Simulation and Modeling of Dermal Absorption Kinetics: What Level of Detail Is Needed?

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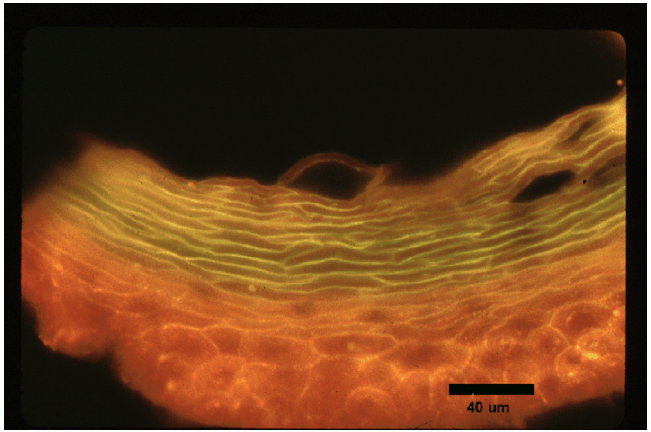


Conflict of Interest Statement

- The opinions offered in this presentation are my own.
- I have no conflict of interest to declare.

Outline/Objectives

Remarks on simulation and modeling will center on three topics:

- Motivation and scale
- Simple dermal absorption models
- Mechanistic dermal absorption models

So what level of detail is needed?

The answer to this question depends on the phenomena one wants to predict and the audience to whom the prediction is addressed.

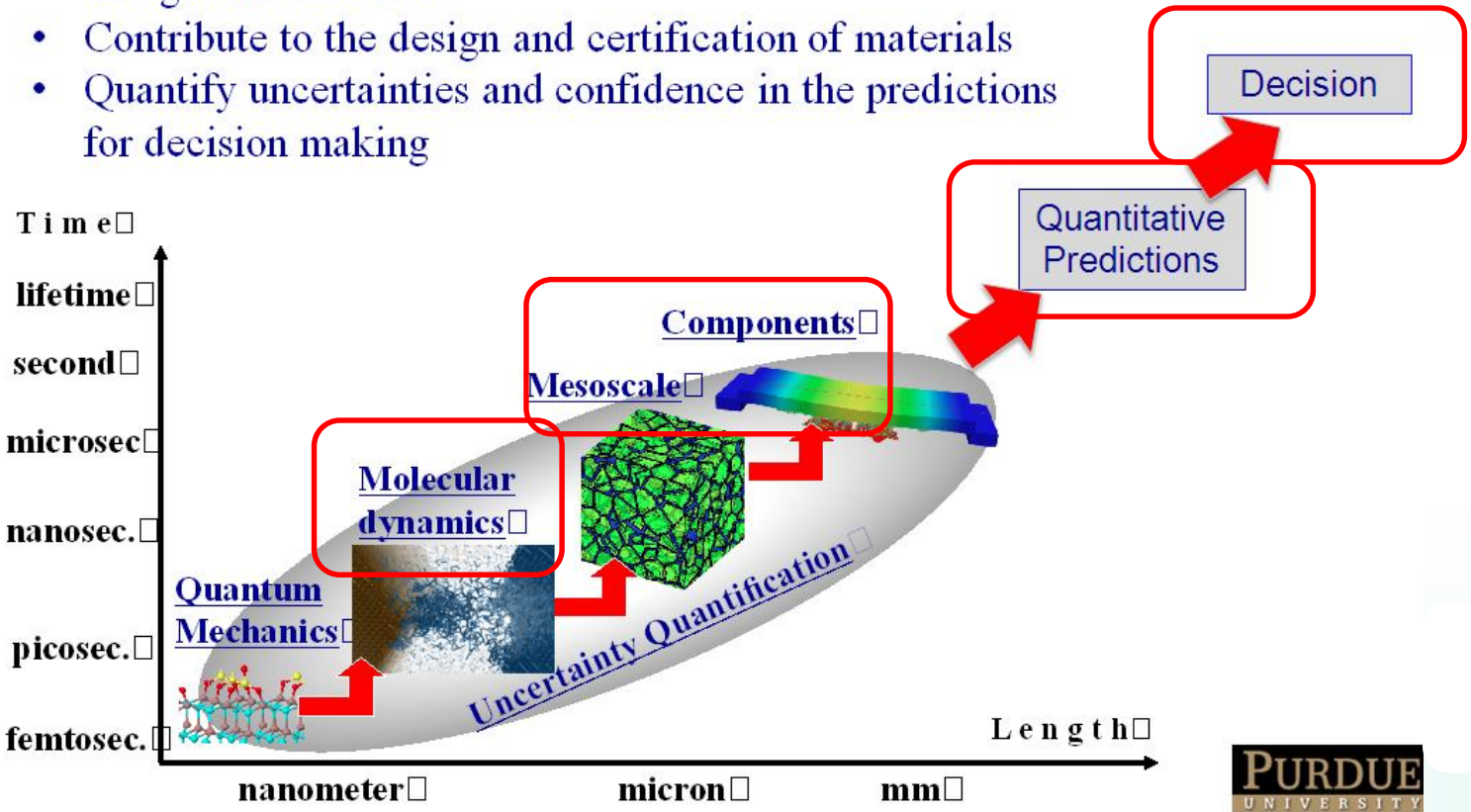
Regulators

Risk assessors

Toxicologists and basic scientists

Multiscale modeling of materials

- Uncover and characterize the molecular-level mechanisms that govern materials
- Contribute to the design and certification of materials
- Quantify uncertainties and confidence in the predictions for decision making



PURDUE UNIVERSITY

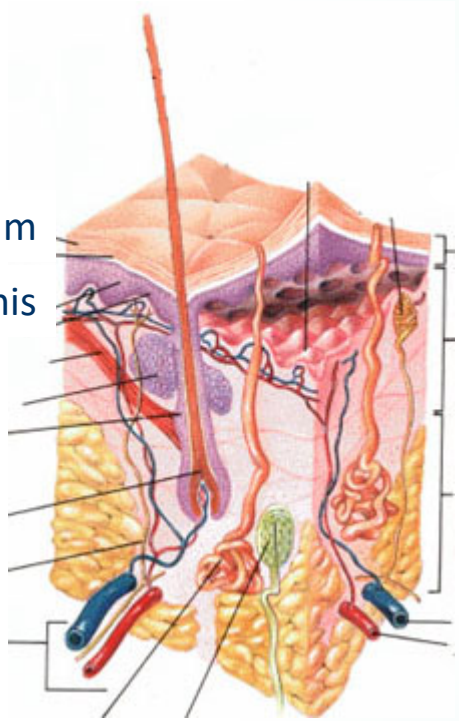
In the spirit of this workshop, I will come at this problem with dermal risk assessment in mind.

Typical Objective of Our Research

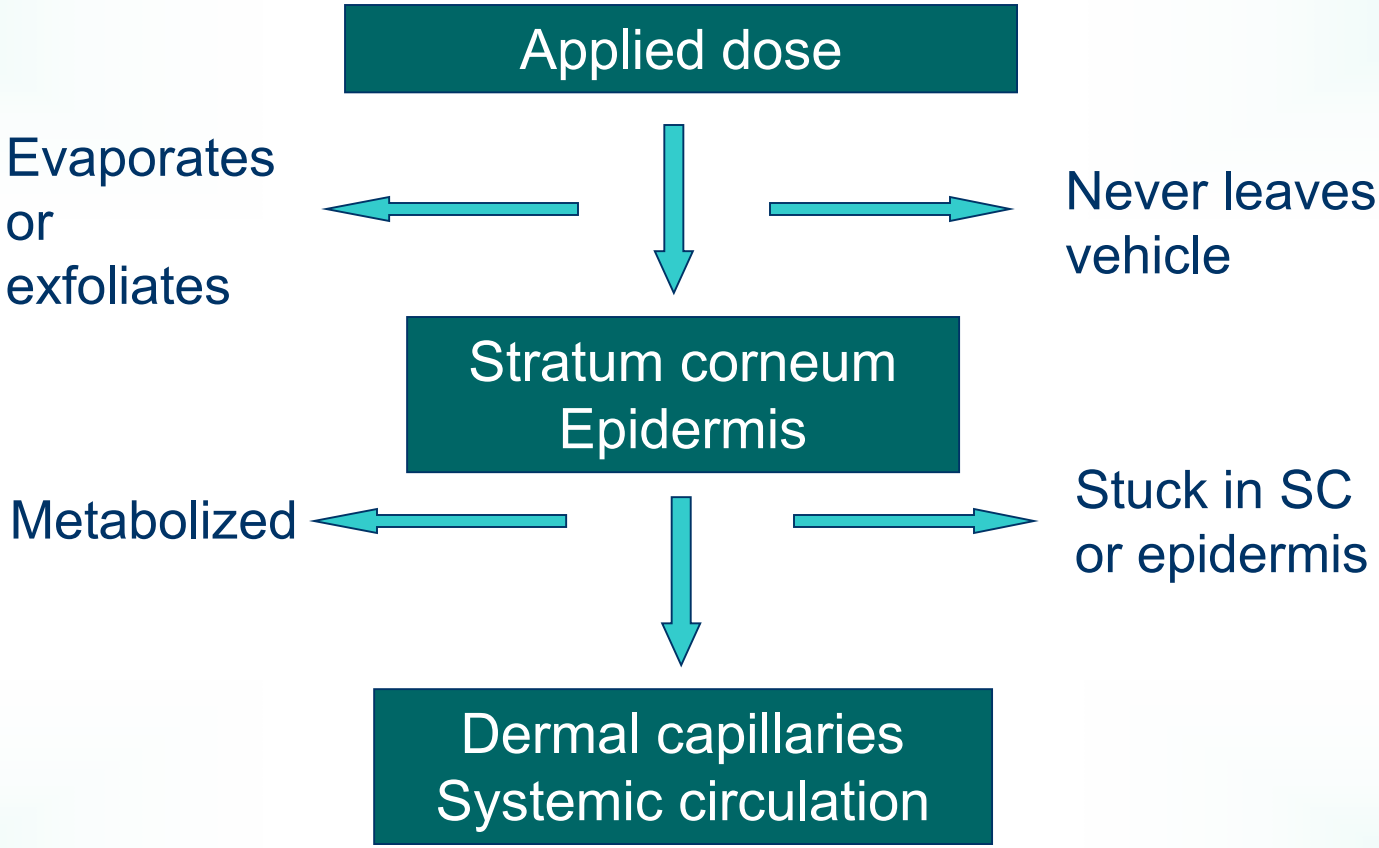
“The results of this project will allow one to (1) explain and (2) reliably predict chemical bioavailability from dermal exposure for a broad range of chemical classes and formulations. It will be possible to run an assessment directly from molecular structure as well as in a higher tier where some experimental data will be fed into the framework.”

The European
Chemical Industry Council

So how much detail do we need to include?



More broadly, what factors determine the fate of topically applied compounds?


Applied dose
Evaporates or exfoliates
Never leaves vehicle
Stratum corneum Epidermis
Metabolized
Stuck in SC or epidermis
Dermal capillaries Systemic circulation

Relevant Factors for Estimating Dermal Absorption

Permeant properties

- Molecular weight
- Lipophilicity
- Water solubility
- Density
- Vapor pressure
- Ionization state
- Protein binding

Environmental factors

- Skin hydration state
- Temperature
- Wind velocity

Dose

- Skin load
- Formulation or vehicle
- Ruboff or washoff

- These exposure factors must be a part of the eventual solution.
- But let’s return to the skin component and take a look at the information yielded by simple skin models…

Skin Model

Size-selective lipid membrane

$$\log k_p = 0.71 \log K_{oct} - 0.0061 \cdot MW - 2.7$$

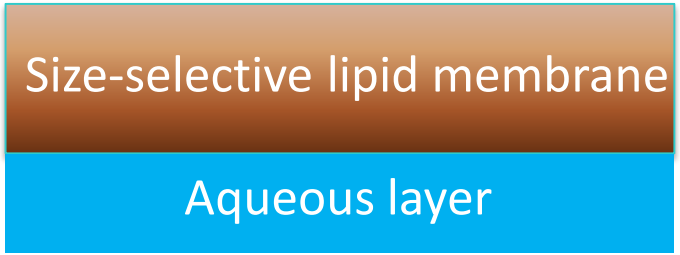
Potts & Guy, 1992

What can be done with it?

- Calculate steady-state skin permeability from aqueous solutions, k_p.
- Multiply k_p by solute concentration in water, C_w, to calculate flux.

  $$J_{ss} = k_p \times C_w$$
- Limit as $C_w \rightarrow S_w$ yields *maximum flux*, J_{max}.
- Total absorption is then Q_{max} = Area $\times$ J_{max} $\times$ T_{exp}.

Skin Model



$$\log k_p = 0.71 \log K_{oct} - 0.0061 \cdot MW - 2.7$$

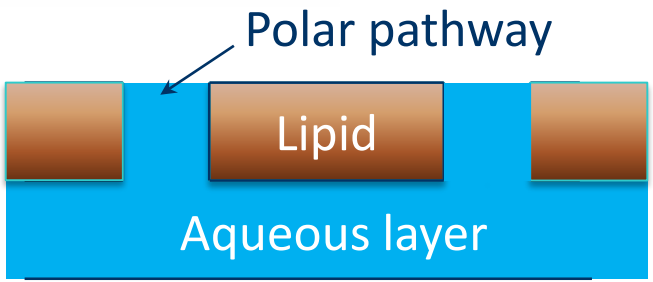
$$k_p^{mod}(\text{cm h}^{-1}) = k_p / \{1 + (k_p \cdot \sqrt{MW})/2.6\}$$

Cleek & Bunge, 1993

What can be done with it?

- Calculate steady-state skin permeability from aqueous solutions, k_p^{mod}.
- Extends lipid membrane model to accommodate highly lipophilic solutes.
- $J_{max} = k_p^{mod} \times S_w$.
- $Q_{max} = \text{Area} \times J_{max} \times T_{exp}$.

Skin Model



$$\frac{1}{k_p} = \frac{1}{k_{aq}} + \frac{1}{(k_{lip} + k_{pol})}$$

Wilschut et al., 1995

What can be done with it?

- "Modified Robinson" model of skin permeability.
- Extends Cleek & Bunge model to accommodate highly polar solutes.
- $J_{max} = k_p \times S_w$.
- $Q_{max} = \text{Area} \times J_{max} \times T_{exp}$.

The Cleek & Bunge method has been recently recommended (again) for dermal risk assessment.

Regulatory Toxicology and Pharmacology 76 (2016) 174–186

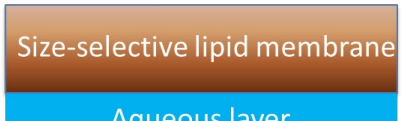
Contents lists available at ScienceDirect

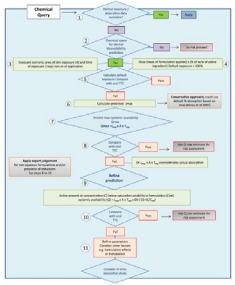
Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Assessing the safety of cosmetic chemicals: Consideration of a flux decision tree to predict dermally delivered systemic dose for comparison with oral TTC (Threshold of Toxicological Concern)

Faith M. Williams [a, *], Helga Rothe [b], Gordon Barrett [c], Alessandro Chiodini [d], Jacqueline Whyte [d], Mark T.D. Cronin [e], Nancy A. Monteiro-Riviere [f], James Plautz [g], Clive Roper [h], Joost Westerhout [i], Chihae Yang [j], Richard H. Guy [k]

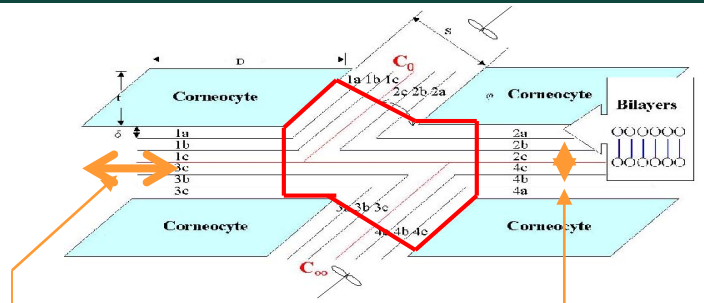




"Tiered decision tree" analysis

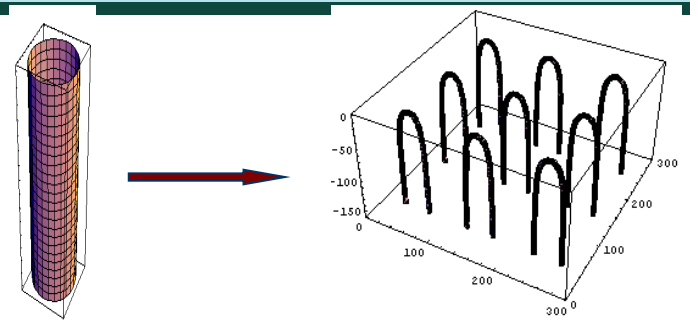
- These models all provide ways of estimating J_{max}, and Q_{max}, numbers that are useful in risk assessment.
- But what if the questions asked are more detailed?
  - How much of a fragrance compound will evaporate during exposure?
  - What is the absorption from a rinse-off product?
  - What is the concentration at the Langerhans cell surface?
  - How much does the skin hydrate during diapering?
  - Can I target delivery to a hair follicle?
- Answers to these questions require more complex models.

Skin Microtransport Models



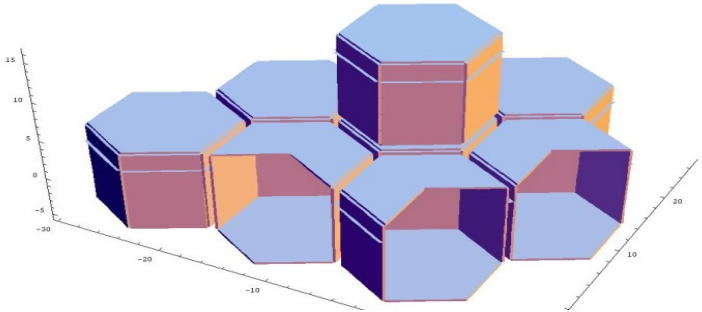
Stratum corneum

Wang et al., *J Pharm Sci*, 2006 & 2007



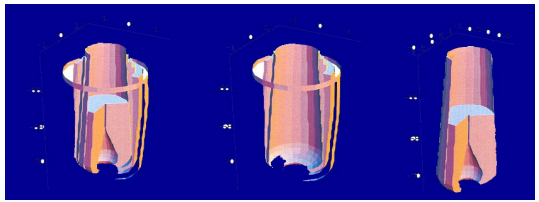
Dermis

Kretsos & Kasting, *Math Biosciences*, 2007;
Ibrahim et al. *J Pharm Sci*, 2012



Viable epidermis

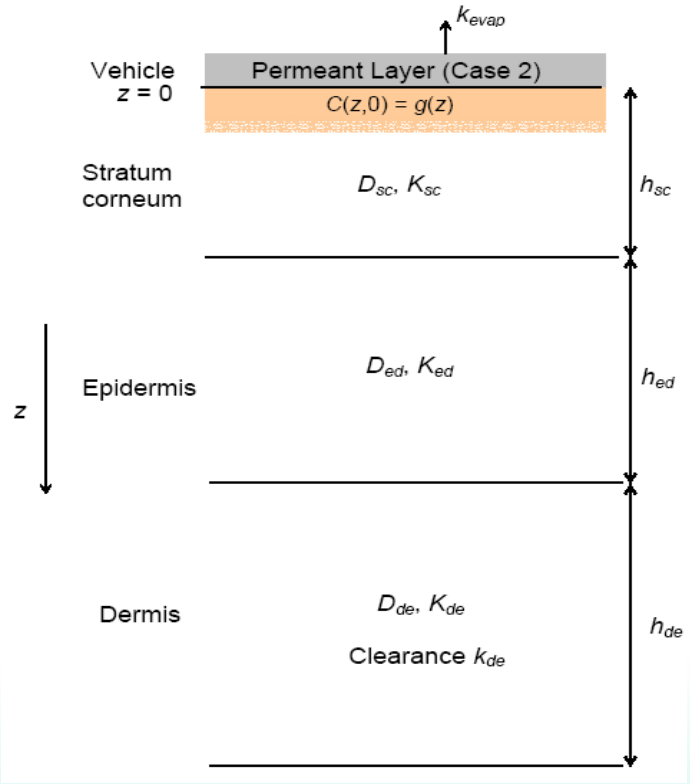
Nitsche & Kasting, *Biophys J*, 2013

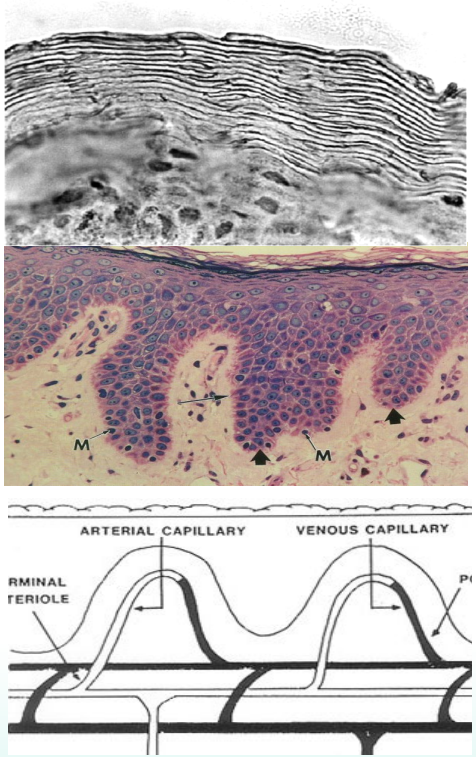


Hair follicle

Dancik PhD thesis, UB, 2006

Effective Medium Model of Skin





Kasting et al., *J Occup Environ Hyg*, 2008

Model Implementation

- The set of differential equations representing mass transport in the one-dimensional model is integrated using a finite difference numerical method.
- We chose Microsoft Excel™ as the first computational platform, with the numerical method supplied as an add-in coded in Visual Basic.
- A Java version of the program may be accessed on the NIOSH website under the name Finite Dose Skin Permeation Calculator.

www.cdc.gov/niosh/topics/skin/finiteskinpermcalc

The Model Considers These Exposure Factors…

Permeant properties

- Molecular weight
- Lipophilicity
- Water solubility
- Density
- Vapor pressure
- Ionization state
- Protein binding

Environmental factors

- Skin hydration state
- Temperature
- Wind velocity

Dose

- Skin load
- Formulation or vehicle
- Ruboff or washoff

Overview of UB/UC Skin Absorption Model

Advanced Drug Delivery Reviews 65 (2013) 221–236

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Design and performance of a spreadsheet-based model for estimating bioavailability of chemicals from dermal exposure ☆

Yuri Dancik [a], Matthew A. Miller [b,*], Joanna Jaworska [a], Gerald B. Kasting [b]

[a] The Procter & Gamble Company, Strombeek-Bever, Belgium
[b] James L. Winkle College of Pharmacy, The University of Cincinnati Academic Health Center, Cincinnati, OH, USA

Dancik et al., *Adv Drug Deliv Revs* **65**:221-236 (2013)

Limitations/Opportunities Presented by UB/UC

- Complex vehicles
- Skin hydration
- Polar compound transport

Complex Vehicles

Vehicle Options in UB/UC Model

- Volatile
  - Permeant is solvent-deposited in upper SC layers
  - Vehicle evaporates prior to simulation
- Immobile
  - Vehicle neither evaporates nor penetrates the skin during the simulation

Solution

- Extend the model to simultaneously track the disposition of multiple ingredients.
- This allows the vehicle to gradually “dry down” on skin while delivering the compound of interest.
- Interactions of excipients with skin, e.g., permeability enhancement, are enabled by this development.

Multicomponent Vehicle Model

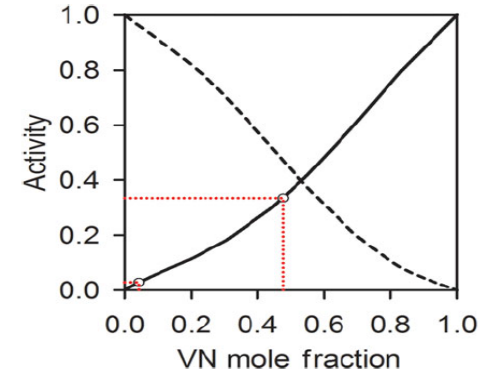
A Spreadsheet-Based Method for Simultaneously Estimating the Disposition of Multiple Ingredients Applied to Skin

MATTHEW A. MILLER, GERALD B. KASTING

James L. Winkle College of Pharmacy, University of Cincinnati Academic Health Center, Cincinnati, Ohio

Journal of Pharmaceutical Sciences

This program tracks the fate of multiple ingredients applied to skin, using a thermodynamically-based approach.



Miller & Kasting, *J Pharm Sci* **104**:2047-2055 (2015)

Skin Hydration

Hydration Options in UB/UC Model

The UB/UC model has permeable corneocytes that swell when the skin is occluded.

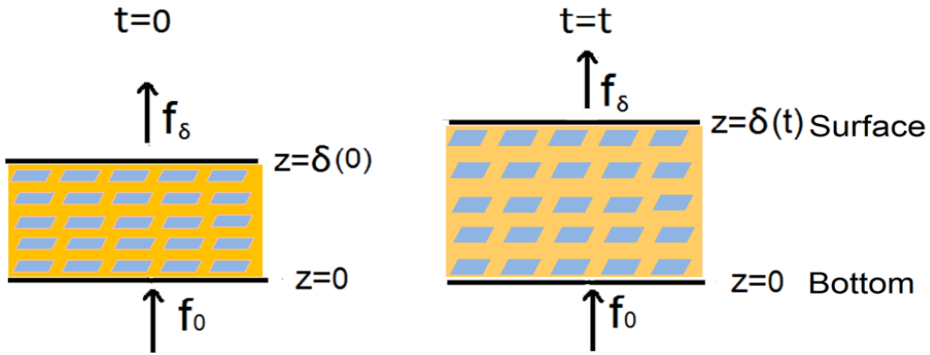
partially hydrated SC

fully hydrated SC

These states are static, thus cannot be changed during the course of a simulation.

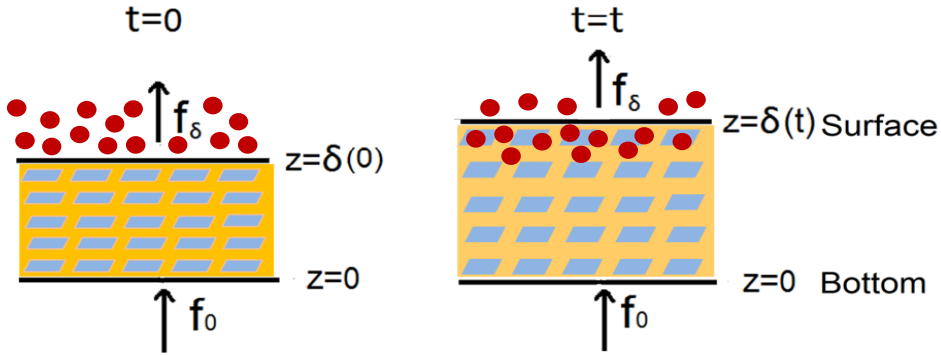
Wang, Kasting & Nitsche, *J Pharm Sci* **95**:620-648 (2006)
Wang, Kasting & Nitsche, *J Pharm Sci* **96**:3024-3051 (2007)

But What Really Happens When Topical Products Are Applied to Skin?



The stratum corneum swells transiently, then returns to the normal hydration state and thickness as the product dries down.

What Else Happens?



Dissolved ingredients are deposited into the upper layers of the stratum corneum via the convective flow.

Skin Swelling Model

Chemical Engineering Science 138 (2015) 164–172

Contents lists available at ScienceDirect

Chemical Engineering Science

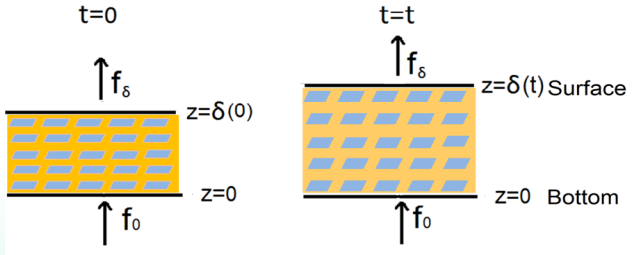
journal homepage: www.elsevier.com/locate/ces

Dynamics of water transport and swelling in human stratum corneum

Xin Li [a], Robert Johnson [b], Ben Weinstein [b], Elizabeth Wilder [b], Ed Smith [b], Gerald B. Kasting [c,*]

[a] UC-P&G Simulation Center, University of Cincinnati, 45220 Cincinnati, OH, United States
[b] Research and Development Department, The Procter and Gamble Company, 45069 Cincinnati, OH, United States
[c] James L. Winkle College of Pharmacy, University of Cincinnati, PO Box 670004, 45267 Cincinnati, OH, United States

This program tracks the movement of water as the stratum corneum hydrates and dehydrates.



Li et al., *Chem Eng Sci* **138**:164-172 (2015)

Baby Care Skin Swelling Application

Accepted: 10 February 2017
DOI: 10.1111/srt.12362

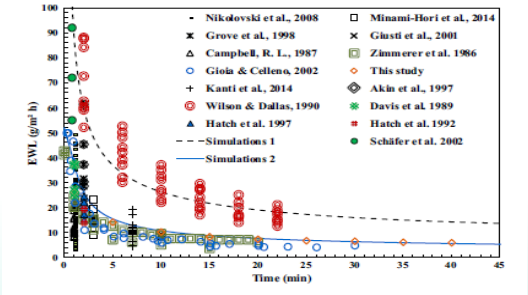
ORIGINAL ARTICLE

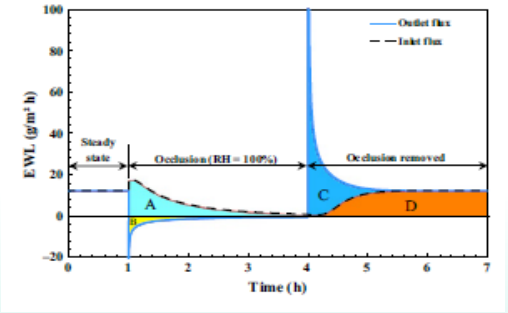
WILEY

Skin hydration analysis by experiment and computer simulations and its implications for diapered skin

M. Saadatmand[1] | K. J. Stone[2] | V. N. Vega[2] | S. Felter[2] | S. Ventura[3] | G. Kasting[3] | J. Jaworska[4]

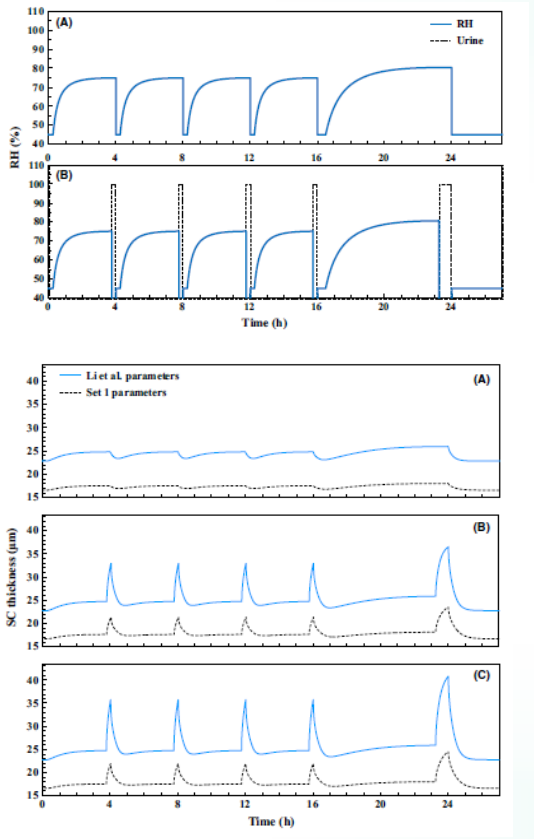
Skin Res Technol. 2017;1–14. wileyonlinelibrary.com/journal/srt





Saadatmand et al., *Skin Res Technol*, 2017

This program estimates changes in baby skin water content and thickness under various diapering scenarios.

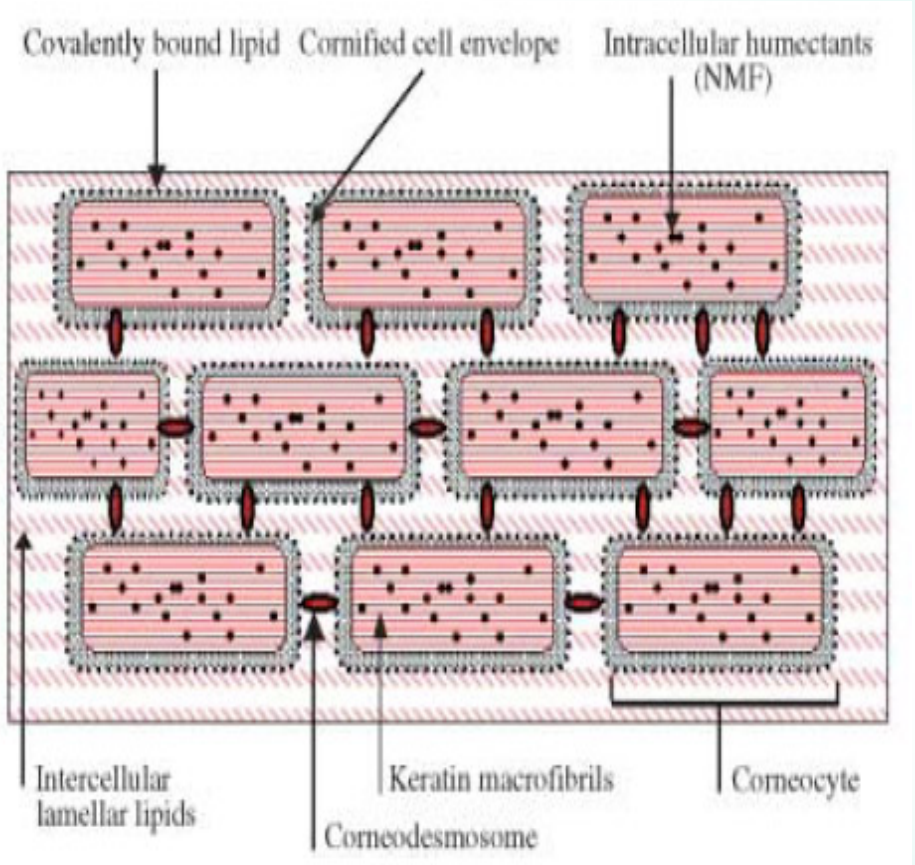


Saadatmand et al., *Skin Res Technol*, 2017

Polar Compound Transport in Skin

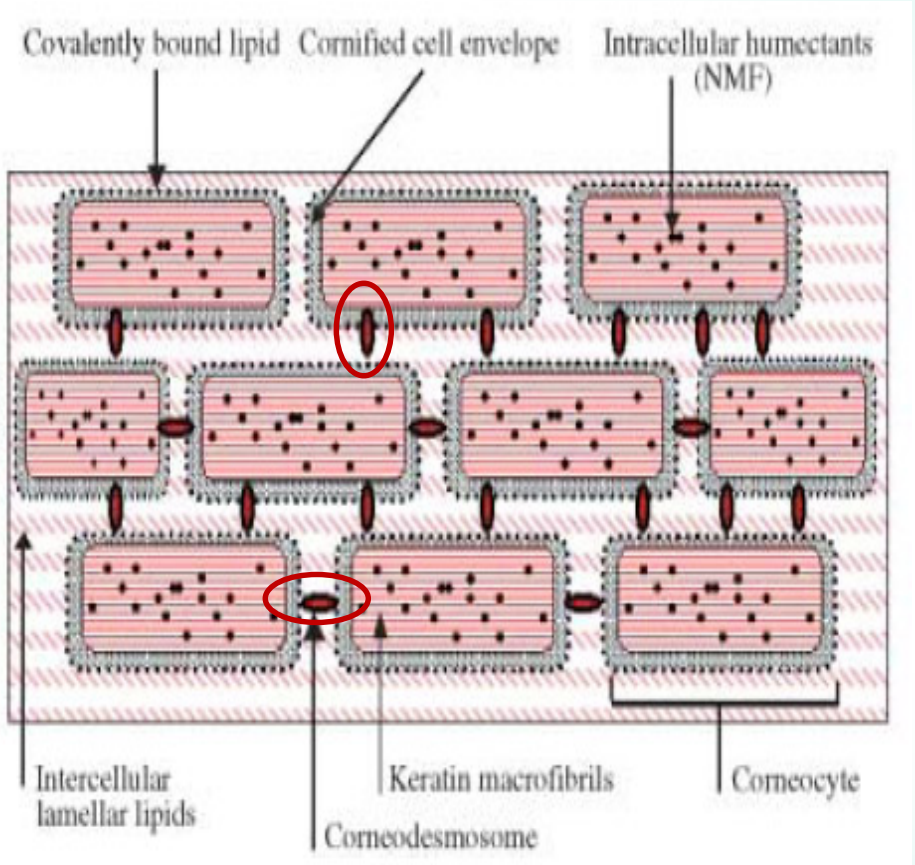
Our Picture of the Polar Pathway…

Start with a recent bricks-and-mortar model of the SC.



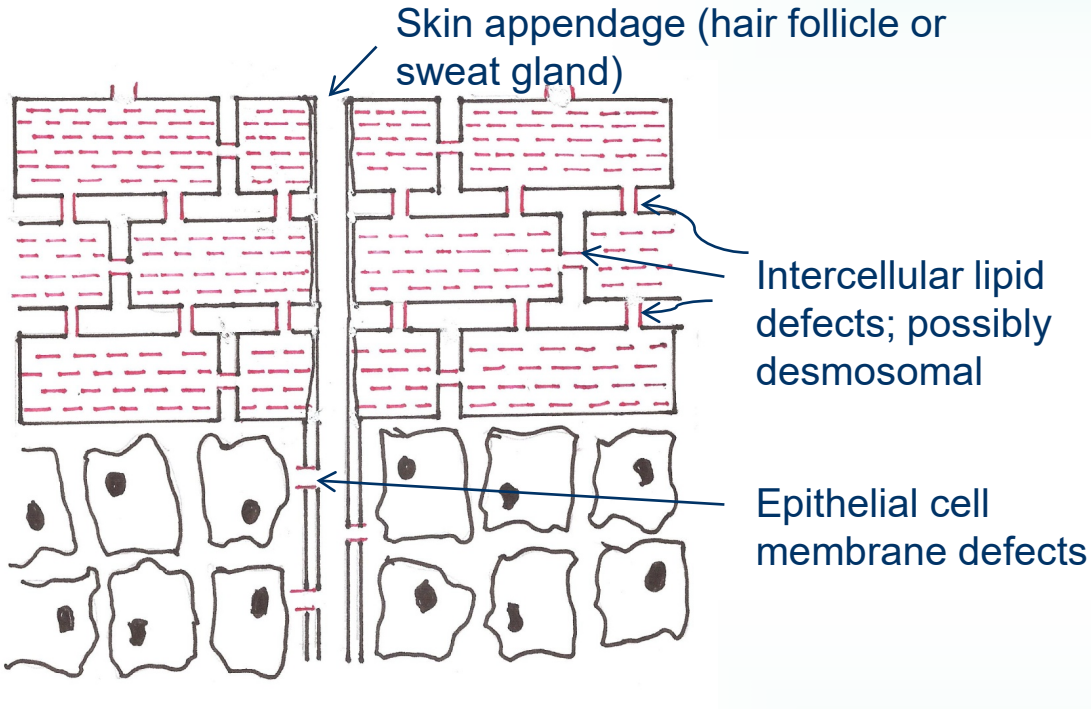
From C. Harding, *Dermatologic Therapy* **17**:6-15 (2004)

Consider that the corneo-desmosomes are a potential leakage route for polar compounds.



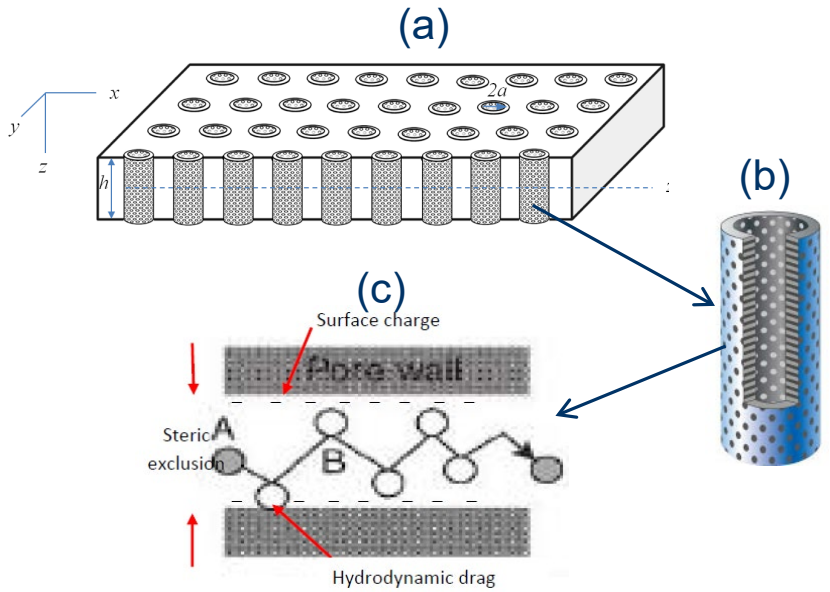
From C. Harding, *Dermatologic Therapy* **17**:6-15 (2004)

Add appendageal shunts.



Kasting et al., *J Pharm Sci* **108**:337-349 (2019).

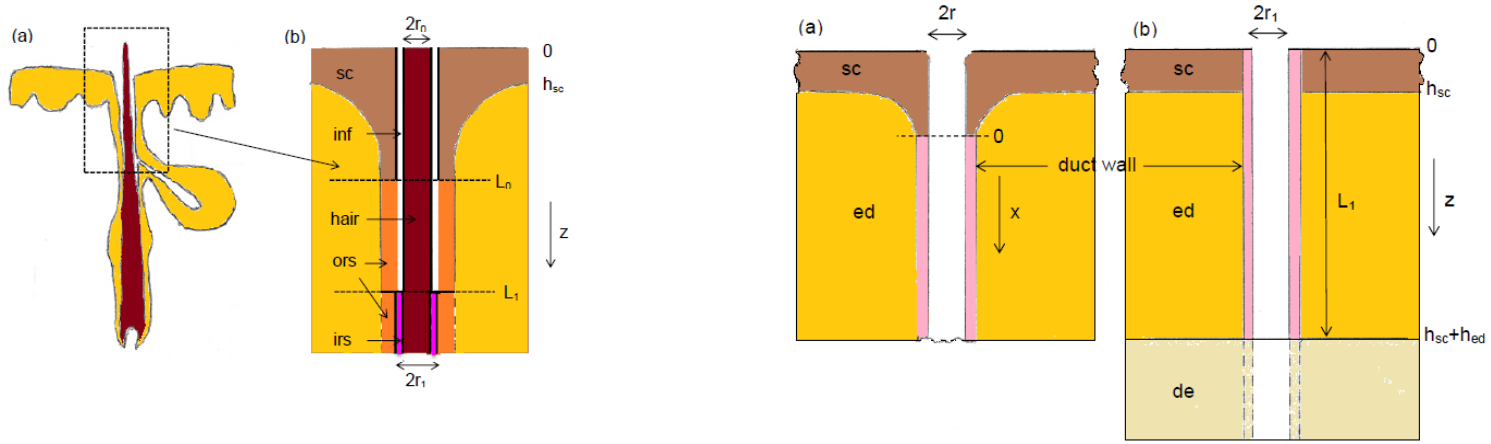
Model as an Array of Cylindrical Shunts



(a) Macroporous membrane
(b) Microporous shunts
(c) Hindered diffusion within micropores

Kasting et al., *J Pharm Sci,* 2019

Hair Follicle and Sweat Duct Variants Are Envisioned



We favor the hair follicle variant for passive diffusion and the sweat duct variant for iontophoretic transport.

Kasting et al., *J Pharm Sci,* 2019

The Proposed Polar Pathway thus Has Two Components

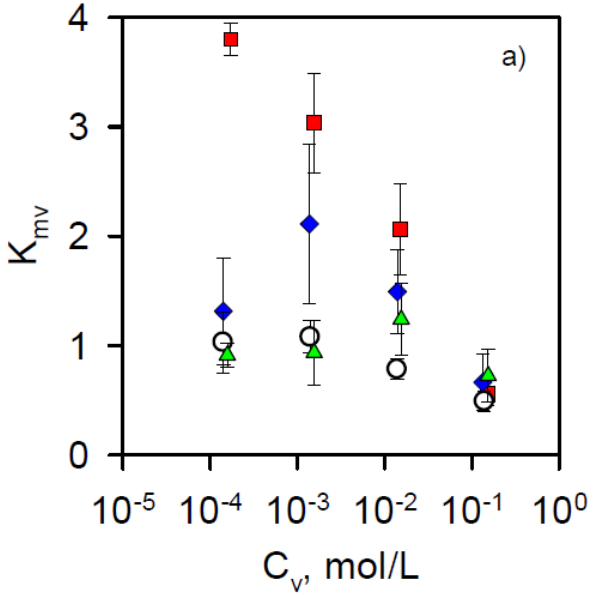
- A distributed component comprised of desmosomes and/or SC lipid defects allowing slow, transcellular diffusion to occur at a very low rate.
- An appendageal component comprised of hair follicles and sweat glands allowing rapid penetration of polar compounds into the lower skin layers, albeit in limited quantities.

The evidence for these elements follows.

Distributed Component

Hydrophilic compounds partition into isolated human SC in substantial quantities.

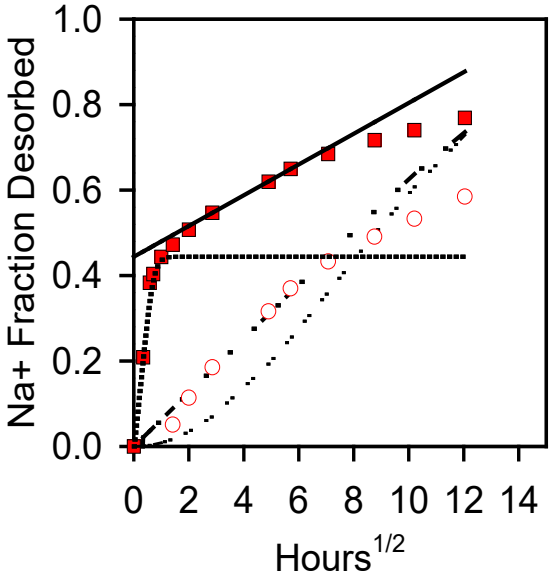
Key:
- Na^+
- Cl^-
- TEA^+
- mannitol



Miller MA et al., *J Control Rel* **261**:307-317 (2017)

Distributed Component

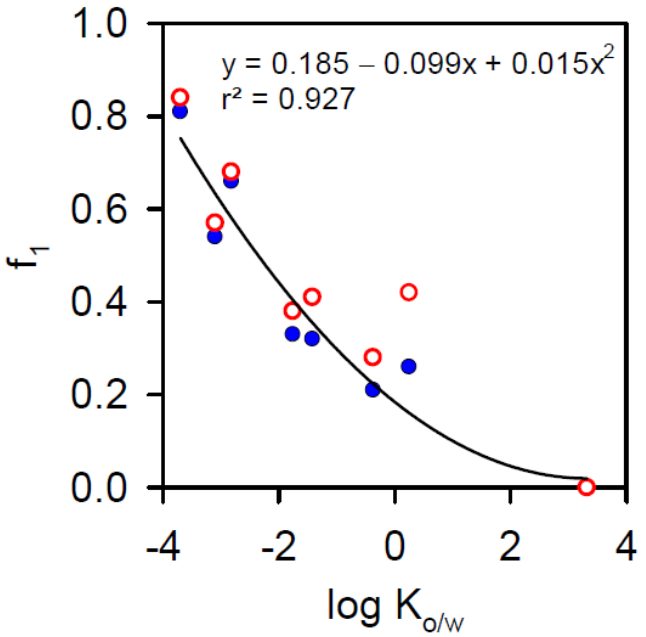
They desorb from isolated human SC in two phases, fast and slow.



Miller et al., *J Control Rel*, 2017

Distributed Component

- The fast phase is a substantial fraction of the total desorption for very hydrophilic permeants, but approaches zero for lipophilic permeants.
- We think of this as desorption from the SC surface and perhaps the desquamating layers.



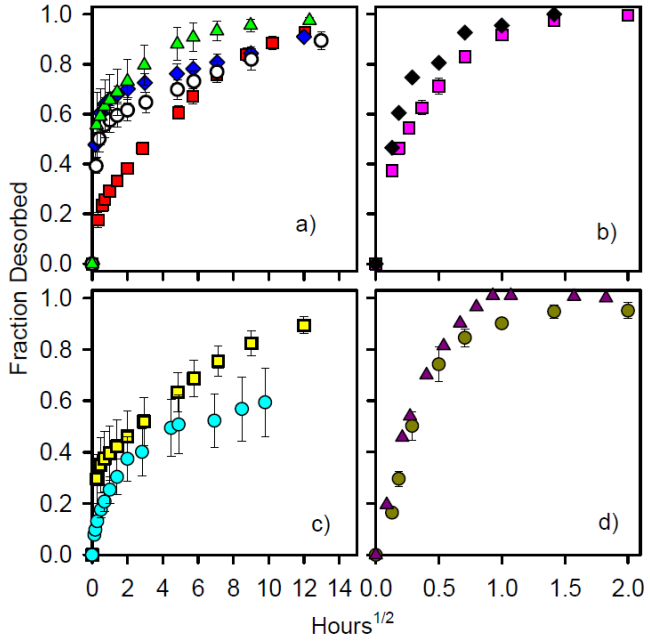
Miller et al., *J Control Rel*, 2017

Distributed Component

Slow-phase desorption for hydrophilic solutes is much more gradual than for lipophilic (or lipid-permeable) solutes.

Panels a) and c): Hydrophilic solutes; time scale > 8 days.

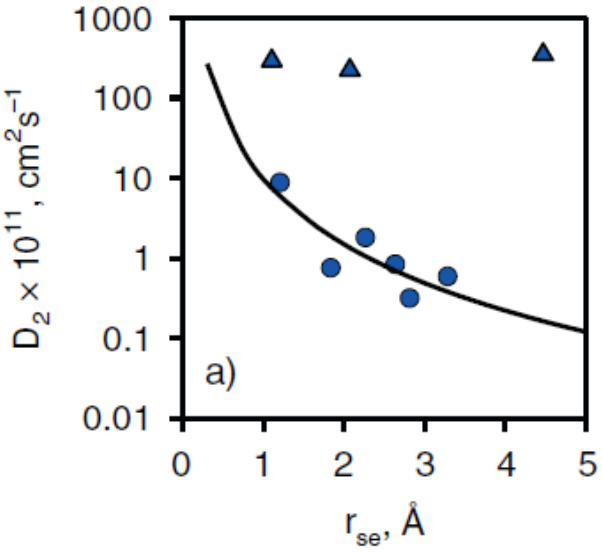
Panels b) and d): Lipophilic and lipid-permeable solutes; time scale 1-4 hours.



Miller et al., *J Control Rel*, 2017

Distributed Component

- Slow-phase desorption rates of hydrophilic compounds are size-selective.
- The equivalent cylindrical pore radius for the transcellular route was estimated to be 8.5 Å (range 6.3-19 Å).

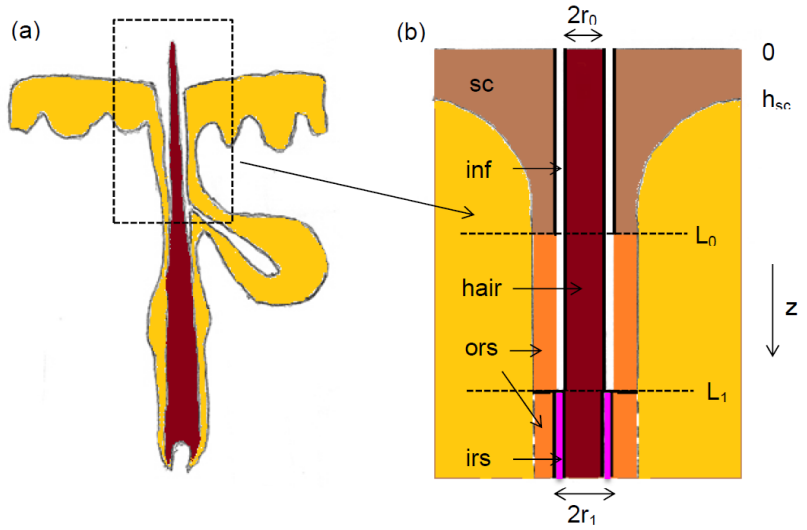


● hydrophilic compounds
▲ lipophilic compounds

Miller et al., *J Control Rel*, 2017

Appendageal Component

- Appendageal permeation is postulated to be primarily associated with high permeability of the lower infundibulum.
- This could arise from a low degree of keratinization of the outer route sheath and/or the presence of the sebaceous duct.



Kasting et al., *J Pharm Sci,* 2019. See also Patzelt and Lademann, 2013 and 2015.

Appendageal Component

- Appendageal permeation is considered to be size-selective, primarily on the basis of numerous iontophoresis studies, as shown on the next slide.
- We chose a cylindrical pore model with an effective pore radius, r_p = 16 Å, to represent the polar component.
- In order to accommodate currently accepted in vitro data, we considered that a small fraction of the appendages (1.5%) were open to the dermis, thus allowing some transport of large, hydrophilic permeants. Whether this is appropriate for in vivo absorption is uncertain.

In Vitro Iontophoresis Studies Establishing Size Selectivity for Appendageal Transport

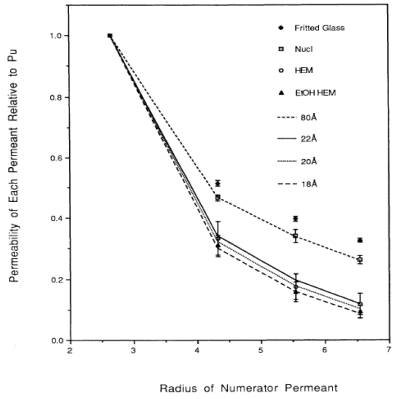
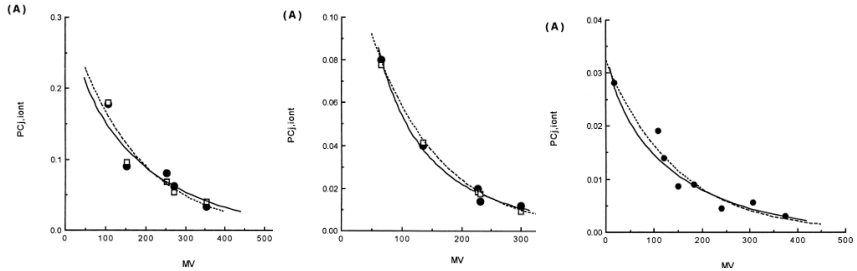
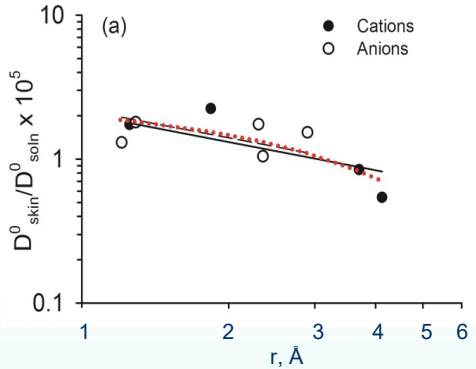


Fig. 6. Relative effect of hindrance for the four membrane systems studied. The superimposed lines correspond to calculated results based upon Eq. (4) and the Rp indicated in the legend.

Peck et al., 1994
r_p = 20 Å



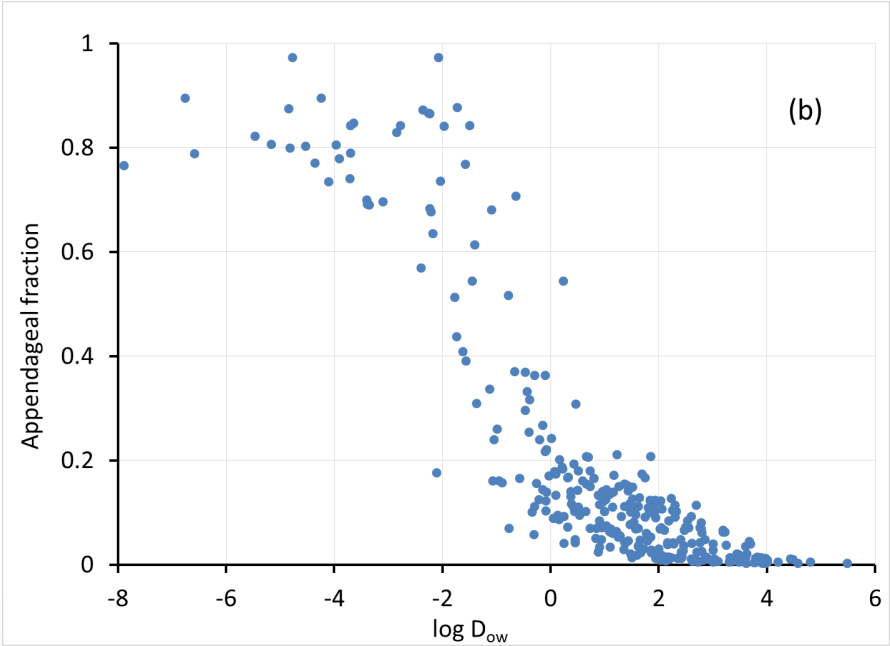
Lai and Roberts, 1999
r_p = 25 Å



Baswan et al., 2016
r_p = 16 Å

Appendageal Component

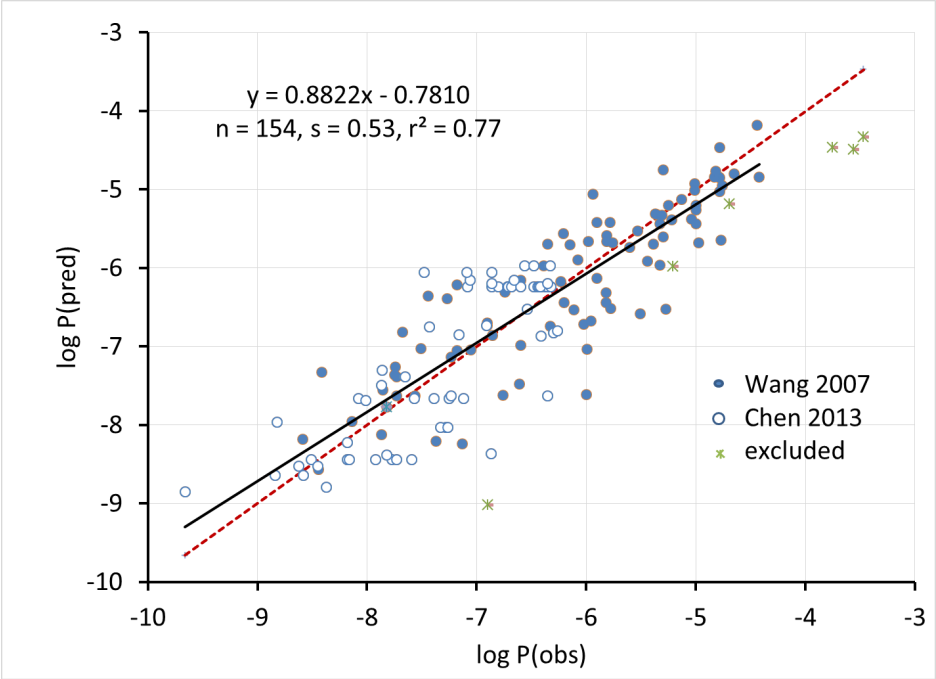
Parameter estimates for two large datasets suggest that appendegeal permeation is a substantial fraction of the total for very hydrophilic compounds.



Kasting et al., *J Pharm Sci,* 2019

Examples of Polar Pathway Model Results

Overall agreement with the steady-state permeability database is significantly improved vs. the original UB/UC model.

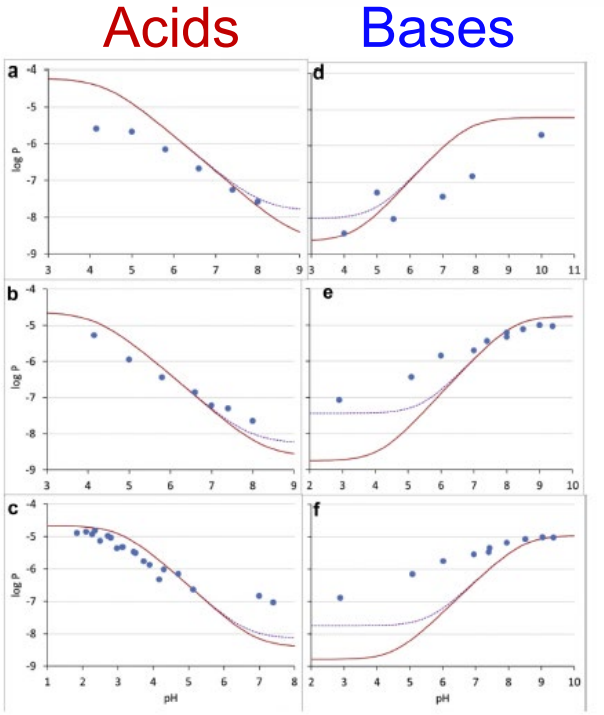


Kasting et al., *J Pharm Sci,* 2019

The model can account for the permeability of weak electrolytes in various stages of ionization. It is pretty successful with weak acids, less so with weak bases.

Graphs show predicted and observed pH-permeability profiles for a) diclofenac; b) naproxen; c) salicylic acid; d) lidocaine; e) fentanyl and f) sufentanyl.

Kasting et al., *J Pharm Sci,* 2019



Our Group Is Gradually Developing Support for this Approach

- Miller MA, Yu F, Kim K and Kasting GB. Uptake and desorption of hydrophilic compounds from human stratum corneum. *J Control Rel* **261**:307-317 (2017).
- Yu F and Kasting GB. A geometrical model for the transport of hydrophilic compounds across the stratum corneum. *Math Biosci* **300**:55-63 (2018).
- Kasting GB, Miller MA, LaCount TD and Jaworska J. A composite model for the transport of hydrophilic and lipophilic compounds across the skin, *J Pharm Sci* **108**:337-349 (2019).

Summary

- Simple skin models are widely used for dermal risk assessment. You should consider this if you simply need to estimate maximum flux or a fraction thereof.
- Mechanistic models including skin microstructure offer answers to more questions, but regulatory acceptance is a ways off.
- The field is driven by the need to provide better answers to both safety and product development questions in a cost-effective manner.

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