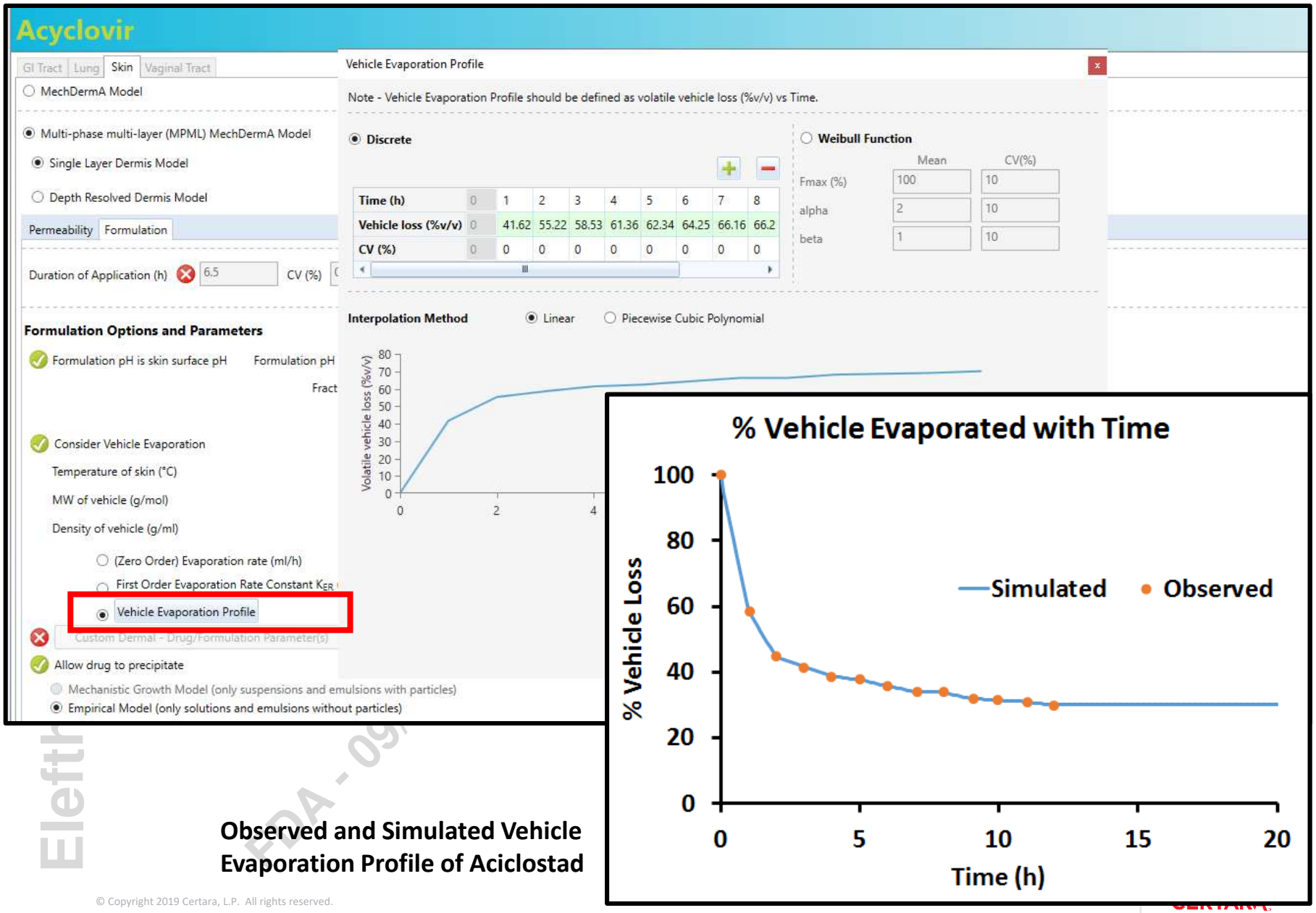
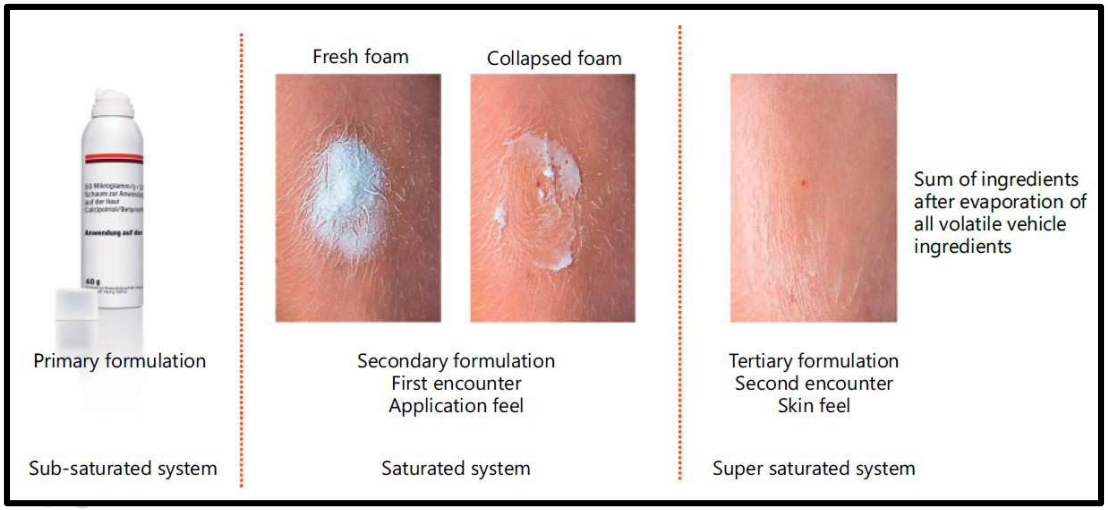
Vehicle Evaporation – User Input Profile Input Option In V19



Observed and Simulated Vehicle Evaporation Profile of Aciclostad

Supersaturation and Precipitation Topical Formulations



Metamorphosis of the vehicle: primary, secondary and tertiary formulation before, during and after the application procedure of a pressurized product.

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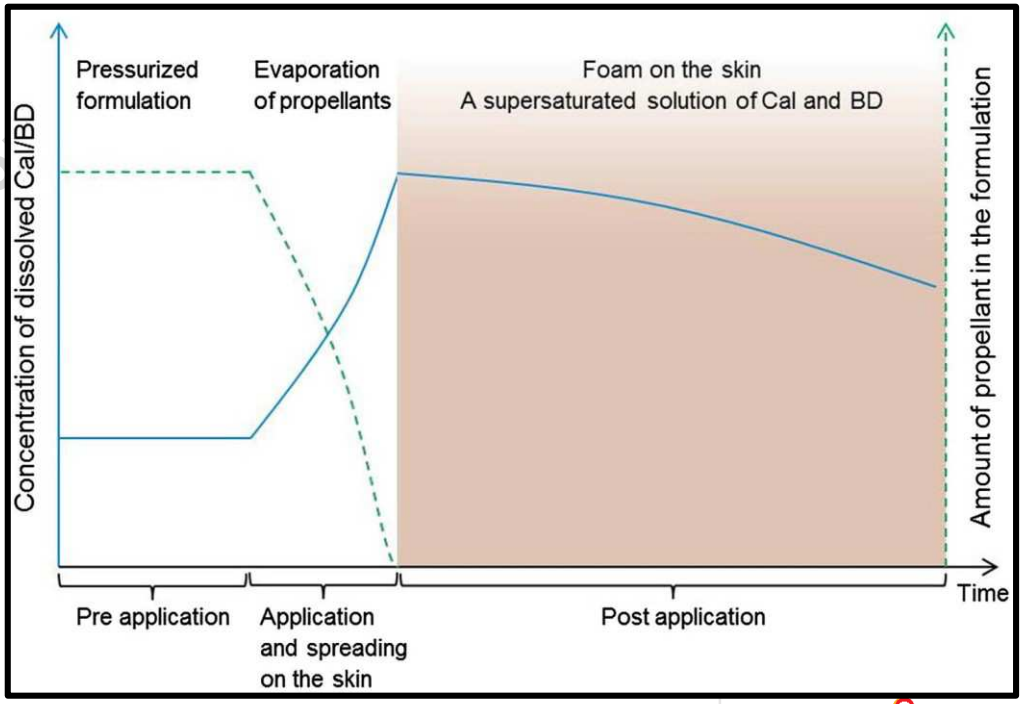

Change in concentration of active ingredients dissolved in the aerosol form formulation over application time. BD Betamethasone dipropionate, Cal calcipotriene.

Image adapted from Lind et al, Dermatol Ther (Heidelb) 2016; 6: 413–425.

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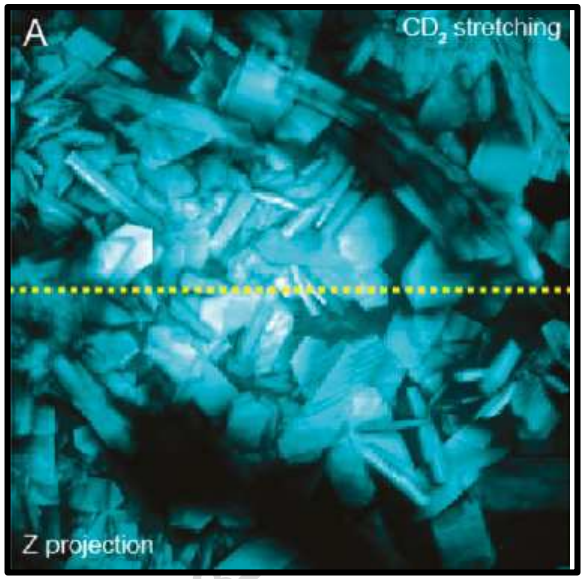
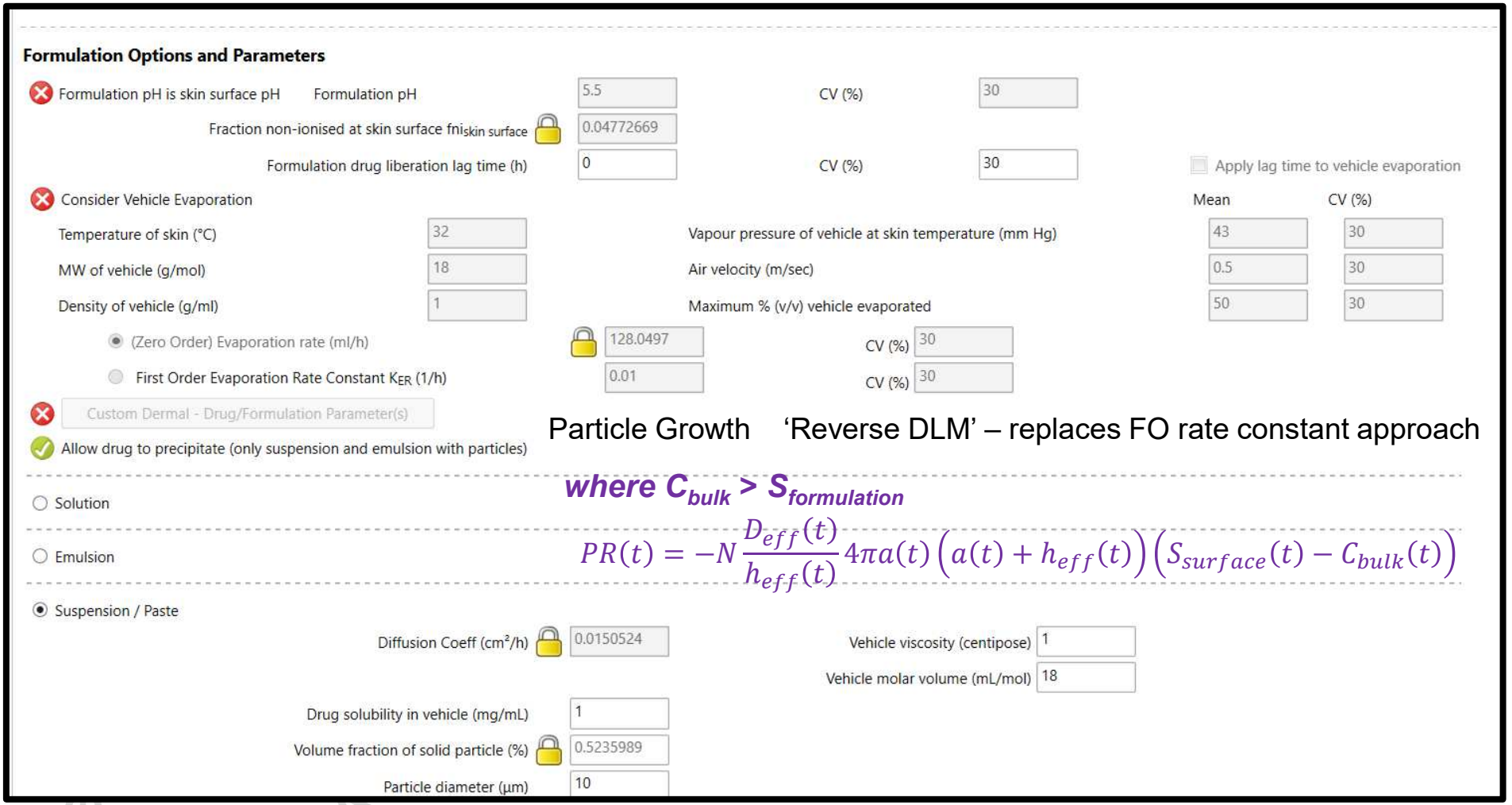
Supersaturation and Precipitation Topical Formulations



Crystal formation on the skin surface 25 min post-topical application of a solution of ibuprofen in PG

Image taken from Saar et al, Mol. Pharmaceutics 2011, 8, 969–975

Supersaturation and Precipitation Model – Screen Design (Already in V18)



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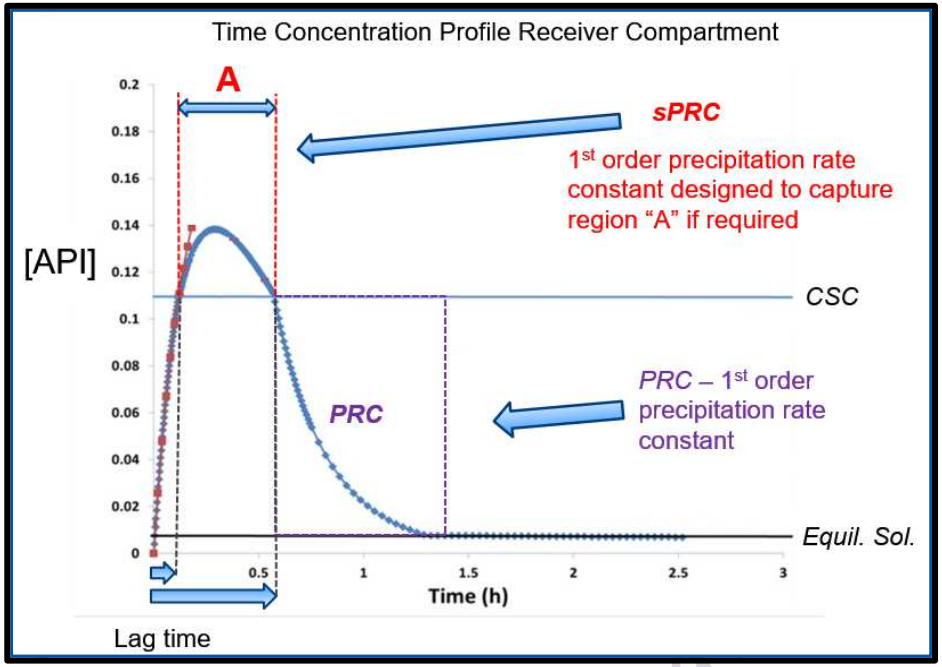
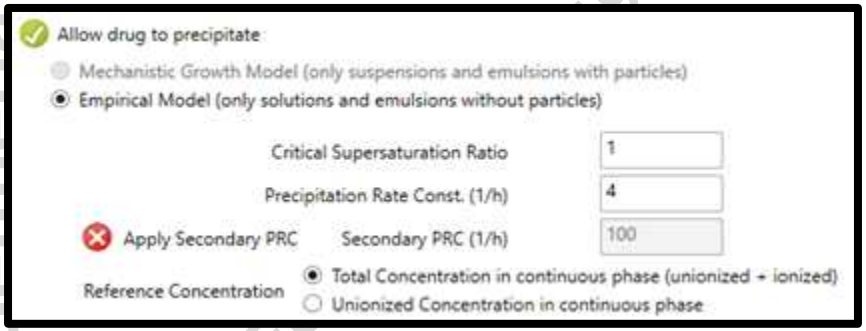
Supersaturation and Precipitation Empirical Model

- Formulation - Solution and Emulsion without particle





Empirical Model

IF supersaturated conditions encountered THEN:

Dissolution stops

Precipitation can only begin when CSC is reached

***CSC* is a critical conc. at which precipitation starts**

[Drug] may continue to rise due to slow permeation of drug from skin

Supersaturated conc. may exceed *CSC* (*CSR* x Eq.Sol)

CSC – Critical Supersaturation Concentration
CSR – Critical Supersaturation Ratio
PRC – Precipitation Rate Constant (1/h)
sPRC – Secondary Precipitation Rate Constant (1/h)

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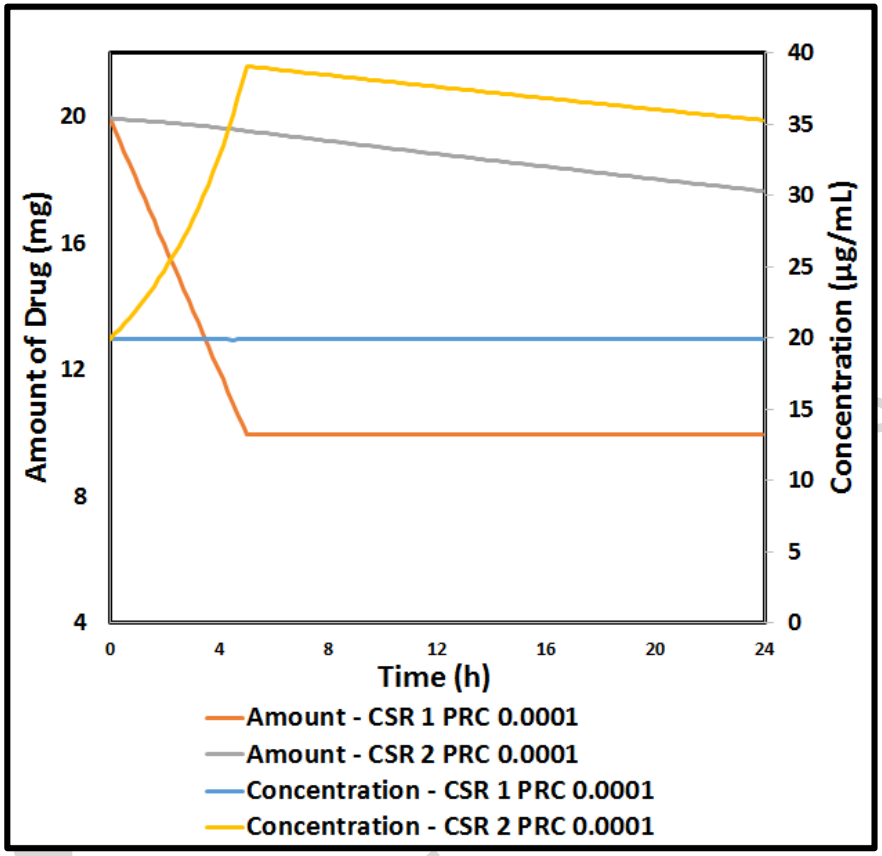
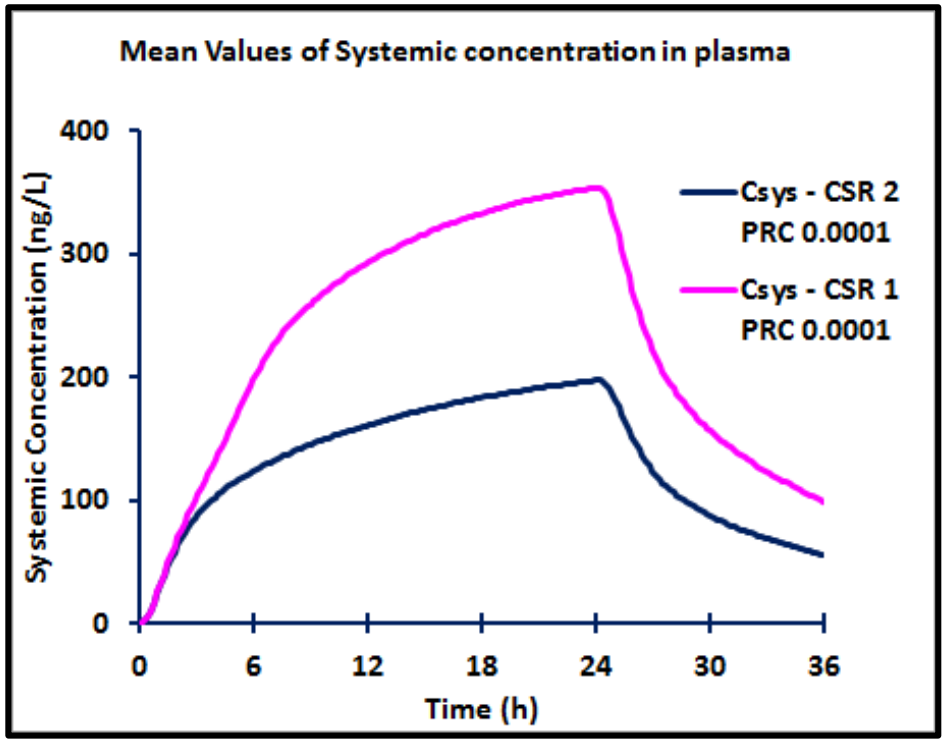
Supersaturation and Precipitation Simcyp Results

Formulation Solution Dose 20 mg Solubility 20 mg/mL

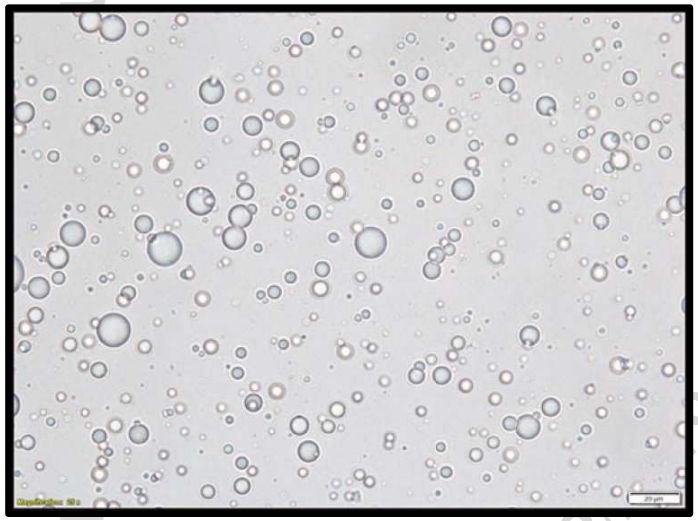
Volume of Formulation 1 mL Vehicle Evaporation = 0.1 mL/h





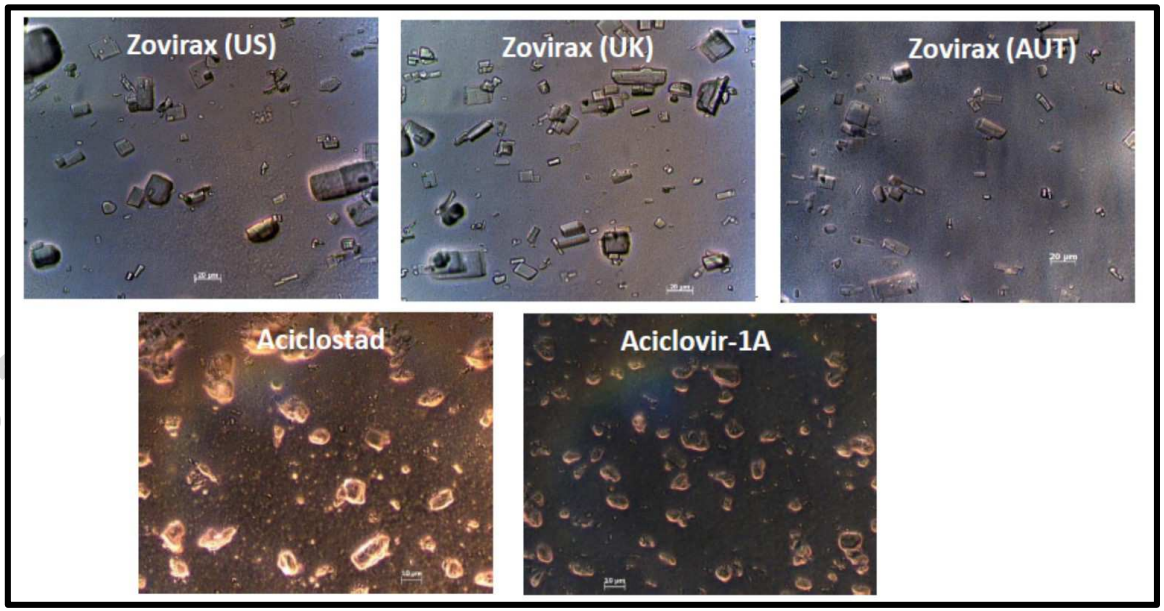
Particle Size Distribution (PSD) – Droplet and Solid Particles

- Topical Emulsion semisolid formulation containing suspended API are most complex pharmaceutical products to develop for application to the skin
- Ratio of dissolved active to suspended active can influence skin permeation
- API PSD or globule PSD can have significant effect on the bioavailability of API



Microscopic picture (Magnification, 500×) of the carbomer "Emulgel" containing dissolved API and dispersed oil globules in the gel matrix.

Taken from book The Role of Excipients in the Microstructure of Topical Semisolid Drug Products



Acyclovir API characterization in five commercial products.
Slide obtained from Prof. Narasimha Murthy (University of Mississippi) Presentation

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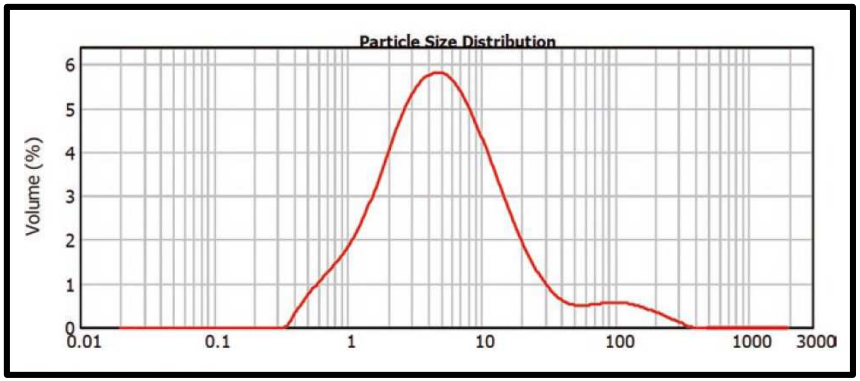
Particle Size Distribution (PSD) – Droplet and Solid Particles

In V19, users can define the particle size distribution (PSD) of the droplets and solid particles as either monodisperse or polydisperse particle size distribution in emulsion and suspension formulation.



Custom Dermal - Drug/Formulation Parameter(s)

Allow drug to precipitate

Solution

Emulsion

Diffusion Coeff (cm²/h) 1.37474885E-(

Vehicle molar volume (mL/mol) 18

Viscosity (centipose) 129062

Volume fraction of dispersed phase (%) 2.4968

Drug solubility ratio dispersed/continuous phase 13.5

Radius of dispersed phase droplets (µm) Monodispersed 1.425 Polydispersed

Droplet permeability (cm/h) 1E-05

Number of droplets per cm³ (N/mL) 2059920944

Particles in continuous phase?

Volume fraction of solid particle (%) 0.5235987755

Drug solubility in continuous phase (mg/mL) 1

Radius of particles (µm) Monodispersed 5 Polydispersed

Particle Count for Precipitation 177776071.43

Number of particles per cm³ (N/mL) 10000000

Density of solid particle (g/mL) 1.2

Suspension / Paste

Dermal Patch

Notes

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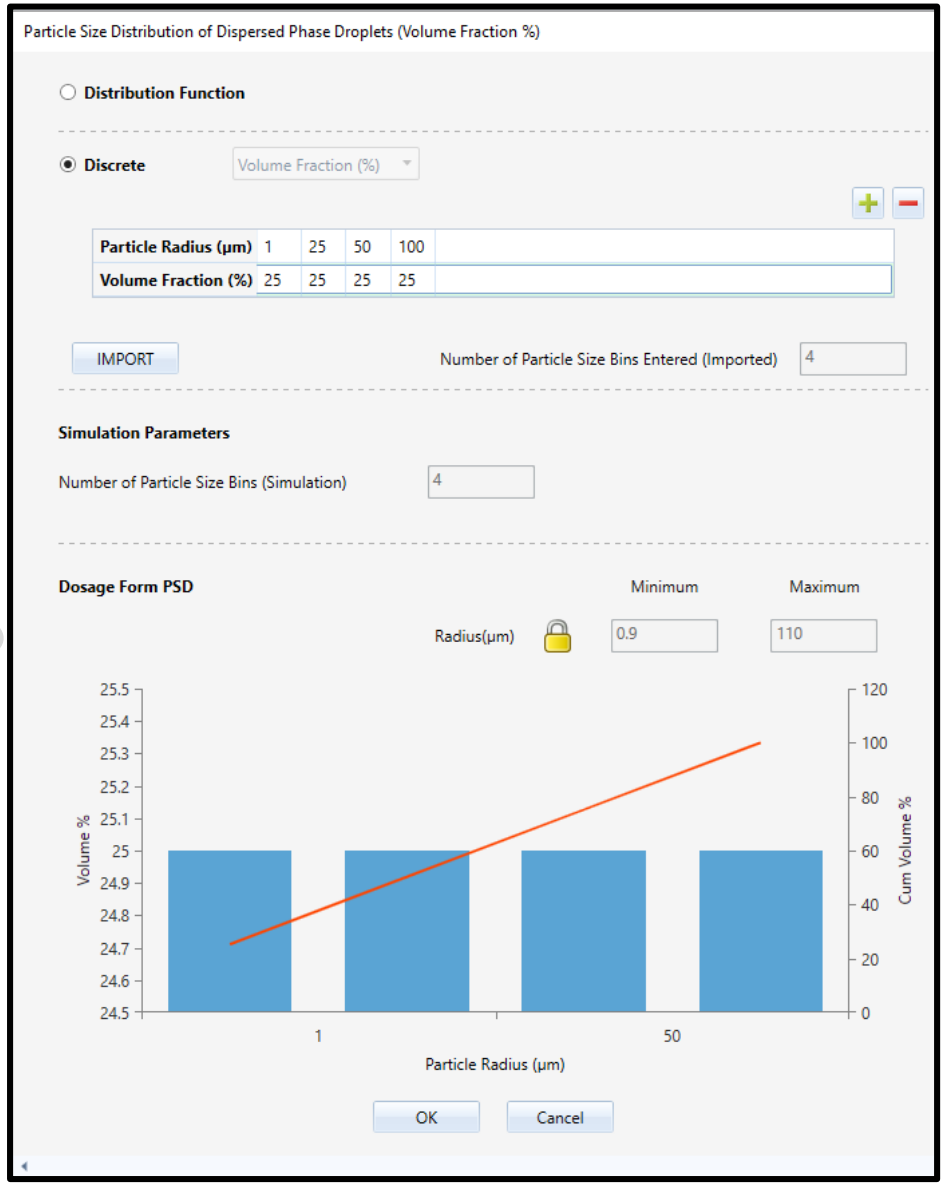
Particle Size Distribution (PSD) – Droplet and Solid Particles



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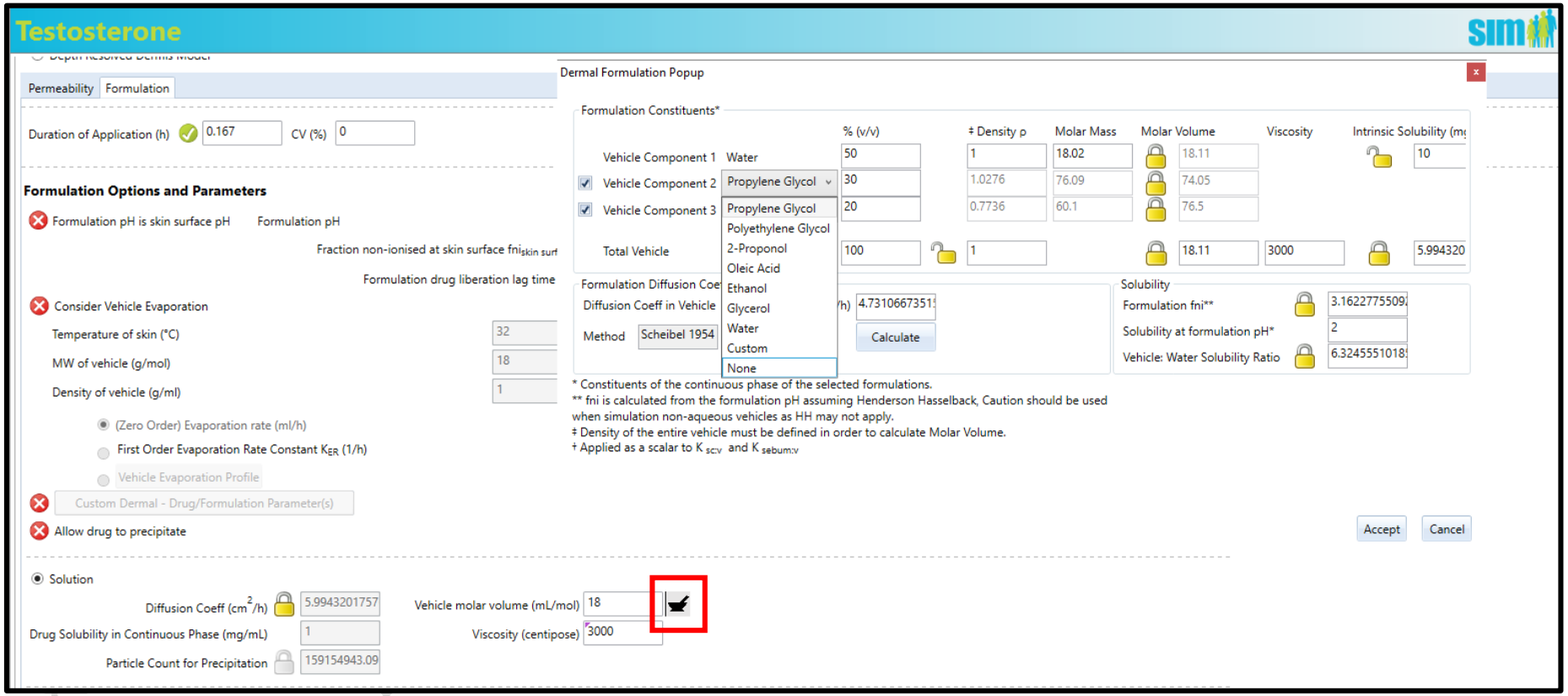
Introduction of Formulation Toolbox

- Allows selection of components of dermal formulations
- Prediction of molar volume of the formulation vehicle
- Correction stratum corneum lipid: water partition coefficient with vehicle: water solubility ratio



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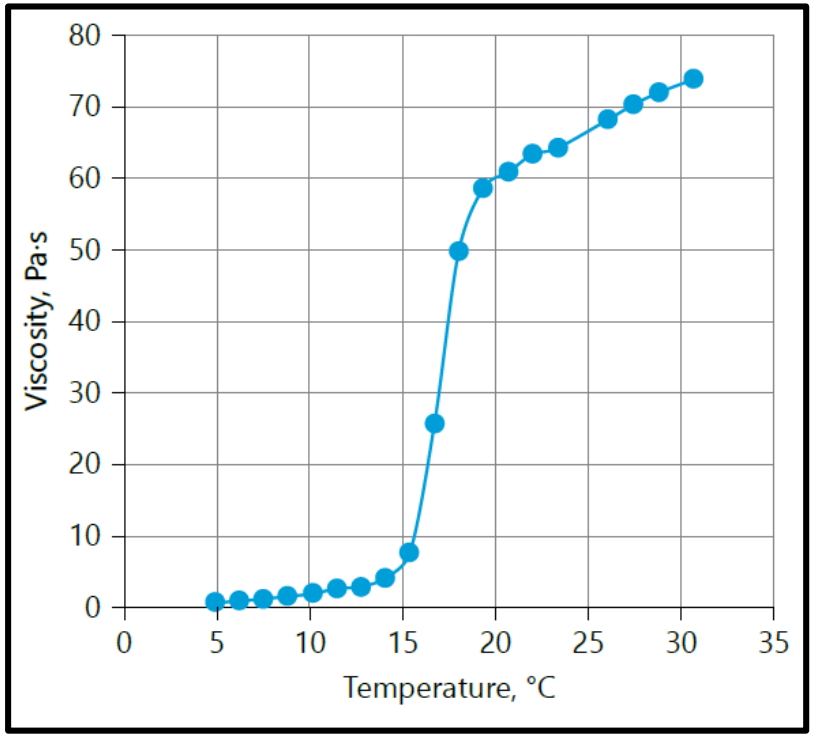
Rheological Considerations

Product	Viscosity, Pa. s			Yield Stress, Pa
	@shear rate: 20 s^{-1}	@ shear rate 3300s^{-1}	@ shear rate: 0.0025 s^{-1}	
Zovirax-USA	17	0.28	8360	50
Zovirax-UK	N/A	N/A	31000	300
Zovirax-AUT	N/A	N/A	30100	300
Aciclostad	3.2	0.06	29300	100
Aciclovir- 1A	2.6	0.06	28100	100
	Dictates the behavior during the initial application	Dictates the behavior during spreading the sample on skin	Dictates at rest condition, i.e., diffusion of drug through thin film	

Viscosity Differences of Commercial Acyclovir Products at Different Shear Rates



Some thermo-sensitive gels show increased product viscosity (Pa·s) at body temperature (°C). As a consequence, a prolonged residence of actives on skin is observed due to increased viscosity of vehicle (e.g., Linoseptic ® [octenidin dihydrochlorid, phenoxyethanol as disinfectants]).

Image adapted from Suber et al, Curr Probl Dermatol. Basel, Karger, 2018, vol 54, pp 152–165

Slide obtained from Prof. Narasimha Murthy (University of Mississippi) Presentation

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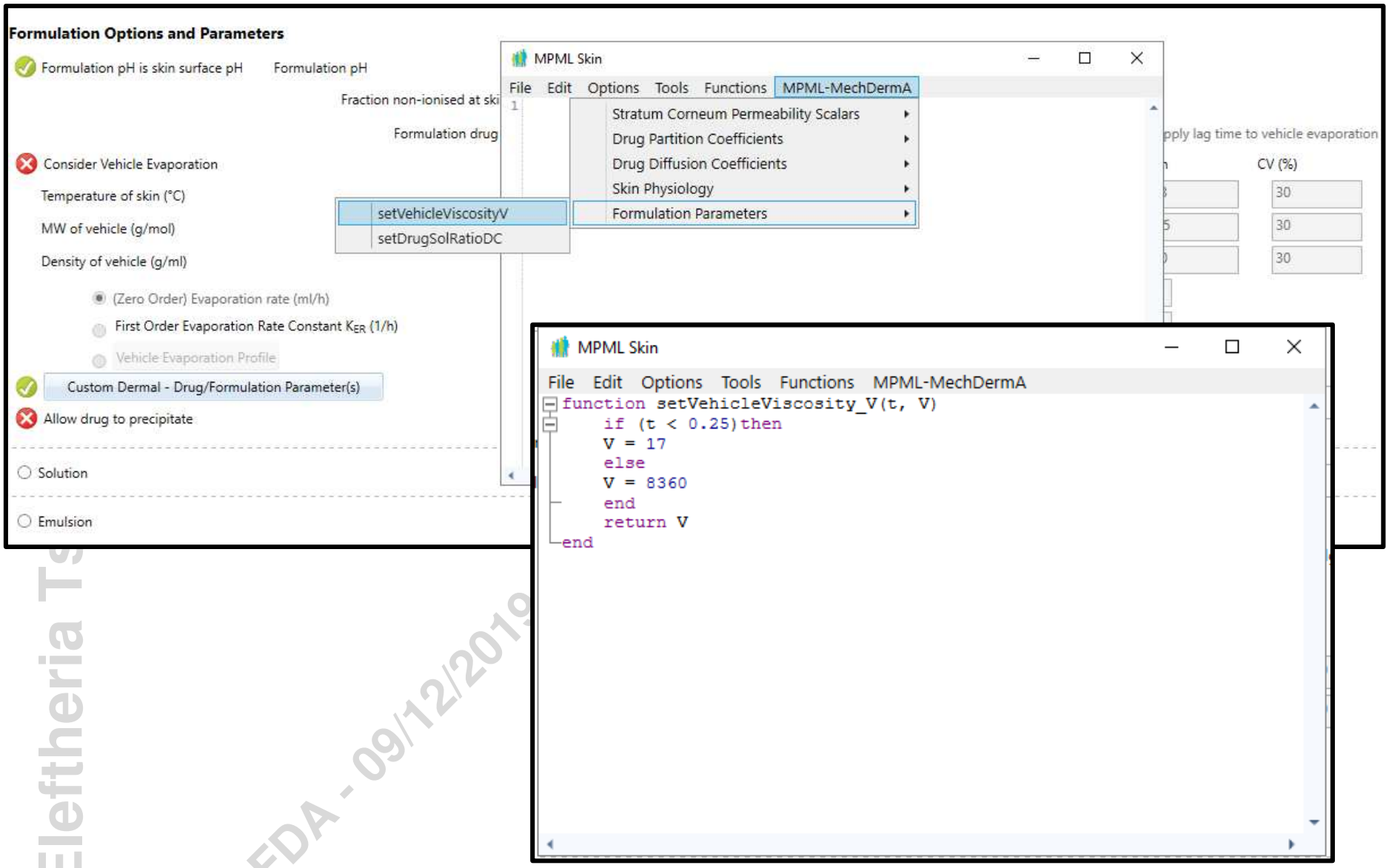
Rheological Considerations – Addition of LUA Functions



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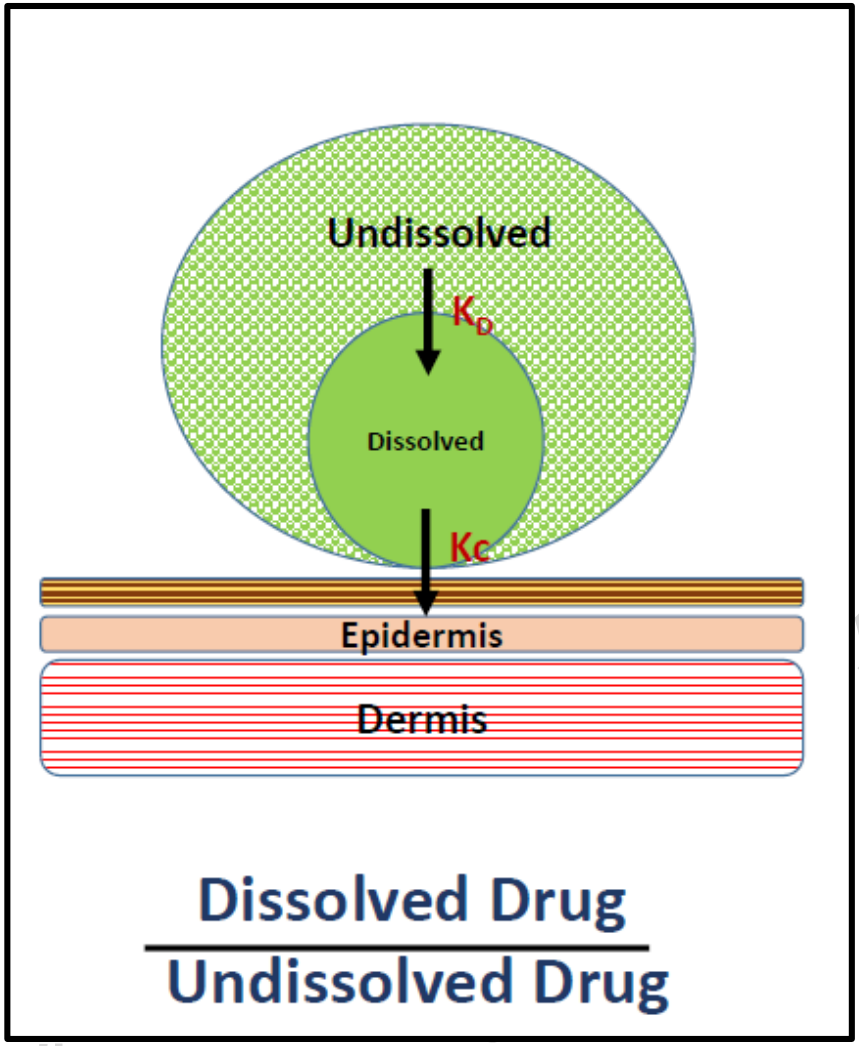
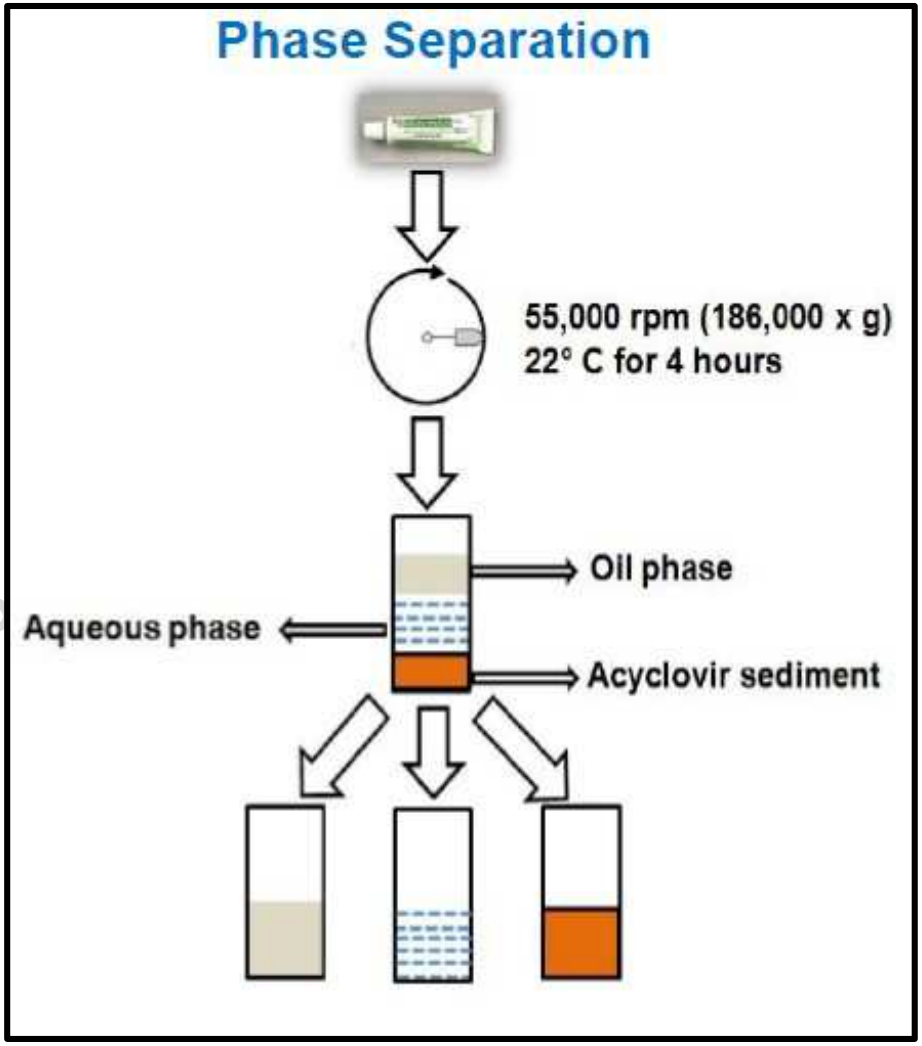
Distribution of Drug in Topical Multi-Phase Systems





Slide obtained from Prof. Narasimha Murthy (University of Mississippi) Presentation

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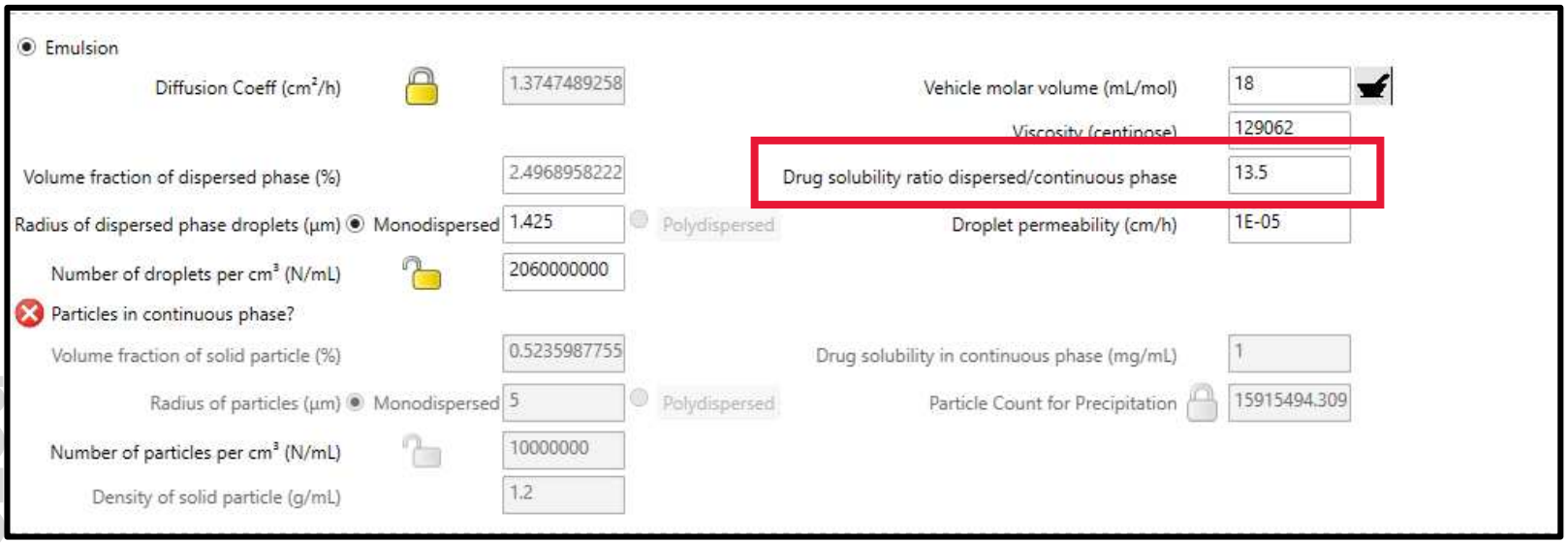
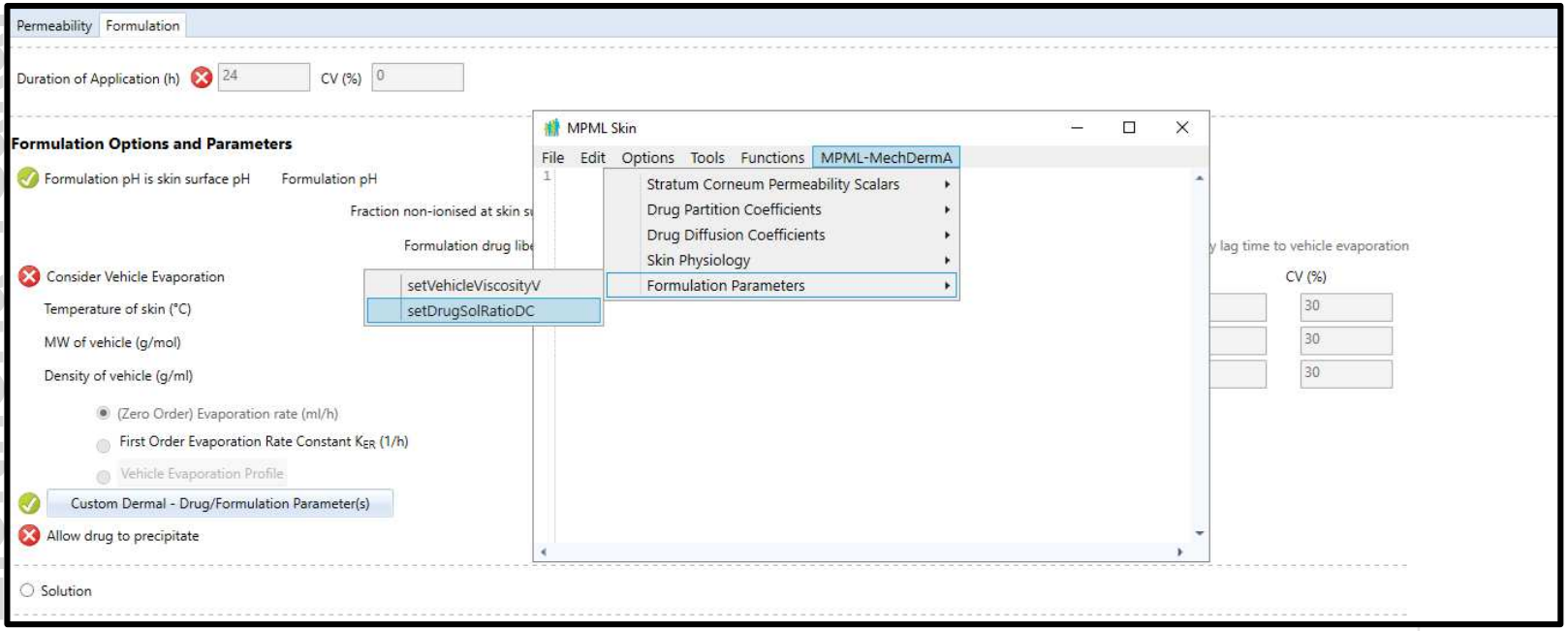
Variation of Drug Solubility Ratio – LUA Script





Updates to the Prediction Toolbox

Pharm Res (2018) 35: 141
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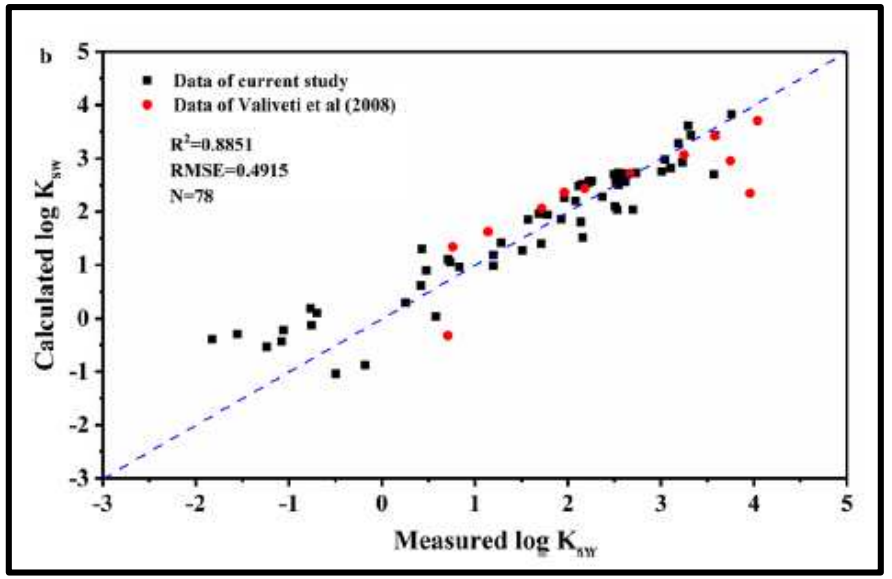
RESEARCH PAPER

Determining the Effect of pH on the Partitioning of Neutral, Cationic and Anionic Chemicals to Artificial Sebum: New Physicochemical Insight and QSPR Model

Senpei Yang[1] · Lingyi Li[1] · Tao Chen[2] · Lujia Han[1] · Guoping Lian[2,3]

$$K_{sb:w,Yang} = \left(f_{ni\ skin\ surface} * \left(\frac{1 + 0.71 * 10^{pH-6.95}}{1 + 10^{pH-6.95}} \right) \right)$$



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Summary of Dermal Quality Attributes V19 Updates

- Input of User-Defined Evaporation File
- Empirical model to define supersaturation and precipitation from solution and emulsion without particle formulations
- Input of polydisperse particle size distribution for globules and solid particles
- Addition of formulation toolbox
- LUA functionality to alter vehicle viscosity and drug distribution ratio between phases
- Addition of new QSAR for Sebum:Water Partition Coefficient

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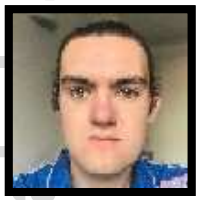

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Questions?

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Simcyp

Release Webinar:

Physiology Related Enhancements

Dermal Enhancements in V19

- Depth Resolved Dermis Model

Developed under FDA grant:

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

(Grant Award #1 U01FD006521-01)

- Comedone Model (Acne)

- Updates to Psoriasis population file

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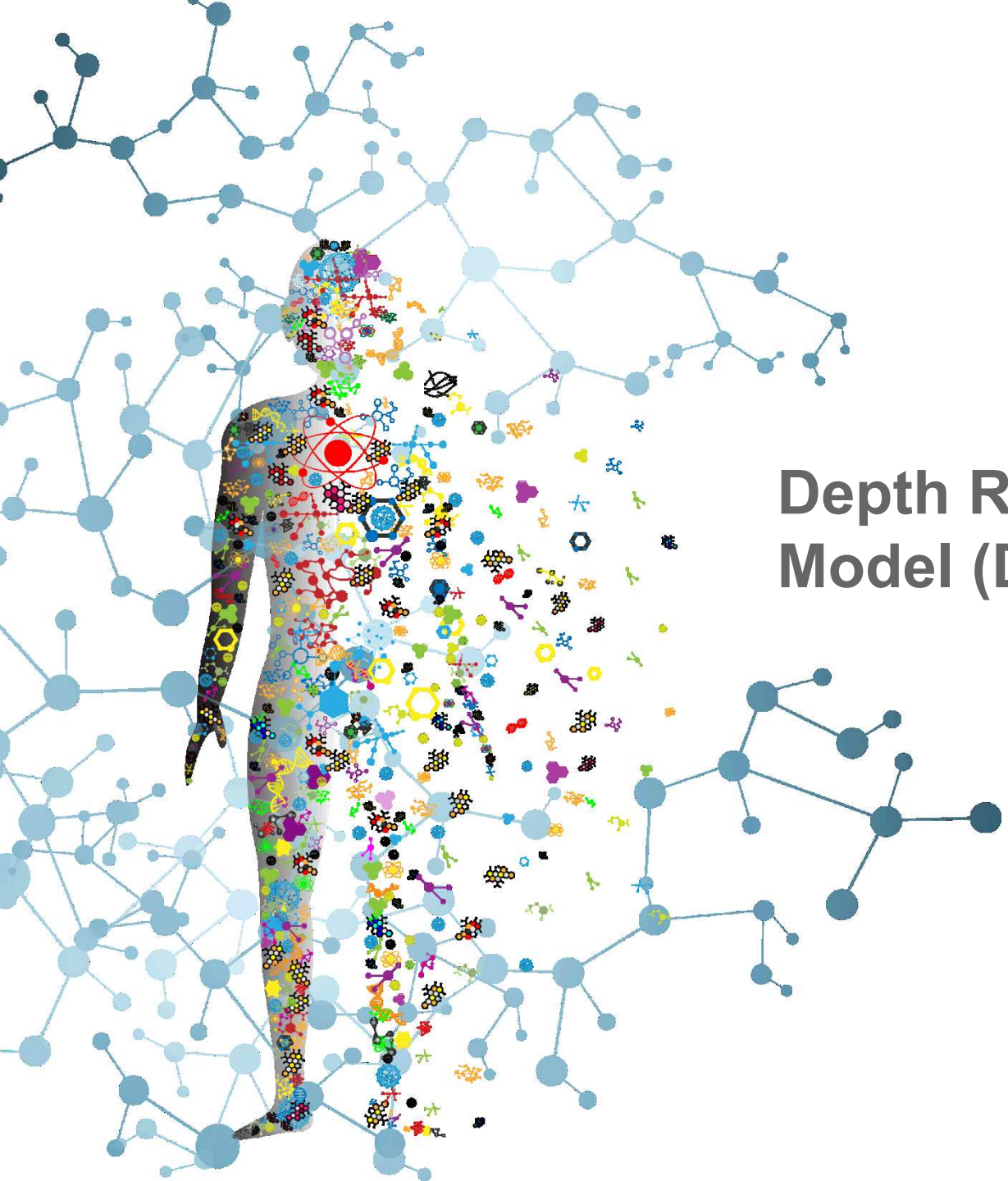

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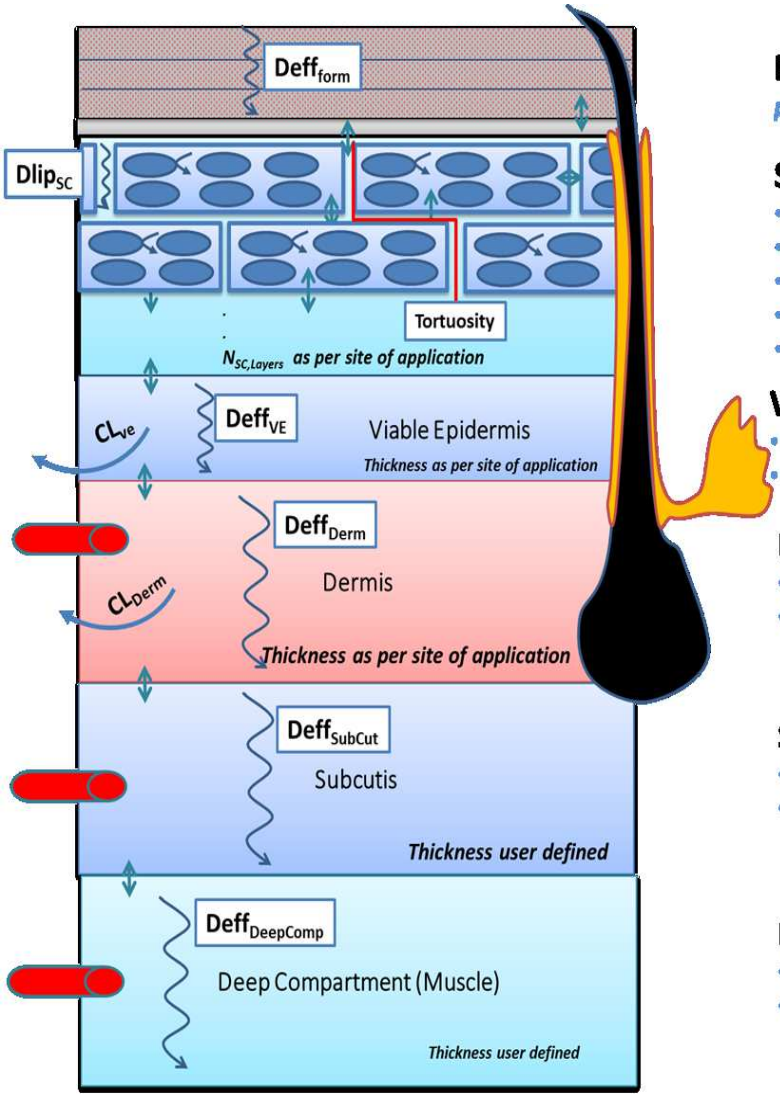
Depth Resolved Dermis Model (DRDM)

Background



Formulation *(Gel, cream, lotions, paste, patch, ointments, etc.)*

Stratum Corneum (SC)
- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and diffusivity*
- *Hair follicle density and size*

Viable Epidermis (VE)
- *Thickness, diffusivity*
- *Metabolism*

Dermis
- *Thickness, diffusivity*
- *Metabolism, blood flow*

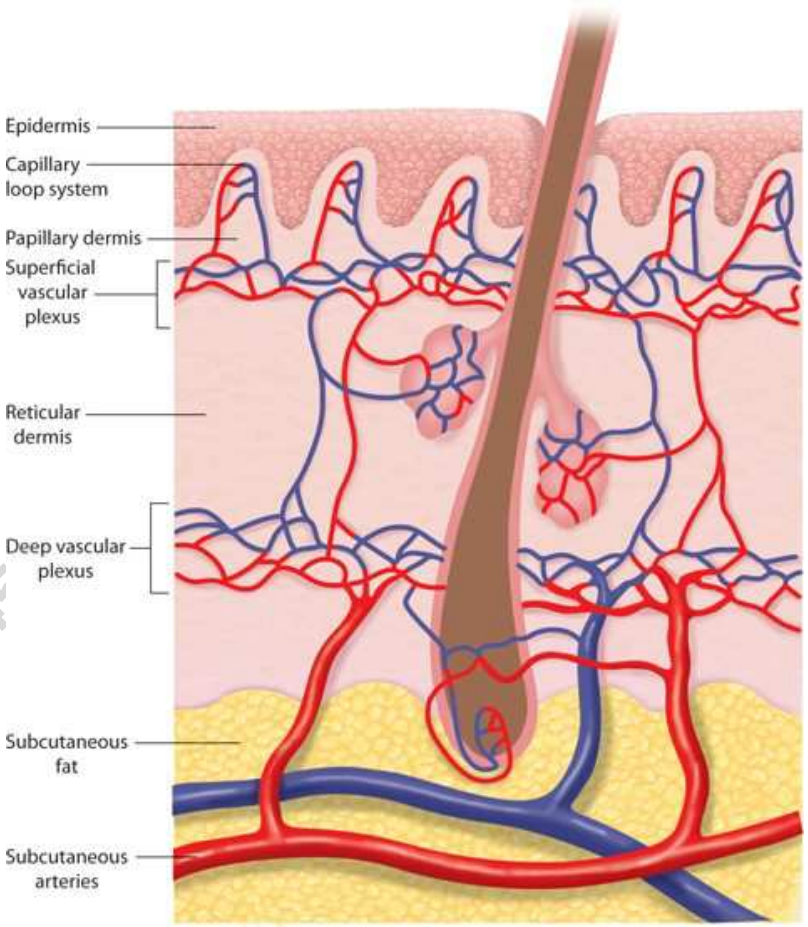
Subcutis
- *Thickness, diffusivity*
- *Blood flow*

Deep Tissue
- *Thickness, diffusivity*
- *Blood flow*

Dermis Physiology

Two distinct layers

- Papillary ~ 200 µm
- Reticular ~ 1000 µm



Source: Rose L. Hamm: *Text and Atlas of Wound Diagnosis and Treatment*: www.accessphysiotherapy.com
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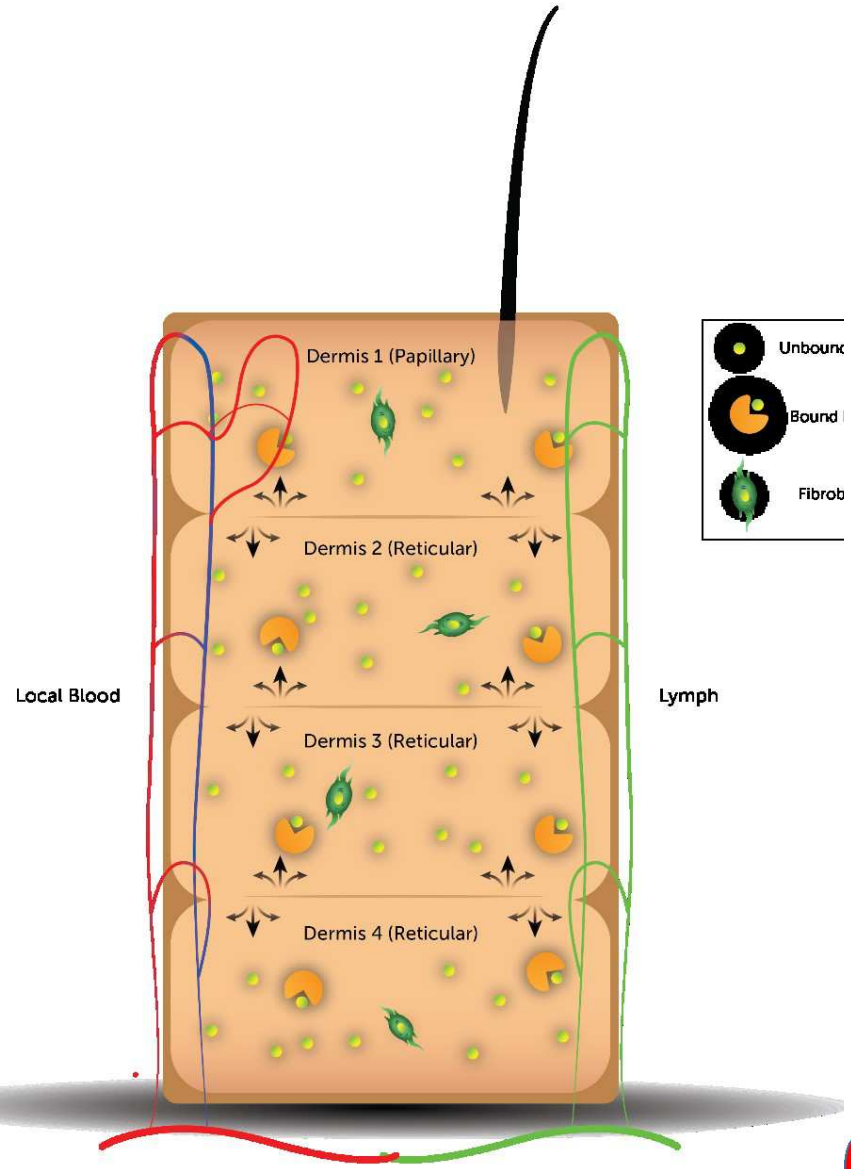
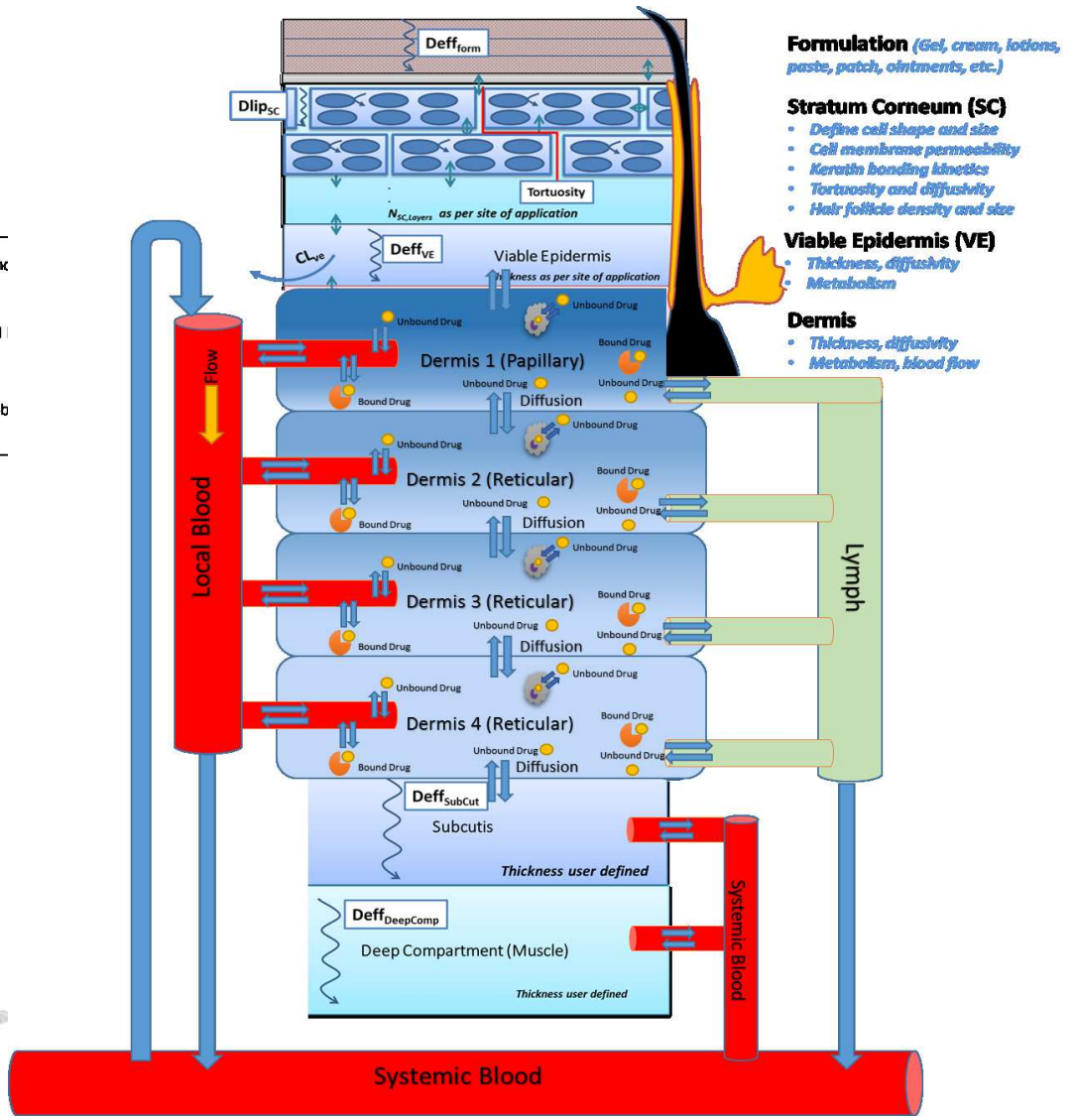
Depth Resolved Dermis Model (DRDM)

Model Development:

- Collect physiology data
- Develop a mechanistic framework to represent this physiology
- Collect measured data for diffusion in the dermis, new mechanistic QSAR developed in house
- Verify with measured concentration-depth data

Depth Resolved Dermis Model





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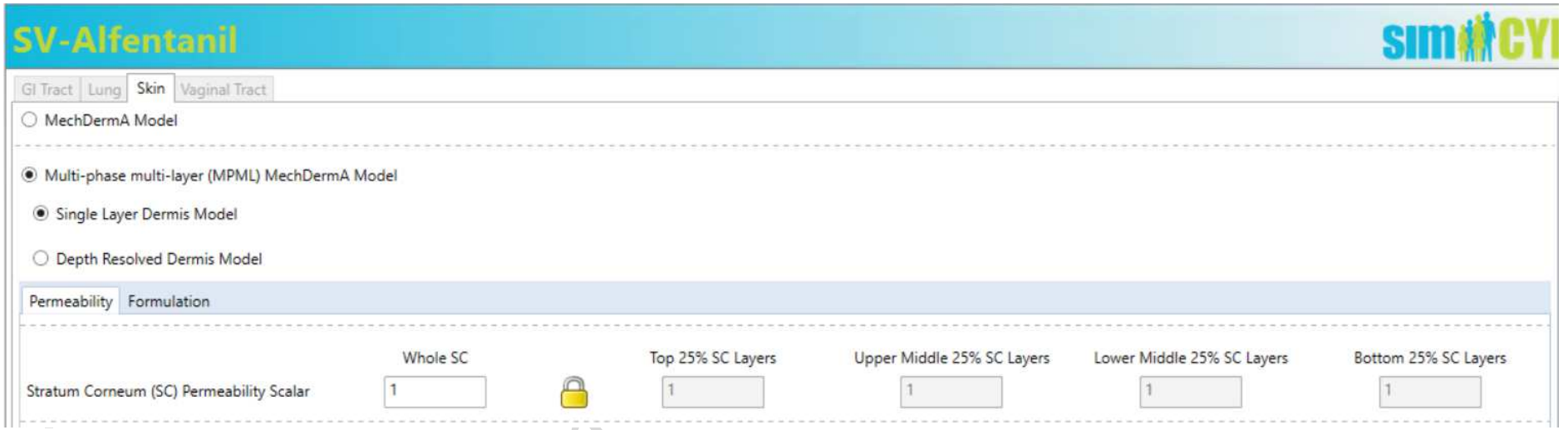
DRDM Screens

Compound Screen



DRDM Screens

Physiology

Dermis

Total Thickness (µm)	1250	45
Regional dermis blood flow scalar*	2.13	0

DRDM Parameters

	Layer Thickness (%)*	Vessel Radii (µm): Capillary Wall Thickness (µm)	Vessel Radii (µm): Capillary Lumen	Vessel Radii (µm): Capillary External	Volume Fraction (cm³/cm³) ǂ: Capillary ǂ Mean	Capillary ǂ CV (%)	Lymph ǂ Mean	Lymph ǂ CV (%)	Fibroblast Mean	Excluded Mean	Interstitial Fluid
Dermis 1	12.24	3.5	1.75	5.25	0.0199	21.85	0.0144	98.98	0.003	0.2567	0.706
Dermis 2	29.25	4.4	7.66	12.06	0.014	37.54	0.0341	98.98	0.003	0.24298	0.706
Dermis 3	29.25	4.4	7.66	12.06	0.014	37.54	0.0341	98.98	0.003	0.27298	0.706
Dermis 4	29.25	4.4	7.66	12.06	0.014	37.54	0.0341	98.98	0.003	0.24298	0.706

Lymph Flow Scalar	1	30	Fraction of ISF accessible by albumin	0.39
			Albumin concentration in accessible spce (g/L)	30.44	34.2

* % of the total dermis thickness. ǂ Capillary and lymph volume fractions are that occupied by lumen + endothelium. ǂ Volume of substituent per cm³ of tissue

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Layer Thickness

Skin Thickness Changes in Normal Aging Skin

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[a]Laboratoire de Biochimie du Tissu Conjonctif, UA CNRS 1174, Faculté de Médecine, Université Paris XII, Créteil; [b]Service d'Anatomie et de Cytologie Pathologique, Groupe Hospitalier Pitié-Salpêtrière, [c]Service de Médecine Interne, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

Table 4. Evolution of the thickness (μm) of the superficial dermis with age

Age, years	Women	Men	Total
20–30	212 (72.3)	256.7 (38)	234.4 (58.5)
30–40	241.9 (44.8)	167.3 (5.2)	204.6 (50.3)
40–50	169.2 (9.5)	185.5 (20.2)	174.6 (11.5
50–60	241.8 (28.3)	180.9 (21.8)	211.3 (43)
60–70	235.5 (32.4)	175 (39.7)	200.9 (46.7)
70–80	251.3 (39.5)	265.7 (76.1)	257.8 (56.2)

Values are mean with the SD given in parentheses.

Table 6. Decrease of the thickness (μm) of the dermis with age

Age, years	Women	Men	Total
20–30	1,802.9 (335)	2,284.9 (475.8)	1,995.5 (420)
30–40	1,494.4 (500)	1,606.4 (520.2)	1,550.4 (476.6)
40–50	1,869.3 (76.9)	1,230.4 (99.6)	1,602.5 (330.8)
50–60	1,519.1 (255.7)	1,460.8 (675.5)	1,495.8 (384.5)
60–70	1,381.4 (657.5)	1,305 (496)	1,330.7 (513.1)	
70–80	1,204.6 (482.2)	1,347.5 (33.9)	1,245.4 (400)

Values are means with the SD given in parentheses.

Dermis Volume Fractions

The exclusion of human serum albumin by human dermal collagenous fibres and within human dermis

Joel L. BERT, Joyce M. MATHIESON and Richard H. PEARCE*
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(*Received 20 August 1981/Accepted 20 October 1981*)

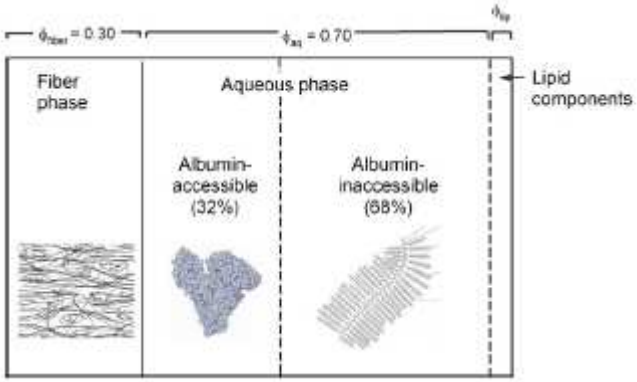

Table 4. *Fluid exclusion of albumin by human dermis*

Five discs of each human dermis were equilibrated with ^{125}I-labelled albumin in phosphate-buffered saline for 14 days at 4°C. The tissue and supernatant fluid were analysed to obtain the following data, as described in detail in the text. The water content of each tissue was determined separately using five additional discs (one was lost for D1).

Property measured	Dermis no. . . . D1	D2	D3
Weight (g)	0.1294 ± 0.0154	0.1270 ± 0.0084	0.1337 ± 0.0118
Water (g/g fresh wt.)	0.6601 ± 0.0049	0.6241 ± 0.0070	0.6429 ± 0.0116
Collagen (g/g fresh wt.)	0.3036 ± 0.0068	0.3351 ± 0.0057	0.2906 ± 0.0075
Collagen + water (g/g fresh wt.)	0.9636 ± 0.0068	0.9592 ± 0.0057	0.9335 ± 0.0075
Collagen (g/g dry wt.)	0.893 ± 0.020	0.891 ± 0.014	0.814 ± 0.021
Swelling ratio (g of swollen tissue/g fresh wt.)	2.30 ± 0.20	1.89 ± 0.04	2.25 ± 0.17
Albumin (mg/g of free fluid)	34.36 ± 0.27	47.70 ± 0.54	35.22 ± 0.46
Fluid in swollen tissue accessible to albumin (g/g fresh wt.)	1.529 ± 0.215	1.001 ± 0.048	1.438 ± 0.197
Insoluble solids (g/g fresh wt.)	0.3177 ± 0.0056	0.3543 ± 0.0076	0.3352 ± 0.0120
Collagen (g/g of insoluble solids)	0.955 ± 0.021	0.946 ± 0.016	0.867 ± 0.022
Swollen tissue fluid (g/g fresh wt.)	1.982 ± 0.204	1.534 ± 0.044	1.918 ± 0.169
Fluid inaccessible to albumin			
(g/g fresh wt.)	0.452 ± 0.027	0.533 ± 0.012	0.475 ± 0.032
(g/g of insoluble solids)	1.424 ± 0.084	1.505 ± 0.034	1.481 ± 0.095
(g/g of collagen)	1.492 ± 0.105	1.592 ± 0.020	1.638 ± 0.135

Dermis Volume Fractions

The exclusion of human serum albumin by human dermal collagenous fibres and within human dermis

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(*Received 20 August 1981/Accepted 20 October 1981*)

TABLE 2
COMPOSITION OF DERMIS AND SERUM, AND RESULTS OF EQUILIBRATION EXPERIMENTS

Property	Mean ± SD (No.) for dermis D1	D2	D3	D4
		Composition of dermis		
Water (g/g fresh wt)	0.6474 ± 0.0059(4)	0.6515 ± 0.0011(4)	0.7242 ± 0.0094(4)	0.6464 ± 0.0035(4)
Fat (g/g fresh wt)	0.0234 ± 0.0078(4)	0.0324 ± 0.0045(4)	0.0383 ± 0.0019(4)	0.0196 ± 0.0053(4)
Insoluble solids (g/g fresh wt)	0.2812 ± 0.0052(4)	0.2768 ± 0.0088(4)	0.2052 ± 0.0083(3)	0.3004 ± 0.0071(4)
Water + fat + insoluble solids (g/g fresh wt)	0.9520 ± 0.0029(4)	0.9606 ± 0.0043(4)	0.9639 ± 0.0045(3)	0.9663 ± 0.0047(4)
Interstitial space, W_1 (g/g fresh wt)	0.6954 ± 0.0036(4)	0.6909 ± 0.0053(4)	0.7561 ± 0.0064(3)	0.6801 ± 0.0072(4)
Collagen (g/g fresh wt)	0.2467 ± 0.0180(2)	0.2658 ± 0.0073(3)	0.1990 ± 0.0016(3)	0.2756 ± 0.0051(3)
(g/g insoluble solids)	0.878 ± 0.064(2)	0.960 ± 0.027(3)	0.970 ± 0.008(3)	0.918 ± 0.017(3)
Albumin (mg/g fresh wt)	7.00 ± 0.37(4)	8.31 ± 0.24(4)	6.13 ± 0.33(4)	4.48 ± 0.27(4)
Serum albumin (mg/g)	37.33 ± 1.67(2)	37.86 ± 0.13(2)	35.54 ± 0.81(2)	32.64 ± 0.42(2)
		Equilibration experiments		
Tissue weight (g)	0.1336 ± 0.0115(3)	0.1269 ± 0.0188(3)	0.1359 ± 0.0045(3)	0.1373 ± 0.0167(3)
Swelling ratio (g swollen tissue/g fresh wt)	1.110 ± 0.043(3)	1.196 ± 0.048(3)	1.018 ± 0.023(3)	1.059 ± 0.031(3)
Recovery of added radioactivity	0.998 ± 0.040(2)	1.015 ± 0.011(2)	1.062 ± 0.040(3)	1.021 ± 0.046(3)

Capillary Density

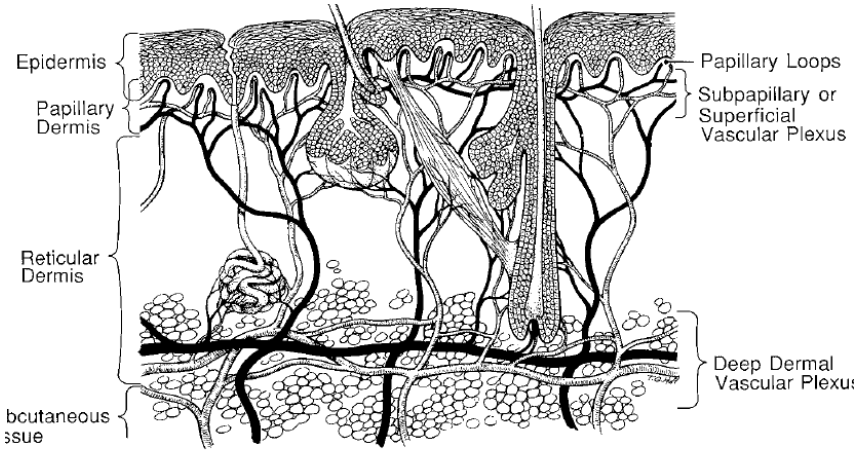


FIG. 1. Schema of the vasculature in two levels of the dermis: papillary and reticular dermi

TABLE III

Differences in Capillary Density of Papillary Dermis Between Head-Face/Neck and Other Regions of the Body Across Six Cadavers

Regions	Grouped Biopsy Sites	Mean ± SD	Significance (p)*
Head Face Neck	1, 2, 3, 4, 5	3.16 ± 0.86	—
Chest Back	6, 15	1.94 ± 0.76	$p < 0.11$
Arm Forearm Hand	7, 9, 10	1.98 ± 0.81	$p < 0.18$
Abdomen Buttock	11, 16	1.96 ± 0.46	$p < 0.006$
Thigh (anterior and posterior)	12, 17	1.48 ± 0.53	$p < 0.007$
Lower leg	13, 14, 18, 19	1.69 ± 0.70	$p < 0.0006$

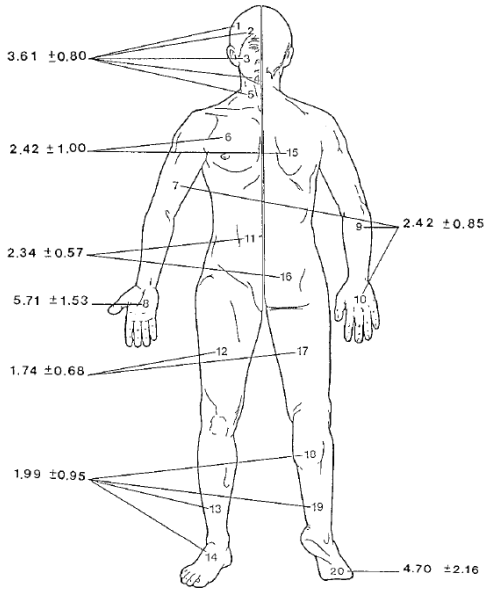
* Significant if $p < 0.05$.

TABLE IV

Differences in Capillary Density of Reticular Dermis Between Head-Face/Neck and Other Regions of the Body Across Six Cadavers

Regions	Grouped Biopsy Sites	Mean ± SD	Significance (p)*
Head Face Neck	1, 2, 3, 4, 5	1.20 ± 0.42	—
Chest Back	6, 15	0.48 ± 0.27	$p < 0.0002$
Arm Forearm Hand	7, 9, 10	0.44 ± 0.23	$p < 0.02$
Abdomen Buttock	11, 16	0.38 ± 0.17	$p < 0.001$
Thigh (anterior and posterior)	12, 17	0.26 ± 0.23	$p < 0.0004$
Lower leg	13, 14, 18, 19	0.30 ± 0.25	$p < 0.01$

* Significant if $p < 0.05$.



Lymphatic Density

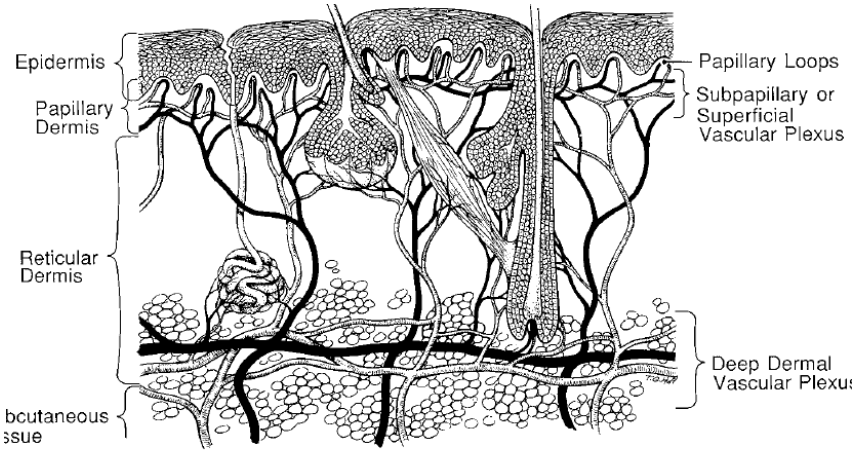
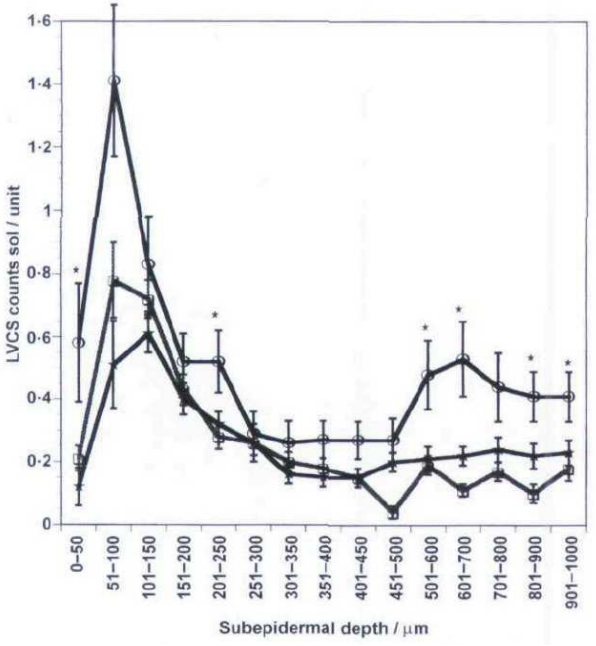


FIG. 1. Schema of the vasculature in two levels of the dermis: papillary and reticular dermi



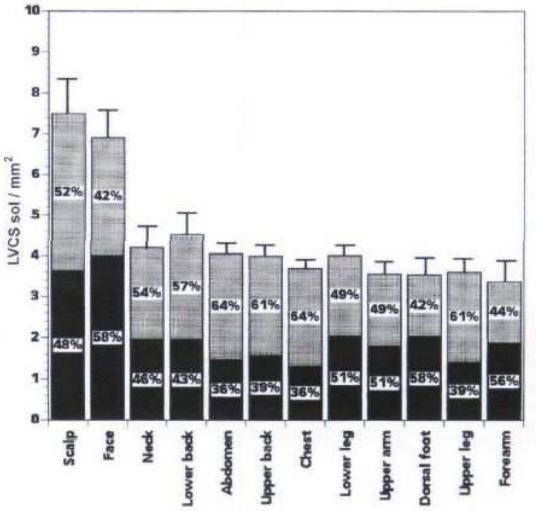


Figure 5. Number of LVCSs per mm² subepidermal skin by site of removal. The percentage of the uppermost quarter of the dermis and the deeper part is indicated. The error bars represent the standard error of the mean. Subepidermal depth: □, 0–250 μm; ■, 251–1000 μm.

Fibroblast Density

Variability of fibroblast morphology *in vivo*: a silver

Table 2.
Relative Volumes Including Variation of the Different Compartments of the Dermis

Compartment	Volume %	Reference
Cells	0.3 ± 0.1	This study
Cell water	0.21 ± 0.07	This study
ISF	40 ± 5.2	12
Lymph	0.3–0.4	Calculated from 16 and 26
Blood plasma	8 ± 0.8	14
Excluded	51.4	This study

Validation of a morphometric method for evaluating fibroblast numbers in normal and pathologic tissues

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27 (1·7)
= 100)
·3 (2·5)
= 100)

Table 2. Fibroblast counting by image analysis in the mid-dermis of normal human donors [(a) fixed in Bouin's solution and embedded in paraffin; (b) Cryostat sections] or in hypertrophic scars [(c) fixed in Bouin's solution and embedded in paraffin]

			Normal skin (paraffin sections)							
a)	Donors	no. age (years)	1 10	2 12	3 15	4 17	5 18	6 20	7 22	8 25
Analyzed Tissue	fibroblasts per 30 fields	(52.5 × 106 μm³)	410 ± 100	483 ± 48	588 ± 114	368 ± 51	672 ± 74	714 ± 60	436 ± 62	582 ± 78
Native Tissue	Fibroblasts per mm³ (correcting factor = 1/3.3)		7800 2364 ± 577	9200 2788 ± 277	11200 3394 ± 658	7000 2121 ± 294	12 800 3879 ± 427	13 600 4121 ± 346	8292 2513 ± 358	11070 3355 ± 450

			Normal skin (paraffin sections)						
b)	Donors	no.	1	2	3	4	5	6	7
Native Tissue	Fibroblasts per mm3		2816 ± 75	3890 ± 206	4444 ± 188	3701 ± 79	3231 ± 150	4638 ± 213	3975 ± 181

			Hypertrophic scars (paraffin sections)			
			1		2	
c)	Donors	no.	'normal'	'rich'	'normal'	'rich'
Native Tissue	Fibroblasts per mm³		4710 ± 562	10 096 ± 639	4823 ± 579	10 890 ± 398

Fibroblast Density

Variability of fibroblast morphology *in vivo*: a silver impregnation study on human digital dermis and subcutis

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Department of Neuroanatomy, University of Düsseldorf, Moorenstrasse 5, 4000 Düsseldorf 1, Germany

(*Accepted 5 April* 1991)

Table 1. *Measurements of fibroblasts in digital skin of a 54-year-old male**

	Cell body size (μm)		Length of longest cell process (μm)	Number of cell processes
	Greater diameter	Lesser diameter		
Papillary dermis	7·30 (1·8) (n = 46)	3·7 (1·0)	22·15 (5·9) (n = 100)	5·27 (1·7) (n = 100)
Subcutis	15·6 (4·5) (n = 50)	8·2 (2·8)	75·9 (21·8) (n = 100)	6·3 (2·5) (n = 100)

* Means with SD in parentheses.

Validation of a morphometric method for evaluating fibroblast numbers in normal and pathologic tissues

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			Normal skin (paraffin sections)						
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			Hypertrophic scars (paraffin sections)			
			1		2	
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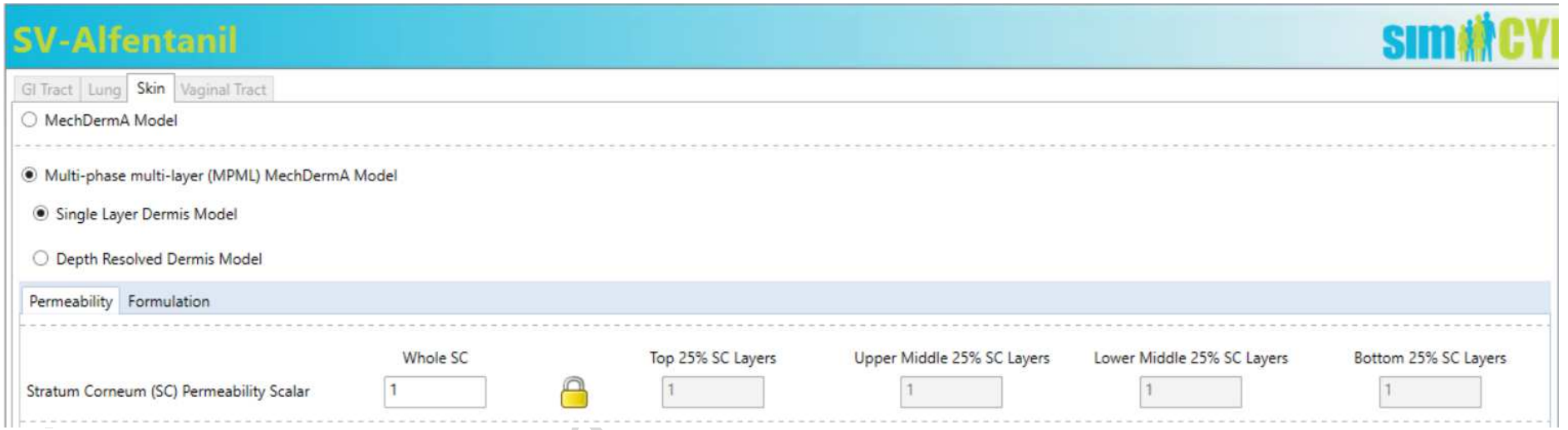
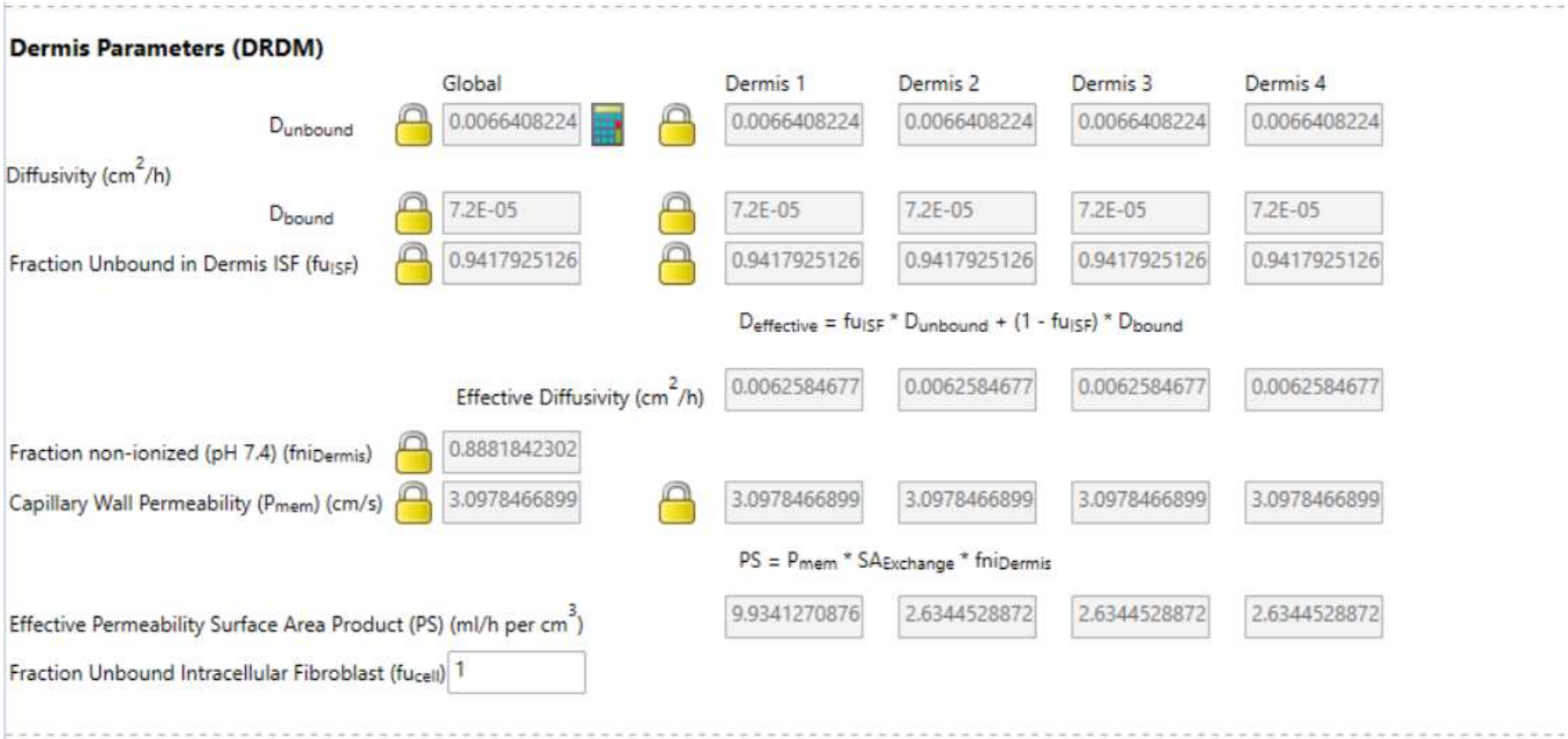
DRDM Screens

Compound Screen



DRDM Screens

Compound Screen



CERTARA

Capillary Permeability

Unbound

Capillary endothelium permeability (Ibrahim *et al*., 2012) :

$$\log P_{\text{mem}} = 1.64\ \log K_{\text{oct}} - 1.37\,\text{MW}^{1/3} + 2.82$$
$$n = 37;\ s = 0.71;\ r^2 = 0.8951 \qquad (24)$$

Permeability Surface Area Product = Capillary permeability * Exchange Surface area * fni

Bound

Two pore theory, matched with our biologics module (negligible impact for small molecules)

Removal by the lymph (<1% of the clearance even for highly bound drugs)

Could be more important for larger drugs, i.e., delivered by microneedles or intradermal injection

IBRAHIM, R., NITSCHE, J. M. & KASTING, G. B. 2012. Dermal clearance model for epidermal bioavailability calculations. *J Pharm Sci,* 101, 2094-108.

Diffusion in the Dermis

Partitioning, diffusivity and clearance of skin permeants in mammalian dermis

Kosmas Kretsos [1], Matthew A. Miller, Grettel Zamora-Estrada, Gerald B. Kasting *

College of Pharmacy, University of Cincinnati Academic Health Center, P.O. Box 670004, Cincinnati, OH 45267-0004, USA

Received 27 October 2005; received in revised form 1 June 2007; accepted 5 June 2007
Available online 23 June 2007

***In Silico* Prediction of Percutaneous Absorption and Disposition Kinetics of Chemicals**

Longjian Chen • Lujia Han • Ouarda Saib • Guoping Lian

Current Model:
(Modified Chen)

$$D_{de}\left(\mathrm{m}^2/\mathrm{s}\right) = \frac{10^{-8.15-0.655\log(MW)}}{0.68 + \dfrac{0.32}{f_u} + 0.025K_{mw}}$$

Diffusion in the Dermis

- Measured effective diffusivity value were collected form the literature. N = 34.

Mechanistic framework:

$$D_{Dermis} = fu_{ISF} * D_{unbound} + (1 - fu_{ISF}) * D_{Bound} \quad (1)$$

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Diffusion in the Dermis

Wilke Chang 1955:

$$D_{unbound}\left(\boldsymbol{cm^2/s}\right) = \left(\frac{7.4 * 10^{-10} * T_{Dermis} * (MW\emptyset_{ISF})^{0.5}}{\eta_{ISF} * V_A{}^{0.6}}\right) \quad (2)$$

Where:

T_{Dermis} = *Absolute Temperature in the Dermis Value* = 310.15 K

$MW\emptyset_{ISF}$ = Solvent Molecular Weight * *Association parameter (assumed the same as water); Value* = 40.68 Da

η_{ISF} = *Viscosity of ISF (assumed the same as lymph measured by* Bouta *et al*., 2014); Value = 0.0181 dyne × s/cm^2

V_A = *Molar Volume of the Molecule (predicted from MW by method described in* Ibrahim *et al*., 2012).

Diffusion in the Dermis

Diffusion of bound drug assumed to be the same as albumin

Direct measurement of interstitial convection and diffusion of albumin in normal and neoplastic tissues by fluorescence photobleaching

(fluorescence recovery/interstitial fluid flow/macromolecular diffusion)

SRIKANTH R. CHARY AND RAKESH K. JAIN*

Department of Chemical Engineering, Carnegie Mellon University, Pittsburgh, PA 15213-3890

Communicated by John M. Prausnitz, May 1, 1989

Self-diffusion in a hyaluronic acid–albumin–water system as studied by NMR

Andrey Filippov,[a,b]* Marina Artamonova,[a] Maya Rudakova,[a] Roustam Gimatdinov[a] and Vladimir Skirda[a]

Plasma pharmacokinetics and interstitial diffusion of macromolecules in a capillary bed

LAWRENCE J. NUGENT AND RAKESH K. JAIN

Department of Chemical Engineering, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Aqueous Diffusivity = 0.0032 cm^2/h

Effective Diffusivity in ISF = 7.2×10^{-5} cm^2/h

Diffusion in the Dermis

fu_{ISF}

$$fu_{Dermis} > fu_{2\%\,solution} > fu_{4\%\,solution} > fu_{plasma} > fu_{predicted}$$

The fraction of drug unbound to albumin in the interstitial fluid of the dermis can be predicted by Equation 3.

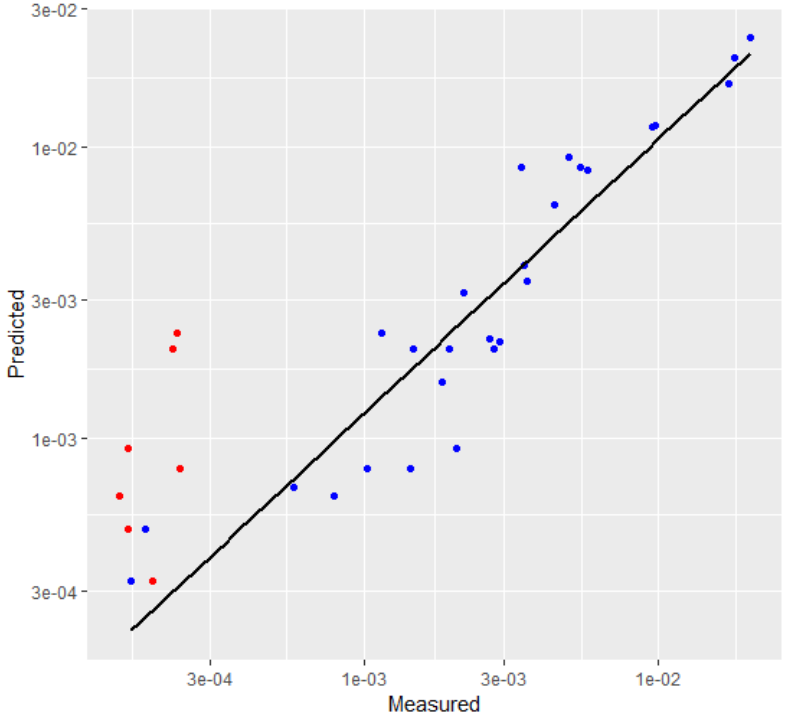
$$fu_{ISF} = \frac{1}{1 + \frac{[P]_{Dermis}}{K_D}} \qquad (3)$$

$[P]_{Dermis}$ = *The abundance of albumin in the dermis ISF;* Value = 454.3 µM (Bert *et al.*, 1986)

K_D = *The affinity constant between the drug and albumin. This can be calculated by rearranging Equation 3 and replacing* fu_{ISF} *and* $[P]_{Dermis}$ *with values for plasma, where measured values of* fu_{Plasma} *are available.*

Diffusion in the Dermis

Full dataset , N=27

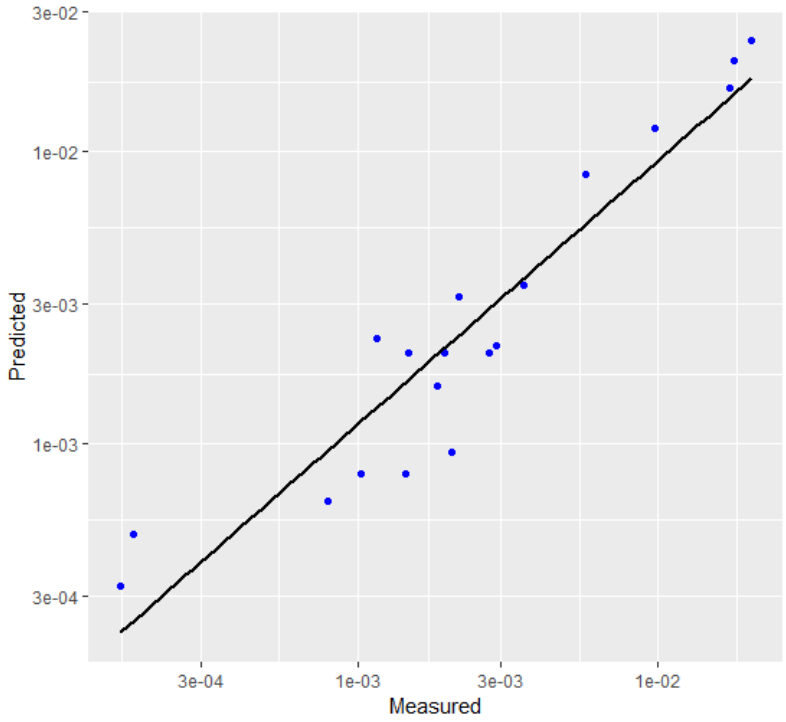


Clarke 2019:
R^2 = 0.94
Slope = 1.12
NRMSE = 9.4%

Modified Chen:
R^2 = 0.96
Slope = 1.17
NRMSE = 9.1%

(Trained with 21 of these observations)

Subset for Measure fu, N=19



Clarke 2019:
R^2 = 0.98
Slope = 1.12
NRMSE = 6.6%

Modified Chen:
R^2 = 0.98
Slope = 1.18
NRMSE = 8.3%

(Trained with 13 of these observations)

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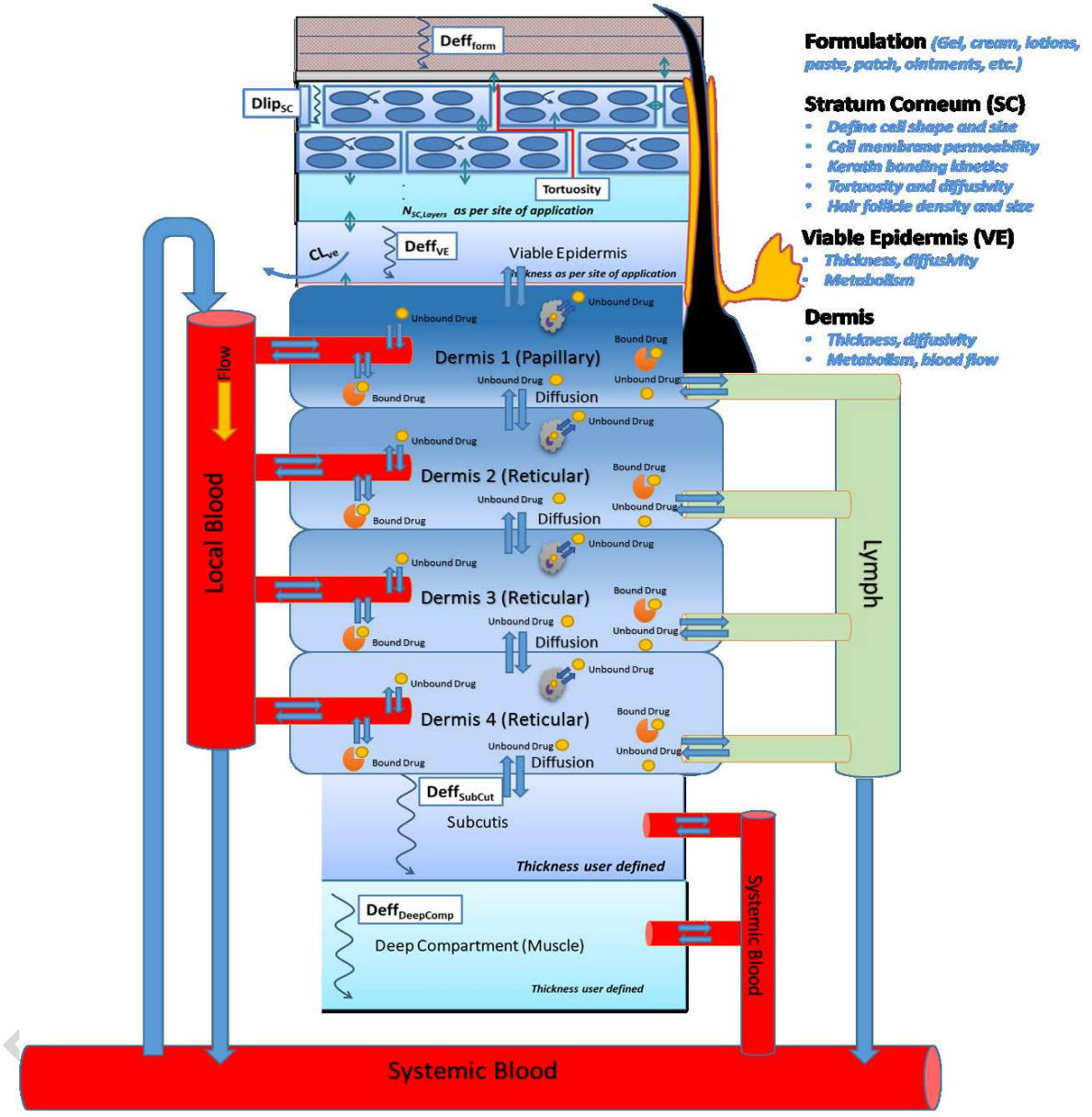
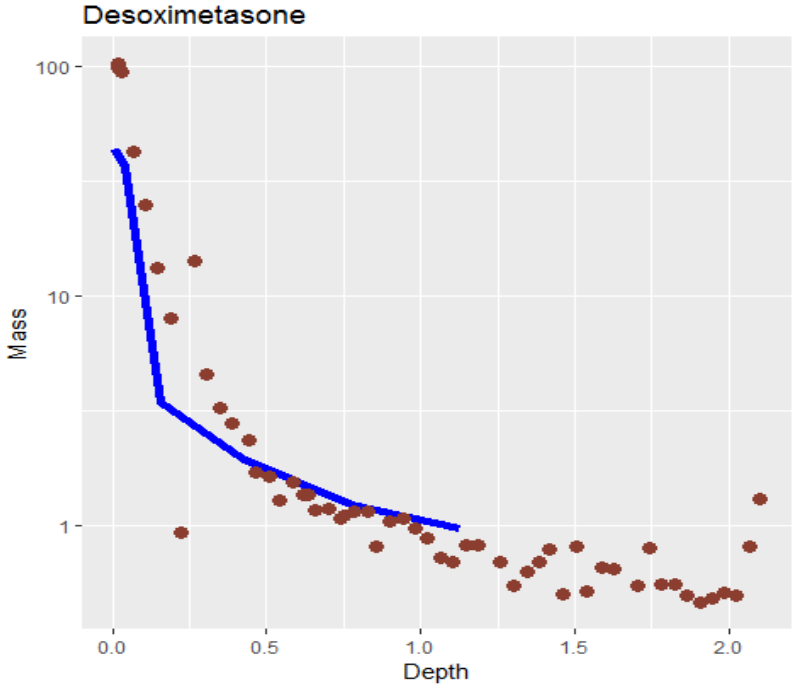
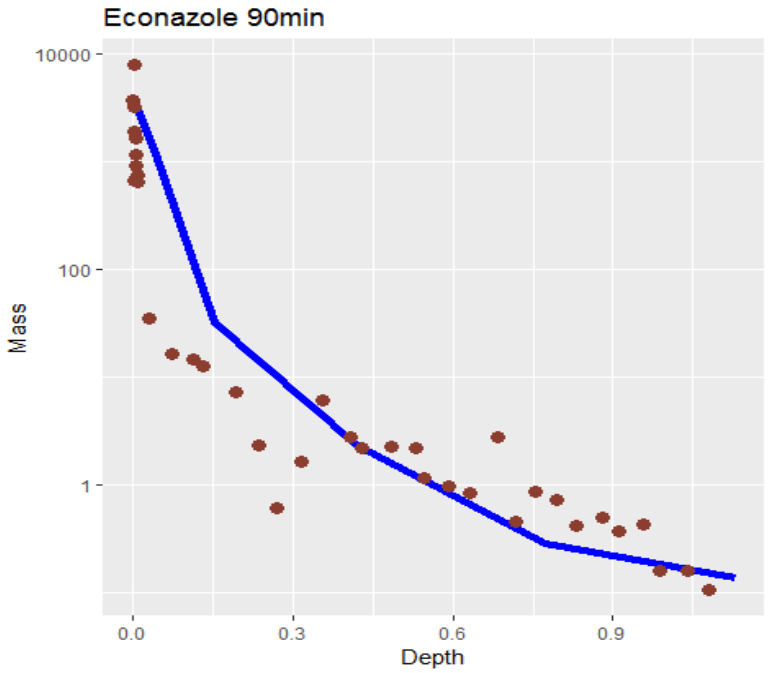
Depth Resolved Dermis Model (DRDM)



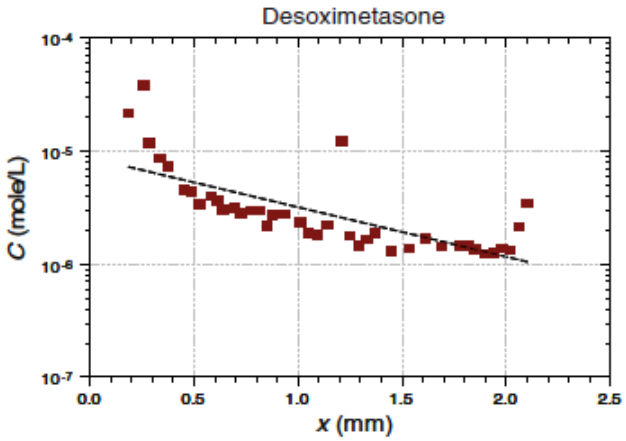
Initial DRDM Verification (in R prototype model)

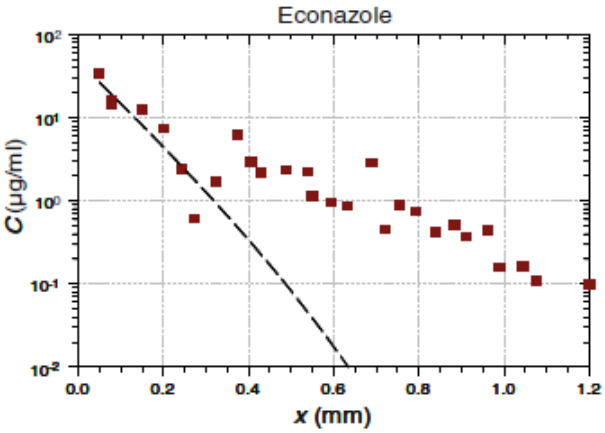
C,initial was fitted, as these studies had limited information about dosing or formulation





Anissimov & Roberts





CERTARA

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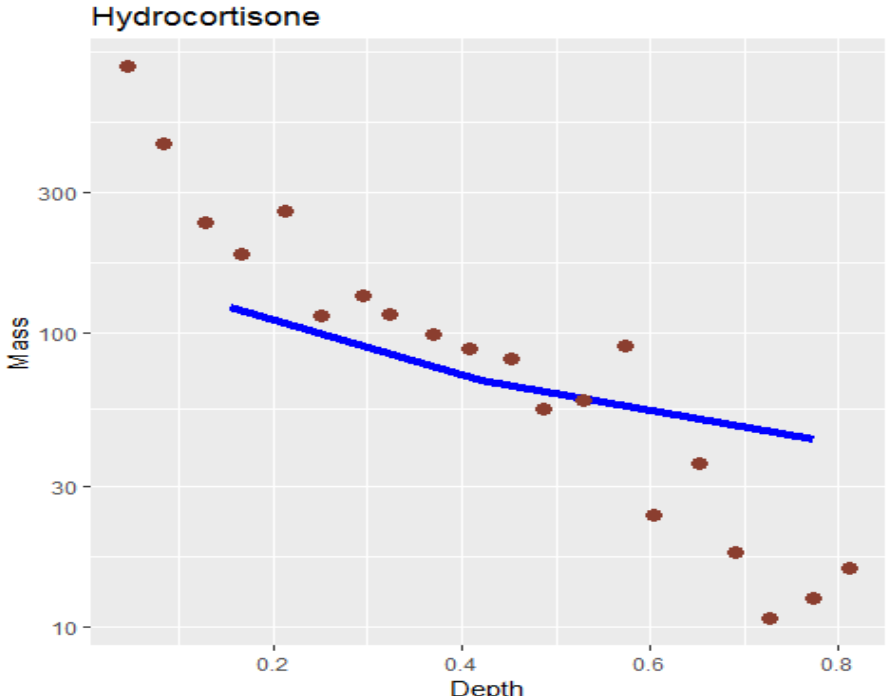
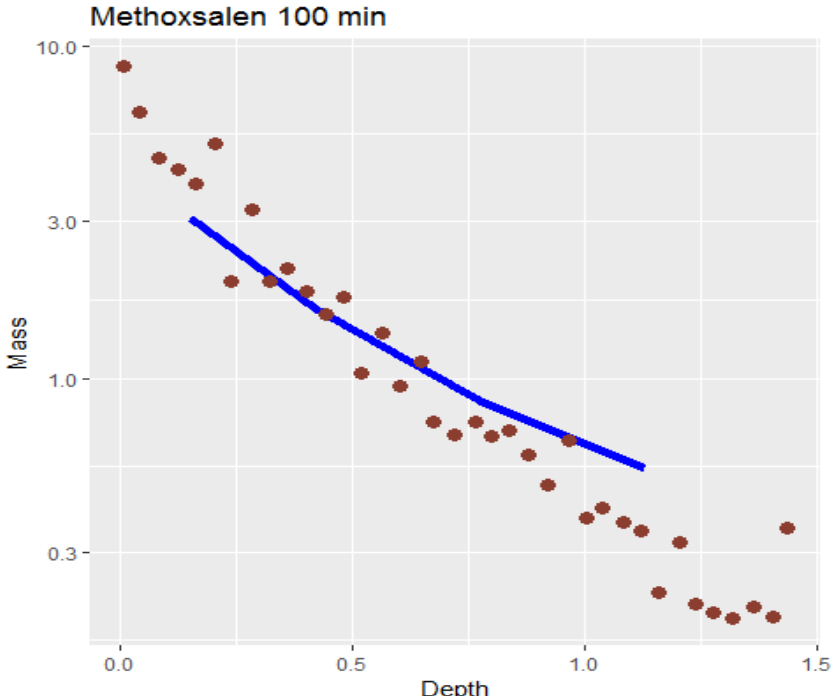
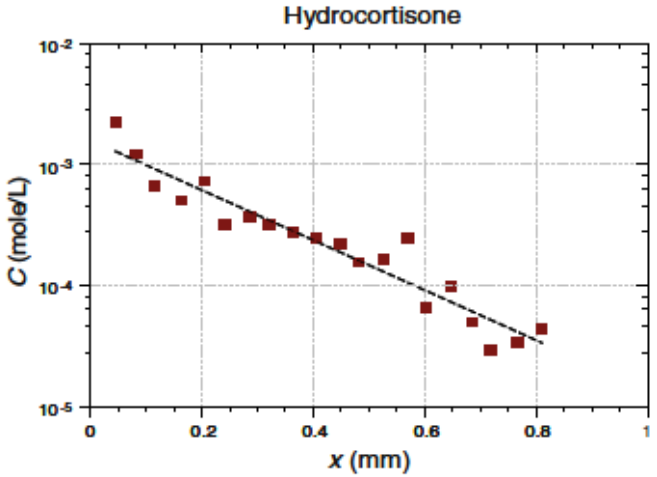
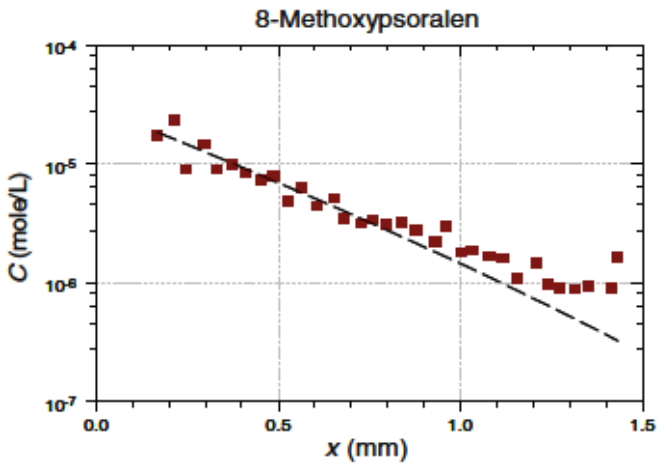




Anissimov & Roberts





CERTARA

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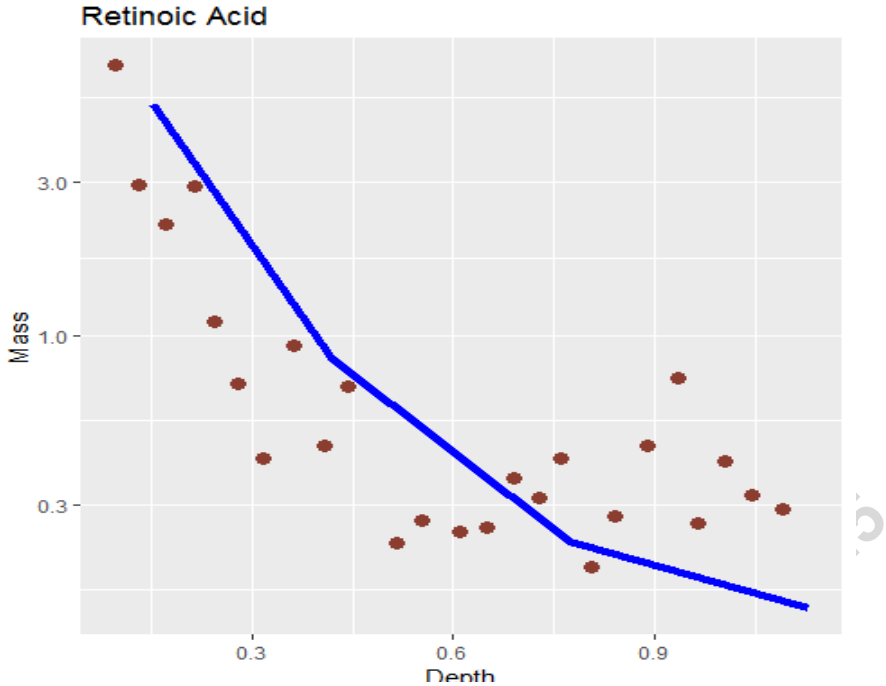
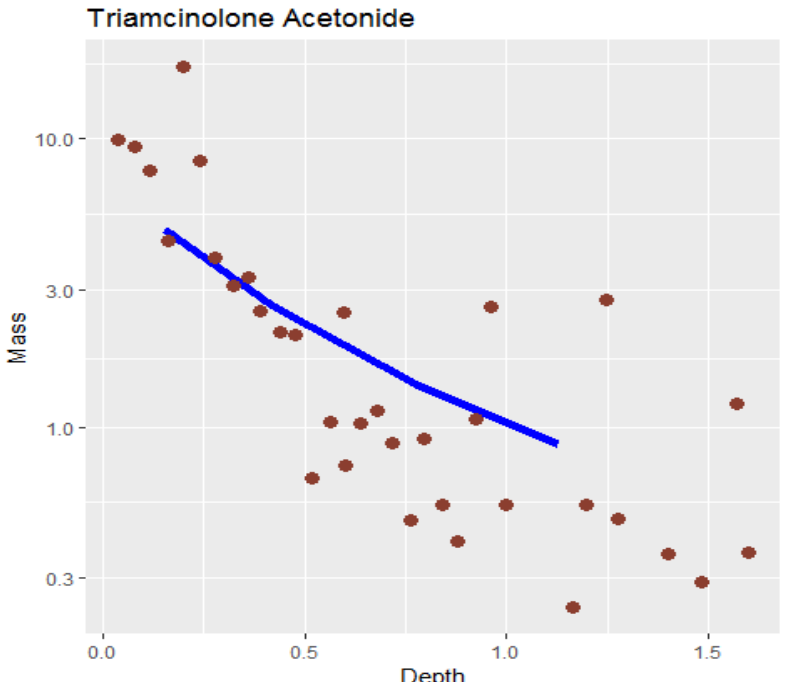
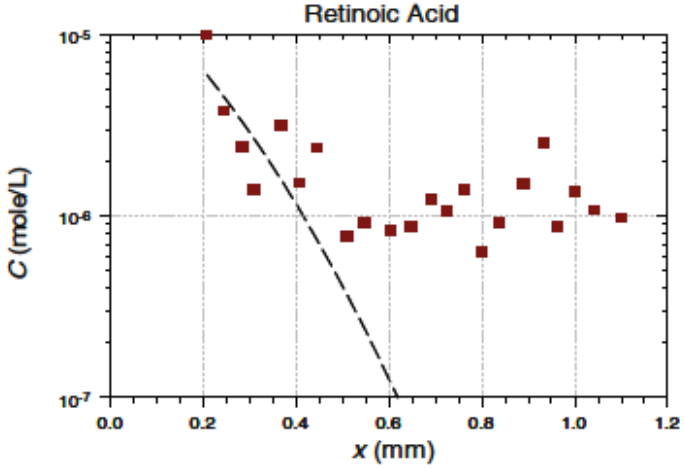
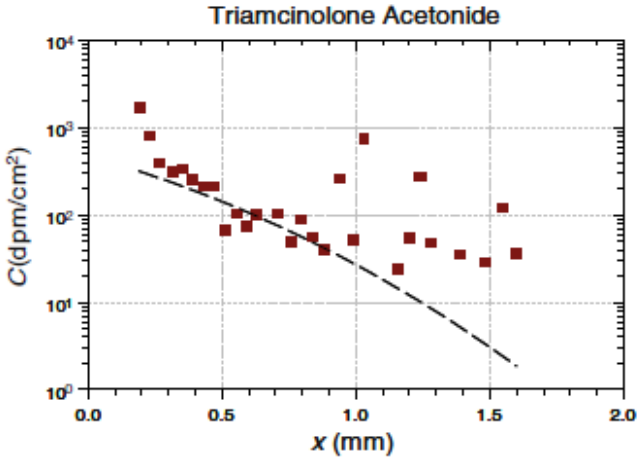




Anissimov & Roberts





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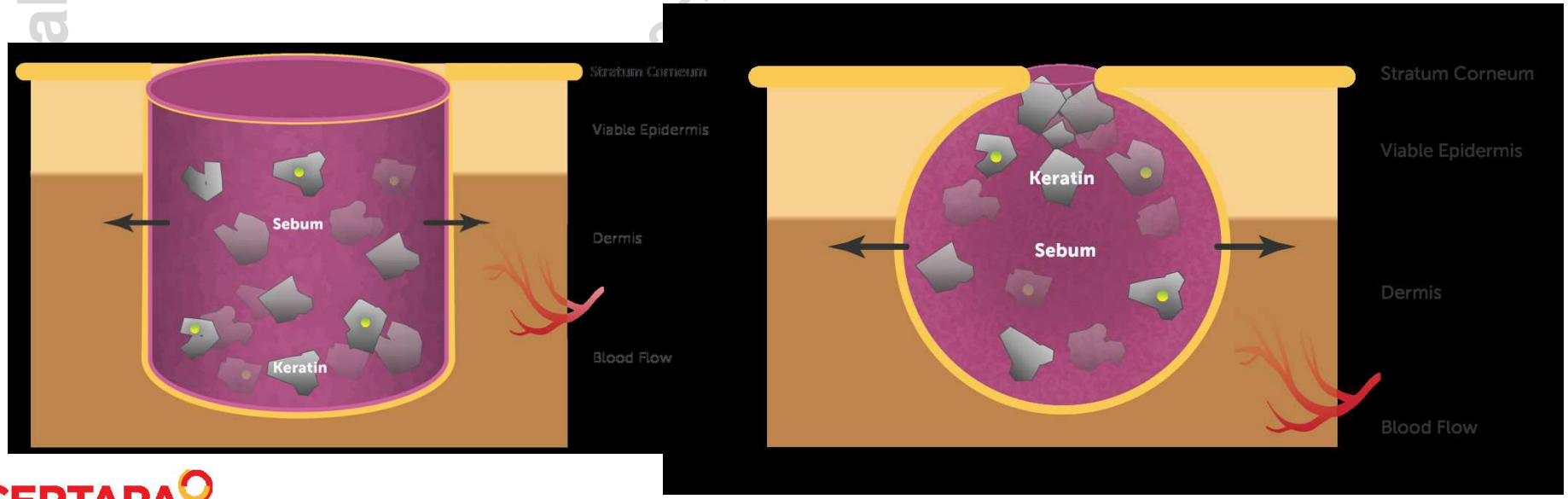
Simcyp

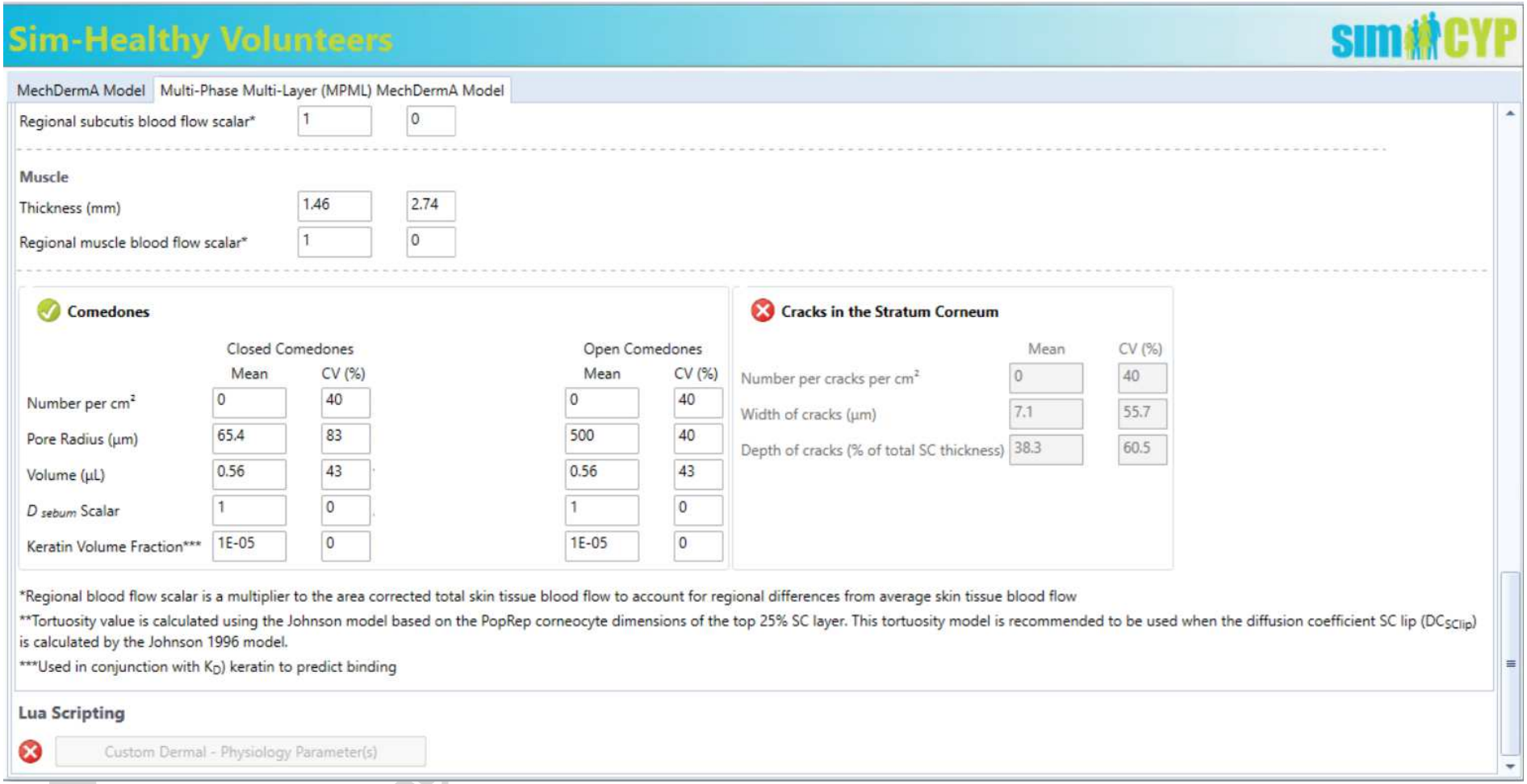
Comedone Model

Comedones

- Drug partition into sebum based on the accessible area
- Drug can bind to keratin in the Comedone
- Drug can only partition out of the Comedone into the Dermis
- When DRDM is active, Comedone can end in any of the four compartments based on the defined volume
- Within each individual, Comedones are all the same size. But different individuals can have different volume.



Comedones - Screens



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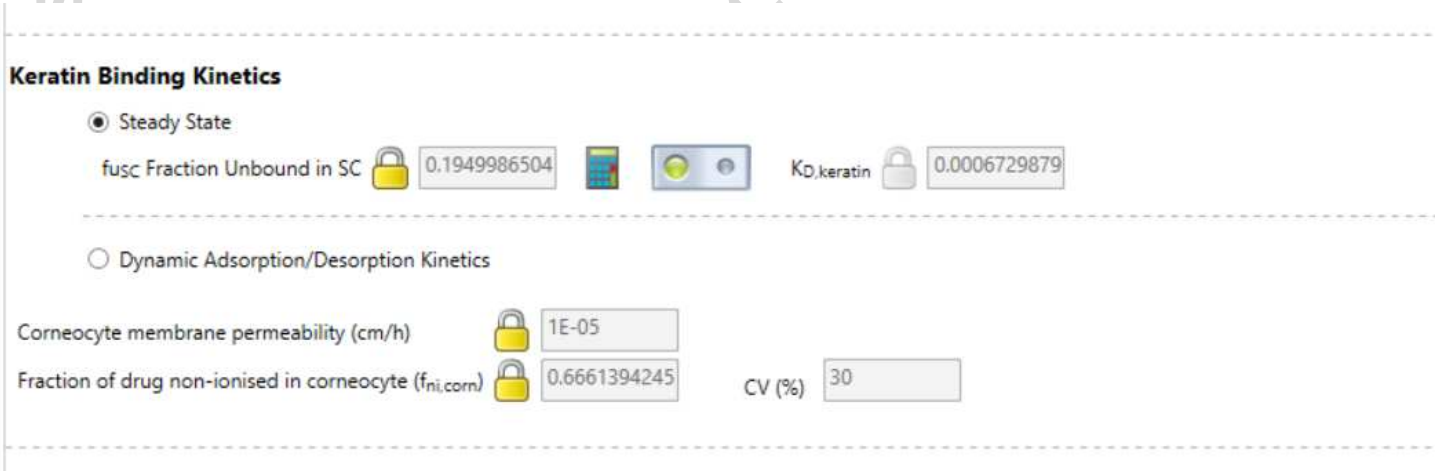
Comedones - Screens

Addition of keratin volume fraction on the population screen

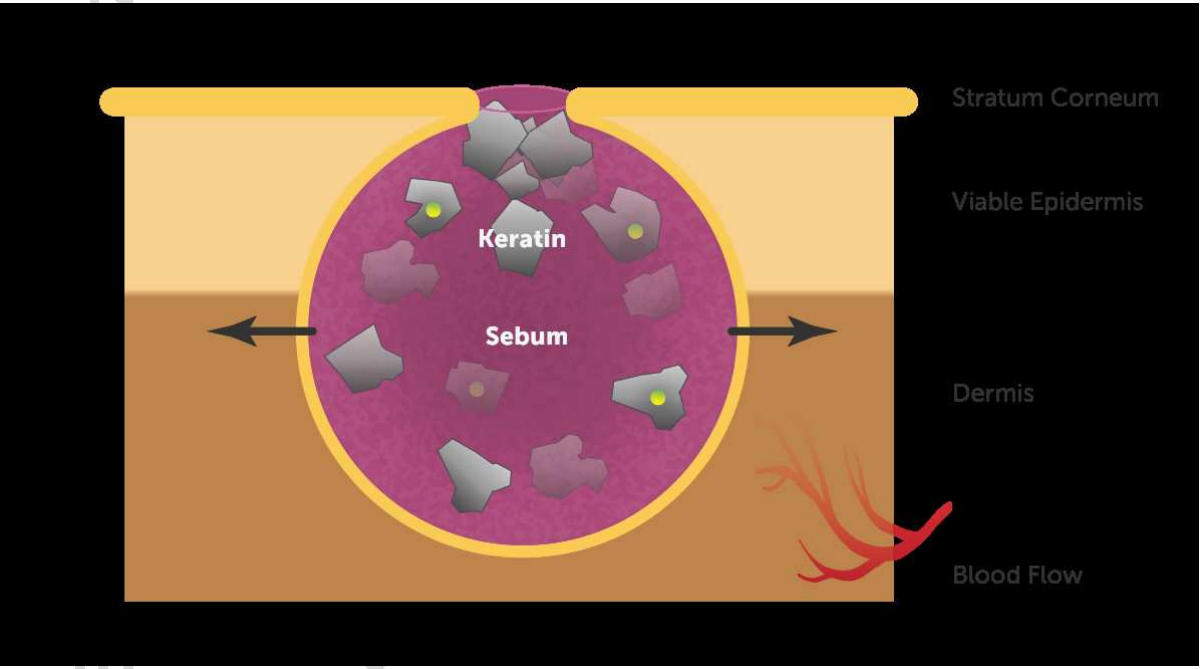
Corneocyte width (µm)		Corneocyte length (µm)		Hydration level (% water volume)		Keratin volume fraction	SC lipid viscosity (centipose)	
Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	Mean	CV (%)
27.7	9.2	34.2	4.1	35.5	17	0.645	75	0
27.7	9.2	34.2	4.1	46.1	11	0.539	75	0
27.7	9.2	34.2	4.1	56.75	7	0.4325	75	0
27.7	9.2	34.2	4.1	67.4	4	0.326	75	0

Addition of an option to use K_D as opposed to fu. This will make binding dependent on keratin volume fraction. And therefore each bin in the SC can have different binding.



Closed Comedones

- Modelled as a truncated sphere



Comedones

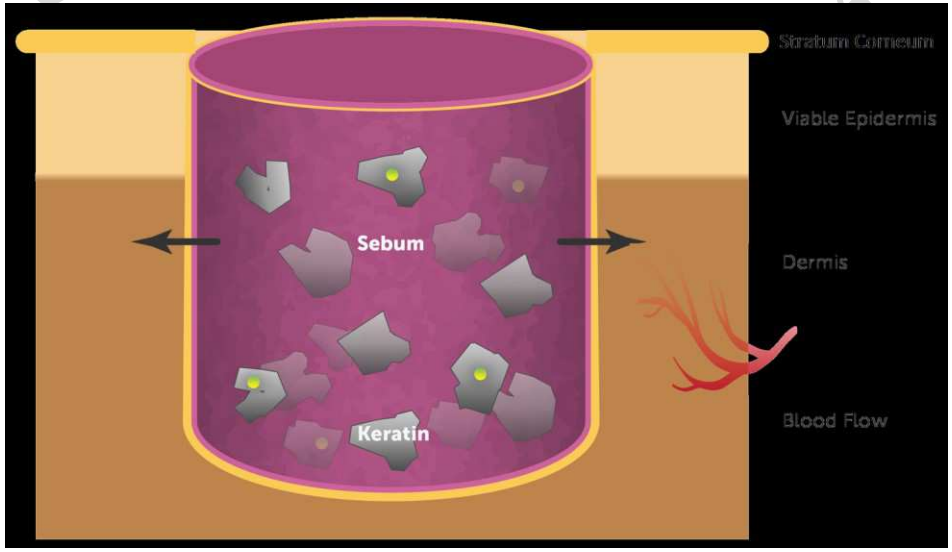
	Closed Comedones	
	Mean	CV (%)
Number per cm²	0	40
Pore Radius (µm)	65.4	83
Volume (µL)	0.56	43
D sebum Scalar	1	0
Keratin Volume Fraction***	1E-05	0

Open Comedones

- Modelled as a cylinder

Comedones

	Closed Comedones		Open Comedones	
	Mean	CV (%)	Mean	CV (%)
Number per cm²	0	40	0	40
Pore Radius (µm)	65.4	83	500	40
Volume (µL)	0.56	43	0.56	43
D sebum Scalar	1	0	1	0
Keratin Volume Fraction***	1E-05	0	1E-05	0



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Simcyp

Updates to Psoriasis Dermal Population for V19

Psoriasis Dermal

First implemented in Version 17 of the Simcyp Simulator.

This population file describes the involved skin of patients with Plaque Psoriasis.

If a population parameter is being updated, there are three possible reasons for this:

- New Data has become available in the literature after the last literature search was completed in 2016.
- New Data has been found that was not picked up in the 2016 literature search
- New Models are available in Simcyp that can now be parameterized for Psoriasis Plaque

Parameters altered in a Psoriatic Plaque

- Surface pH ↓
- Surface Temperature ↑
- Corneocyte Surface Area ↓
- Corneocyte thickness ↑
- Number of Stratum Corneum layers ↑
- Cracks in the Stratum Corneum
- Tortuosity ↓
- Stratum Corneum hydration ↓
- Viable Epidermis Thickness ↑
- Dermis Thickness ↑
- Capillary Volume Fraction in the Dermis ↑
- Lymph Volume Fraction in the Dermis ↑
- Lymph Flow in the Dermis ↑
- Interstitial Fluid Volume Fraction in the Dermis ↑
- Blood Flow in the Dermis ↑
- Blood Flow in the Subcutis ↑
- Albumin concentration in plasma ↓
- Albumin concentration in the Dermis ↓

New for V19

Reanalysed for V19

Same as V17

Surface Temperature

CUTANEOUS BLOOD FLOW IN PSORIASIS MEASURED BY ^{133}XENON CLEARANCE*

ALLAN NYFORS, M.D. AND HANS W. ROTHENBORG, M.D., D.P.H. (LONDON)

Increased average temperature, Mean 33.7°

TABLE I

Blood flow calculated from the initial slope in curves recorded for 20–30 minutes

Patients			Skin blood flow (ml/100 g × min)		Skin temperature			Controls			Skin blood flow
No./name	Age	Sex	normal	psoriasis	normal	psoriasis	diff.	No./name	Age	Sex	
1. H.O.	64	m	6.5	8.8	31.6	33.0	1.4	1. N.D.	48	f	3.1
2. S.C.	23	m	16.2	24.3	31.0	32.5	1.5	2. V.H.	58	f	4.4
3. F.M.	66	m	8.8	13.9	33.0	35.5	2.5	3. E.J.	67	f	5.4
4. A.L.	59	f	4.1	6.6	32.0	34.0	2.0	4. J.N.	41	f	6.1
5. A.N.	18	f	3.7	6.5	32.0	33.0	1.0	5. N.M.	31	m	6.1
6. S.P.	13	f	3.5	6.4	31.0	31.5	0.5	6. N.C.	42	f	7.5
7. E.H.	44	m	6.8	12.1	31.5	35.0	3.5	7. N.M.	27	f	8.1
8. J.P.	36	f	4.8	9.7	34.0	35.0	1.0	8. N.W.	62	m	8.1
9. H.B.	56	m	13.1	26.9	—	—	—	9. P.N.	18	m	8.5
10. E.L.	59	m	2.0	4.4	33.2	33.4	0.2	10. M.A.	29	m	7.5
11. A.N.	71	f	9.2	20.2	32.6	33.8	1.2				
12. M.L.	14	f	6.1	15.1	33.0	35.0	2.0				
13. A.L.	59	m	3.6	11.8	32.0	33.0	1.0				
14. C.L.	32	f	2.9	10.3	31.8	33.2	1.4				
15. L.P.	32	f	1.1	4.5	32.0	33.5	1.5				
Total	646		92.4	181.5	450.7	471.4	20.7		423		64.8
Mean	43		6.16	12.1	32.2	33.7	1.5		42		6.5

M	6.16	12.1
s^2	17.50	48.34
σ	5.73	
t	3.06	
$0.01 > p > 0.001$		

Corneocyte Dimensions

- Corneocytes are thicker with a smaller surface area, similar volume.
- Low patient numbers, but all tell a similar story.
- We can use these dimensions to calculate tortuosity (feature added in V18)

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

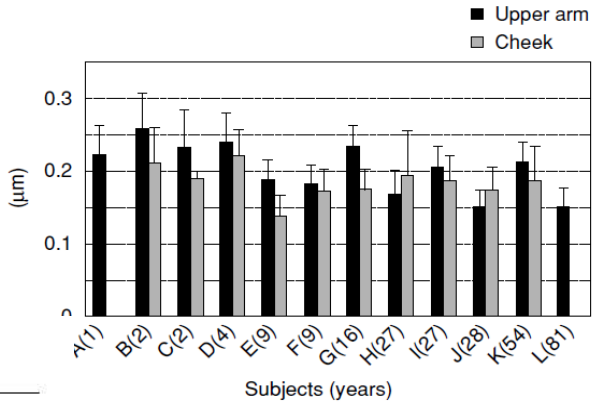
Nobuo Kashibuchi[1], Yoshikazu Hirai[1], Kenichiro O'Goshi[2] and Hachiro Tagami[2]

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

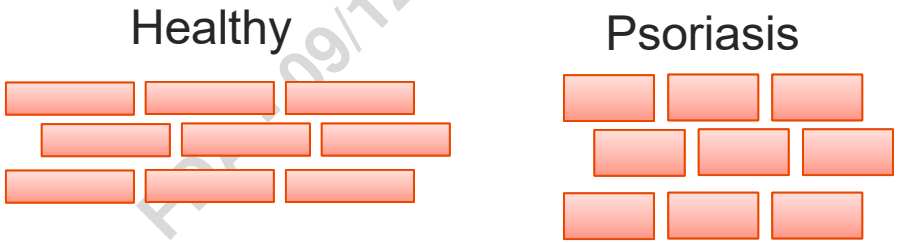
TABLE 3. Parameters of corneocytes from the involved and uninvolved sites of psoriatic patients

		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, $n = 20$.



Mean thickness of the corneocytes of various aged subjects at various locations. Mean thickness of the corneocytes from the flexor surface of the upper arm decreased with age. ıst, the corneocytes from the cheek showed no such a relause of its great individual differences. Data are reported as SD (n = 20 corneocytes).



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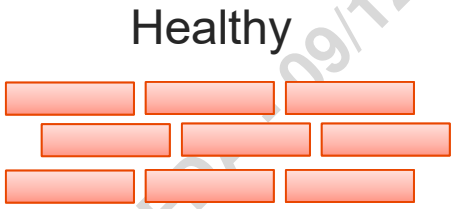
Surface Area Measurements of Psoriatic Corneocytes: Effects of Intralesional Steroid Therapy

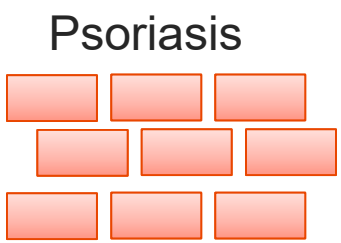
HERBERT GOLDSCHMIDT, M.D.

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





Corneocyte Dimensions

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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

Surface area measurements (Before Treatment) Plaque vs Healthy controls

Ratio = 0.73 - agrees with the Kashibuchi data (0.79).

Final Ratios:

Thickness : 2.25

Surface Area : 0.75

CERTARA

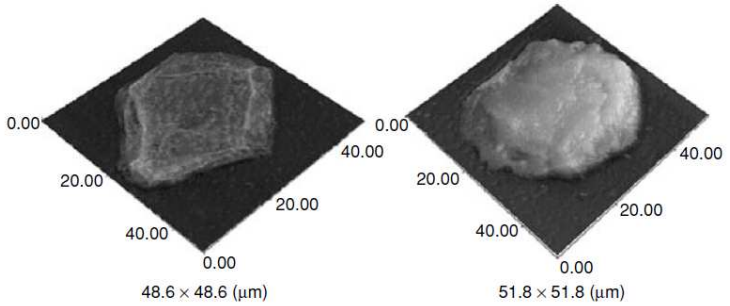
Corneocyte Dimensions

Final Ratios:

Thickness : 2.25

Surface Area : 0.75

Fig. 12. The appearance of corneocyte obtained from involved site or uninvolved site of a psoriatic patient. Corneocytes from involved site (right) had thicker and rounded form than those from uninvolved site (left). In contrast to the corneocytes from uninvolved site from AD patient, corneocytes from uninvolved site from psoriatic patient had a similar shape to normal corneocyte.

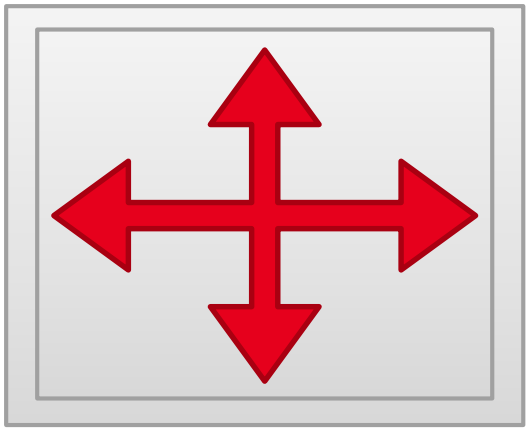


Assumptions:

- Topological Aspect ratio remains the same (to scale)
- Shape is cuboidal

Example:

Volar Forearm	(μm)	
	Healthy	Plaque
Thickness	0.59	1.35
Width	29.6	26.3
Length	36.4	32.3



Number of SC layers

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

No studies measuring number of layers specifically.

Therefore calculated from SC thickness and corneocyte thickness

Mean ratio of SC thickness from healthy to plaque = **2.37**

(Palm omitted from calculation)

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.

Hydration

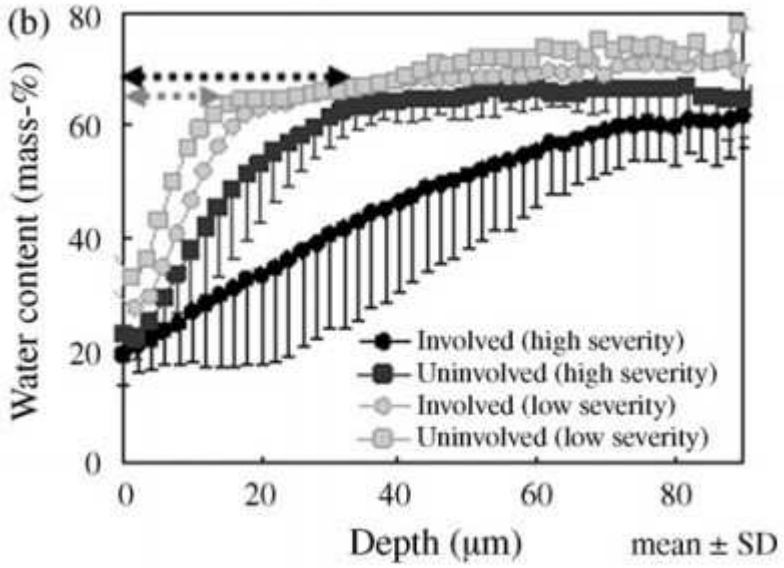
A proton NMR study on the hydration of normal *versus* psoriatic stratum corneum: linking distinguishable reservoirs to anatomical structures

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



Number of SC layers

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

Will also affect keratin binding as keratin content = 1 - water content

Example hydration for forearm:

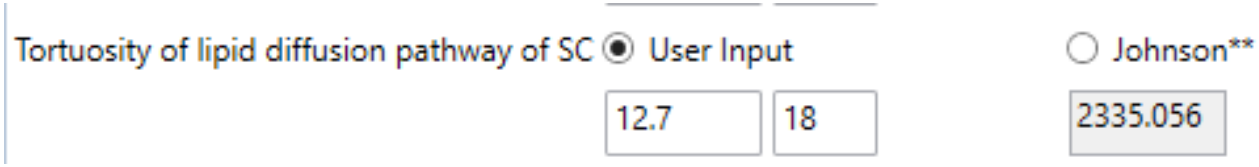
	Healthy	Plaque
Bin1	33.9	29.72
BIn2	44.7	33.32
Bin3	55.5	35.81
Bin4	66.4	41.75

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

CERTARA

Tortuosity



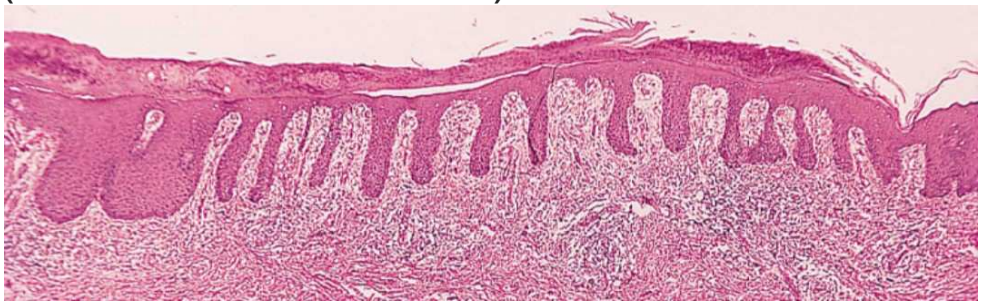
Johnson tortuosity will automatically recalculate from corneocyte dimensions:

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

Simcyp Default of 12.7 has been scaled to reflect this difference based on the ratio calculated by Johnson. Average new value ~ **6**

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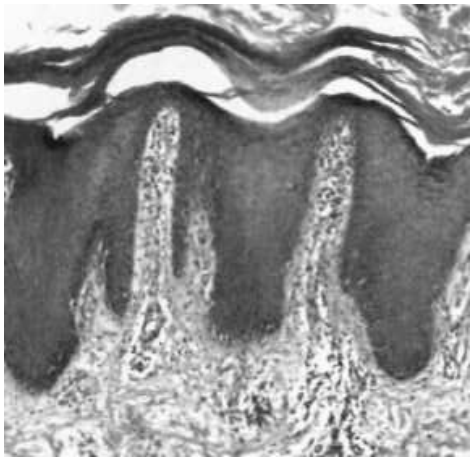
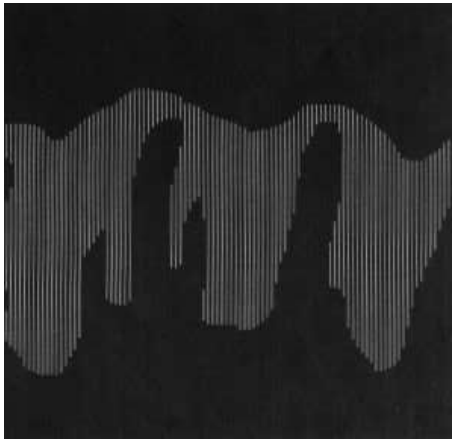
The number of subjects in each group is given in parentheses. The data are reported as medians in micrometers.

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

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

Viable Epidermis Thickness

Several studies, various techniques inc. ultrasound, biopsy and confocal microscopy.

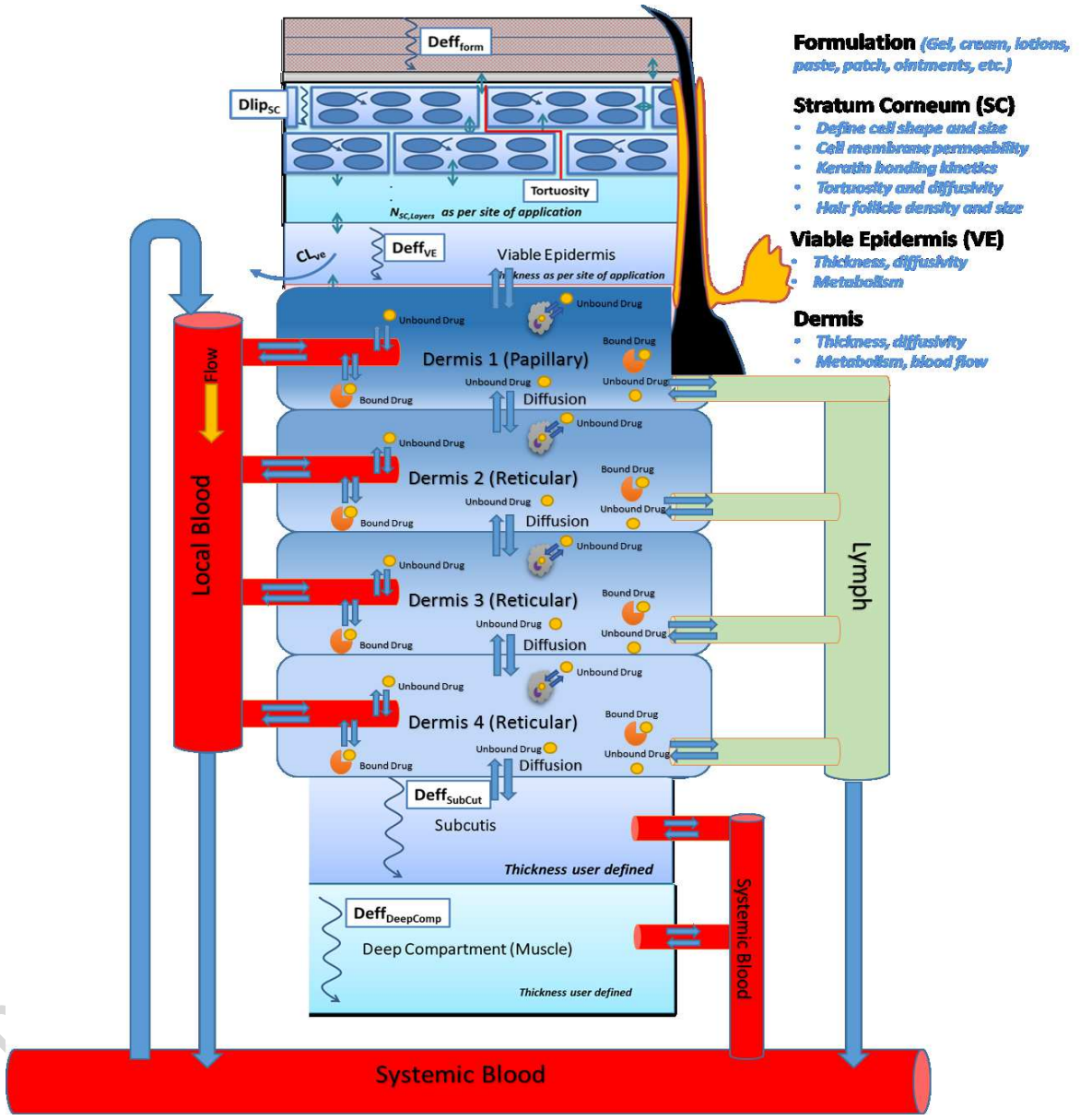
Ratio of 2.5-fold to healthy

Assumption:

Thickness is half way between the bottom of the supra-papillary plate and the bottom of the rete ridge.

Body site	Healthy	Plaque
Back	45.66	118.17
Fore head	50.05	129.53
Inner Fore arm	41.96	108.59
Outer Fore arm	53.57	138.64
Upper Forearm	51.80	134.06
Face	46.87	121.30
Leg (Lower)	57.36	148.45
Leg (Upper)	40.00	103.52

Depth Resolved Dermis Model (DRDM)



Capillary Volume Fraction

Quantification of microvascular changes in the skin in patients with psoriasis

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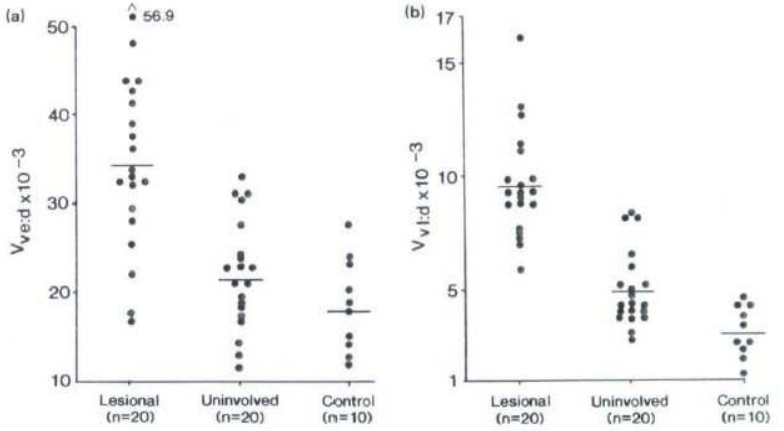
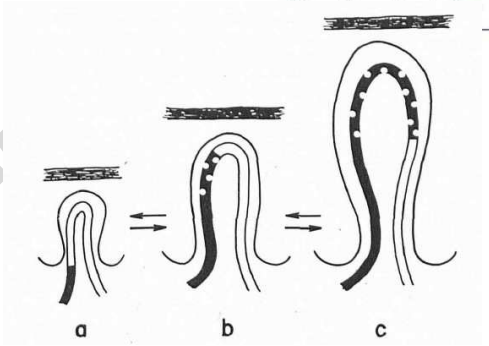
Accepted for publication 29 January 1992



Psoriasis patients					Control subjects			
No.	Age	Sex	Body site	Biopsy site	No.	Age	Sex	Biopsy site
101	34	F	L. elbow	Margin	1	34	F	L. elbow
102	40	M	R. thigh	Centre	2	27	F	L. elbow
103	62	F	R. elbow	Margin	3	29	M	L. elbow
104	33	M	L. elbow	Margin	4	30	M	Back
105	29	M	L. elbow	Margin	5	60	F	Abdomen
106	29	M	L. elbow	Margin	6	29	M	Abdomen
107	60	F	Abdomen	Margin	7	65	F	R. elbow
108	30	M	Back	Margin	8	67	M	L. elbow
109	65	F	L. elbow	Margin	9	65	F	L. elbow
110	36	M	Back	Margin	10	10	M	R. thigh
111	76	M	L. elbow	Centre				
112	29	M	Abdomen	Centre				
113	48	M	L. buttock	Margin				
114	37	M	Back	Centre				
115	35	M	L. elbow	Centre				
116	40	M	L. knee	Centre				
117	35	F	L. foot, med. aspect	Centre				
118	41	F	L. elbow	Centre				
119	26	F	L. elbow	Centre				
				Centre				



- Data measuring capillary endothelial and luminal volume fractions in the dermis can be used to parameterise the DRDM model.

- Biopsies taken from various body sites and sexes, however data between groups could not be separated.

Capillary Volume Fraction

***In vivo* volumetric imaging of microcirculation within human skin under psoriatic conditions using optical microangiography**

Imaging of Vessel Density

Cannot be used directly, but agrees with Barton Data (1.5 – 2 x increase between uninvolved and lesion)

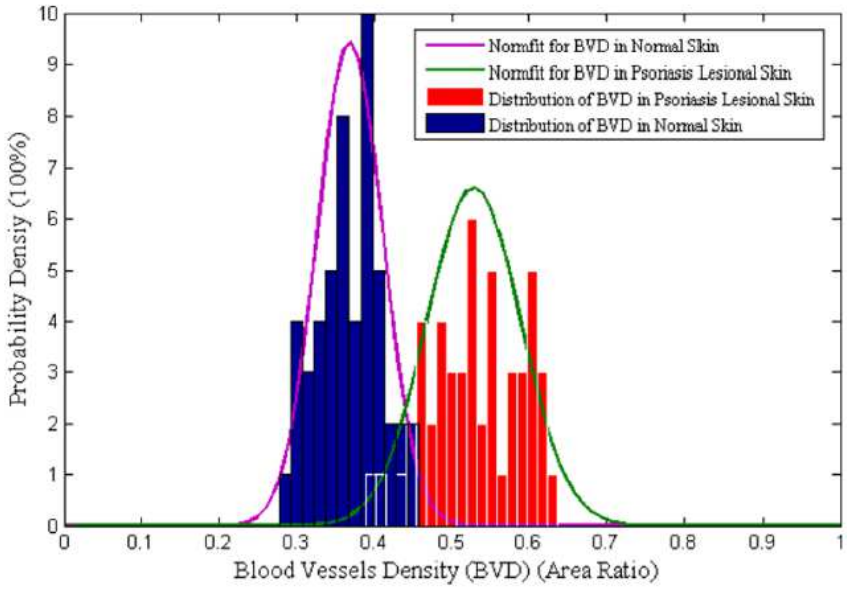
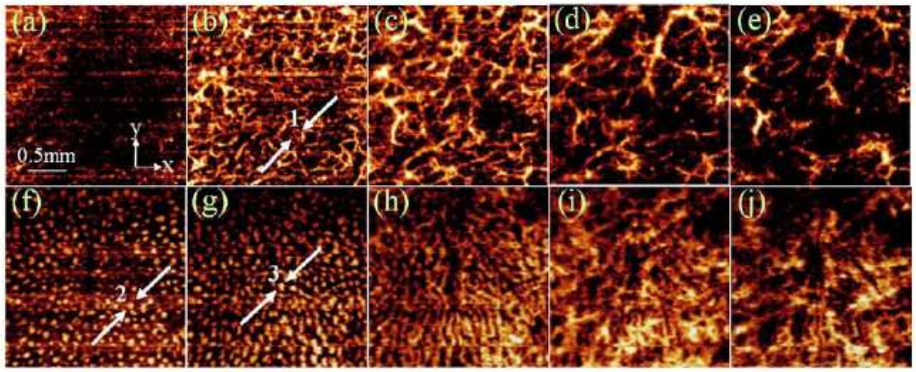


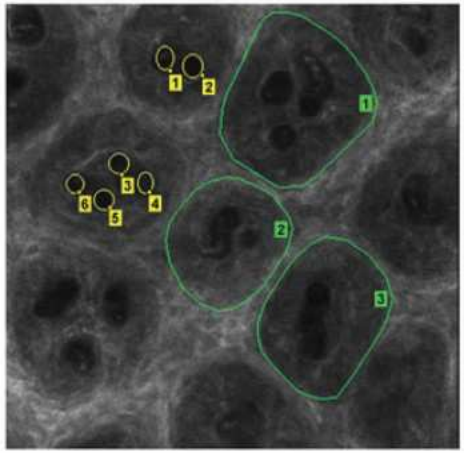
Fig. 7.
Histogram distribution for the blood vessel density (*BVD*) values obtained from the normal skin and psoriatic skin. Blue bars are for the normal skin and the red bars for psoriatic lesion skin. The bell-curves are obtained by fitting the *BVD* values in each group to the normal distribution function.



Capillary Diameter

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

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



Capillaries Parameters

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	Area	Perim.	Feret
1	235	54.978	20.224
2	268	58.119	20.396
3	228	53.407	17.692
4	185	48.695	18.248
5	228	53.407	17.692
6	188	48.695	16.492

Dermal Papillae Parameters

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	Area	Perim.	Feret
1	14005	434.709	151.251
2	8984	341.092	115.261
3	11119.750	387.017	139.032

Figure 1. Micromorphological parameters of dermal papillae and dermal capillaries. The parameters of the dermal papillae (green contour lines) and of capillary vessels (yellow circles) were measured using Image J 1.45 analysis software. The parameters investigated were area, Perim and Feret. Perim, perimeter; Feret, Feret's diameter.

ULTRASTRUCTURE OF THE CAPILLARY LOOPS IN THE DERMAL PAPILLAE OF PSORIASIS

IRWIN M. BRAVERMAN, M.D., AND AGNES YEN, B.S., M.S.

Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut, U. S. A.

TABLE I. *Dimensions of intrapapillary capillary loops (outside endothelial tube diameters)*

	Ascending limb (μm)	Crest (μm)	Descending limb (μm)
Pustular psoriasis (15 loops)	6–10[a]	8.8–16[b]	8.5–17[c]
Pustular psoriasis after treatment (4 loops)	6–10	8–9	8–10
Psoriasis vulgaris (25 loops)	6–9.6	8–16	7.2–17[c]
Psoriasis vulgaris after treatment (6 loops)	6–8.4	6–8.4	7.2–12
Normal skin	3.5–6	3.5–6	3.5–6

[a] One loop of the 15 had an ascending limb of 14–16 μm.
[b] One loop of the 15 had a crest of 18–24 μm.
[c] In 2 loops the lower half of the descending limb increased in width to 20–30 μm.

Transvascular Leakage

> Transvascular leakage

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

TABLE III.

	Case No.	TER_{alb}[a] (% IVM·hr^{-1})
	1	9.1
	2	7.6
	3	6.4
	4	6.8
	5	7.0
	6	7.3
	7	7.5
	8	7.3
	9	11.4
	10	8.8
	11	8.6
Patients	Mean	8.0
	± SD	1.4
Controls	Mean	5.1
	± SD	1.2
$p <$		0.001

[a] TER = transcapillary escape rate; alb = a
^{131}I-albumin and ^{125}I-IgG.

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

PV/IFV	TER (% IVM × hr^{-1})	A_b/A_s(% × hr^{-1}) I	A_b/A_s(% × hr^{-1}) II
0.33	8.3	9.9	14.1
0.31	7.6	5.1	29.9
0.32	7.5	1.6	16.1
0.33	5.8	3.3	6.2
0.40	3.5	8.9	11.9
0.29	6.8	7.3	27.6
0.23	8.6	4.7	9.9
0.29	6.4	4.4	11.5
—	—	—	—
—	—	—	—
0.31	6.8	5.7	15.9
0.05	1.6	2.8	8.5
			<0.02
0.39	5.1		8.3
0.06	1.2		2.6
<0.01	<0.05	NS	<0.02

Microvascular Protein Leakage in Extensive Skin Diseases: Aspects of the Transport Mechanisms

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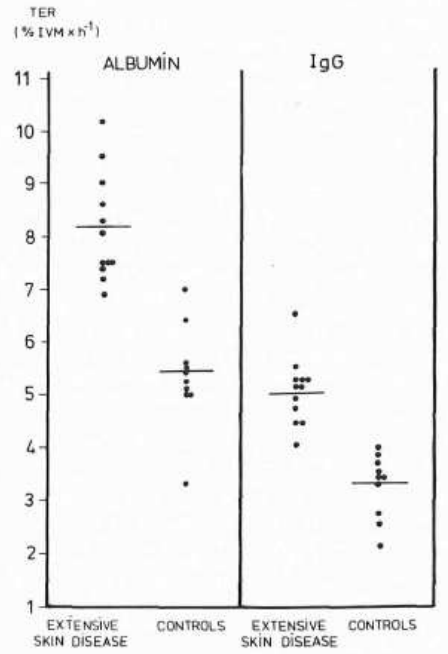

FIG 1. Transcapillary escape rate of albumin and IgG in patients ith extensive skin disease and controls. The solid line represents the ean value.

CERTARA

Interstitial Fluid

> ISF Volume

Plasma and Interstitial Fluid Volume in Extensive Skin Disease

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The mean values of plasma volume (PV), extracellular fluid volume (ECV), interstitial fluid volume (IFV), and PV/IFV ratio in 17 patients with extensive skin disease and 18 normal subjects

		PV				ECV				IFV				PV
		ml	ml/kg	ml/cm	1/m²	ml	ml/kg	ml/cm	1/m²	ml	ml/kg	ml/cm	1/m²	IFV
Patients	Mean	2916	37.5	17.1	1.54	11407	146	66.8	6.01	8439	109	49.8	4.47	0.35
	± SD	487	6.5	2.3	0.17	8630	22	9.4	0.55	1456	17	7.8	0.48	0.05
Controls	Mean	3110	45.0	18.0	1.69	10666	155	61.7	5.82	7556	110	43.8	4.13	0.42
	± SD	525	4.7	2.5	0.18	1823	21	9.2	0.75	1371	18	7.2	0.62	0.05
$p <$		NS	0.001	NS	0.05	NS	NS	NS	NS	NS	NS	NS	NS	0.001

The volumes are given in absolute figures (ml) and related to body weight (ml/kg), body height (ml/cm) and body surface area (1/m²).

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

Table I. Clinical data, plasma volume (PV), extracellular fluid volume (ECV), interstitial fluid volume (IFV), transcapillary escape rate of albumin (TER), appearance rate of labeled albumin in blister fluid (A_b/A_s) from uninvolved (I) and involved (II) skin in ten patients with psoriasis

Case No.	Surface area (m²)	Skin involvement (%)	PV (liter/m²)	ECV (liter/m²)	IFV (liter/m²)
1	2.18	80	1.93	7.71	5.78
2	2.08	70	1.85	7.77	5.92
3	1.88	40	1.35	5.57	4.22
4	2.01	30	1.35	5.43	4.08
5	1.93	40	1.87	6.56	4.69
6	1.88	40	1.34	5.96	4.62
7	1.83	60	1.09	5.85	4.76
8	1.73	50	1.47	6.54	5.07
9	2.15	40	—	—	—
10	1.95	60	—	—	—
Patients					
Mean	1.96	51	1.53	6.42	4.89
±S.D.	0.14	16	0.31	0.91	0.67
p					
*Controls**					
Mean	1.80		1.64	5.91	4.27
±S.D.	0.19		0.15	0.75	0.67
p	NS		NS	NS	NS

*Values from Rossing N, Worm A-M: Clin Physiol 1:275, 1981.

Lymph

> Lymph Flow

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.
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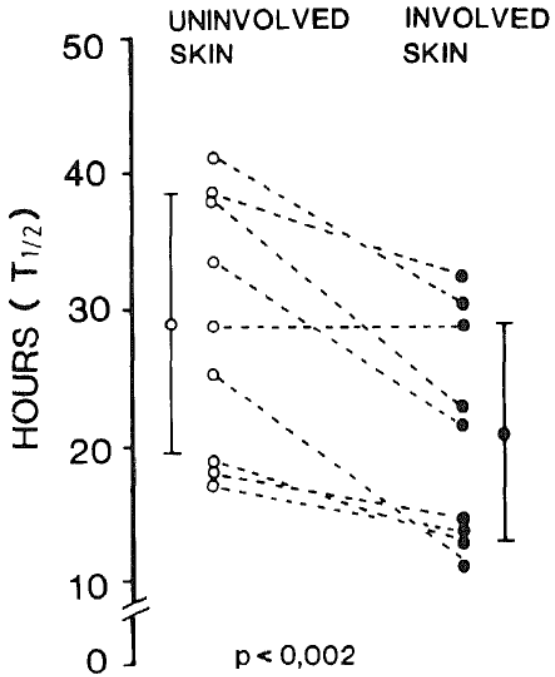


Fig. 2. Radiolabelled albumin clearance (T½) in uninvolved (○) and involved (●) skin of nine patients with psoriasis. Vertical bars represent means ± S.D.

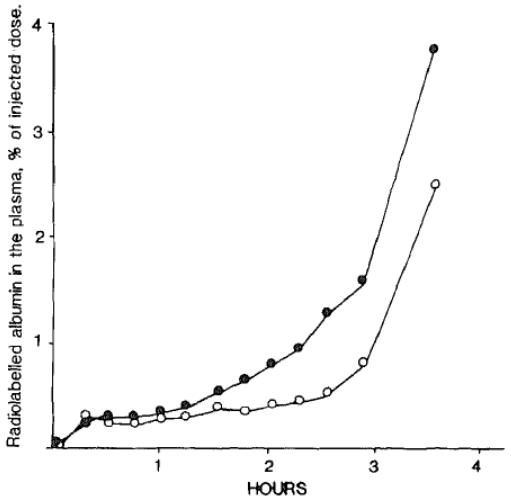


Fig. 3. An example of the plasma appearance rate during the resting period of radiolabelled albumin injected intradermally in uninvolved (○) and involved (●) skin of a patient with psoriasis. About 3 hours after the injection the patient was allowed to move.

> Lymph vessel density

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

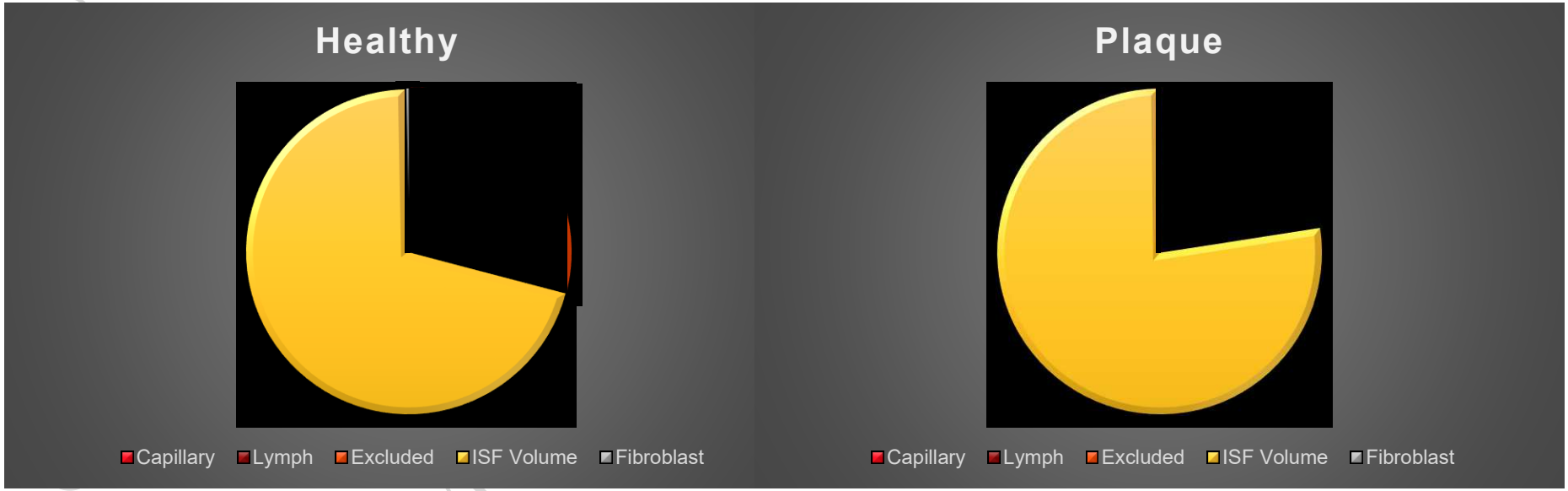
Table 2 Density of lymphatic vessels in skin of psoriatic plaque and normal skin control

	Psoriasis, n = 32 (n mm^{-1})[a]	Control, n = 32 (n mm^{-1})[a]	P-value[b]
Lymphatics (all sizes)[c]	10·01 ± 6·09	3·58 ± 1·31	< 0·001
Inside dermal papillae[d]	3·36 ± 3·62	0·01 ± 0·03	< 0·001
Lymphatics < 10 μm[c]	3·58 ± 3·52	1·47 ± 0·94	0·002
Inside dermal papillae[d]	1·25 ± 2·02	0·01 ± 0·02	< 0·001
Lymphatics 10–17 μm[c]	4·03 ± 2·68	1·47 ± 0·89	< 0·001
Inside dermal papillae[d]	1·48 ± 1·60	0·00 ± 0·03	< 0·001
Lymphatics 18–24 μm[c]	1·58 ± 1·49	0·33 ± 0·25	< 0·001
Inside dermal papillae[d]	0·48 ± 0·59	0·00 ± 0·00	< 0·001
Lymphatics > 24 μm[c]	0·82 ± 0·67	0·32 ± 0·51	< 0·001
Inside dermal papillae[d]	0·15 ± 0·28	0·00 ± 0·00	< 0·001

[a]Mean ± SD. [b]Asymptotic significance level (two-tailed) Mann–Whitney U-test. [c]All stained vessel segments above the upper horizontal blood plexus. [d]Positive segments between elongated rete ridges.

Volume Fractions

Volume fraction of Dermis Components for DRDM



DRDM Screens

Physiology

Dermis

Total Thickness (µm)	1250	45
Regional dermis blood flow scalar*	2.13	0

DRDM Parameters

	Layer Thickness (%)*	Vessel Radii (µm): Capillary Wall Thickness (µm)	Vessel Radii (µm): Capillary Lumen	Vessel Radii (µm): Capillary External	Volume Fraction (cm³/cm³) ǂ: Capillary ǂ Mean	Capillary ǂ CV (%)	Lymph ǂ Mean	Lymph ǂ CV (%)	Fibroblast Mean	Excluded Mean	Interstitial Fluid
Dermis 1	12.24	3.5	1.75	5.25	0.0199	21.85	0.0144	98.98	0.003	0.2567	0.706
Dermis 2	29.25	4.4	7.66	12.06	0.014	37.54	0.0341	98.98	0.003	0.24298	0.706
Dermis 3	29.25	4.4	7.66	12.06	0.014	37.54	0.0341	98.98	0.003	0.27298	0.706
Dermis 4	29.25	4.4	7.66	12.06	0.014	37.54	0.0341	98.98	0.003	0.24298	0.706

Lymph Flow Scalar	1	30	Fraction of ISF accessible by albumin	0.39
			Albumin concentration in accessible spce (g/L)	30.44	34.2

* % of the total dermis thickness. ǂ Capillary and lymph volume fractions are that occupied by lumen + endothelium. ǂ Volume of substituent per cm³ of tissue

Dermis Blood Flow

- Many studies available with various techniques employed
- Consistent finding of > blood flow, ranging from 1.7 – 13.5 fold.

Assumption:

Because all studies found minimal difference between uninvolved and healthy BF (<1.5 fold).

Uninvolved was assumed “healthy” to calculate ratios where healthy control was not used

Study	Method	Final Ratio to ‘healthy’
NYFORS 1970	Xe washout	1.70
Klemp 1983	Xe washout	10.16
Klemp 1985	Xe washout	4.10
Klemp 1985	Xe washout	13.50
Ferguson 1961	I Washout	2.45
Yosopivitch 2003	LDV	2.88
Goh 2004	LDPI	2.78
Hern 2005	LDPI	9.08
Khan 1987	LDV	6.69
Ascheim 1966	Na washout	1.79
	Mean Ratio	**5.52**

Subcutis Blood Flow

Two studies by Klemp *et al*, Xe washout draw a similar conclusion.

Study	Method	Final Ratio to healthy
Klemp 1985a	Xe washout	1.571
Klemp 1985b	Xe washout	1.776
	Mean	1.67

Albumin

Several studies suggest a decreased albumin content in both serum and ISF.

	N	Serum	ISF
Staberg	10	0.889	0.754
Worm	2	0.841	0.850
Worm	6	0.841	0.681
Sheikh	100	0.918	
Weighted Mean Ratio to healthy		0.910	0.740

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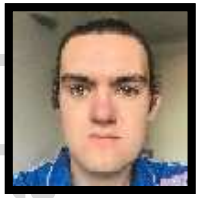

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Questions?

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