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Dermatological Drug Products Workshop: Developmental & Regulatory Considerations
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Mathematical Modeling of Skin Absorption and Transport: Foundation Lecture

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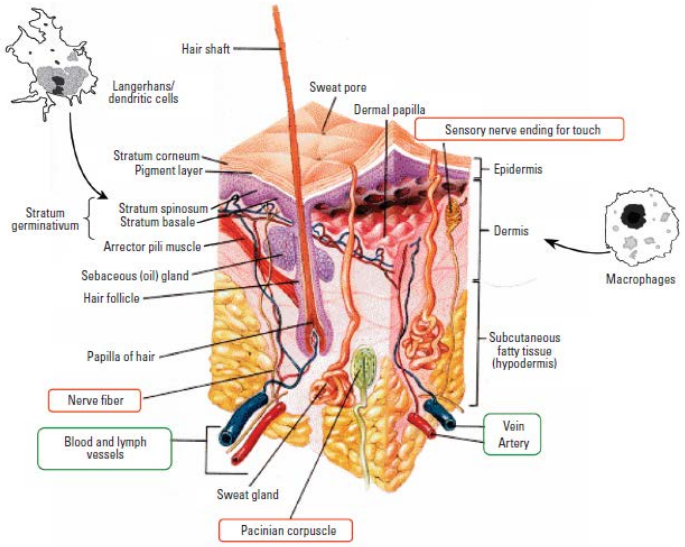
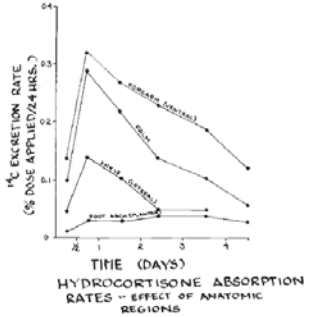
Mathematical Modeling of Skin Absorption and Transport: Foundation Lecture

Topics to be covered:

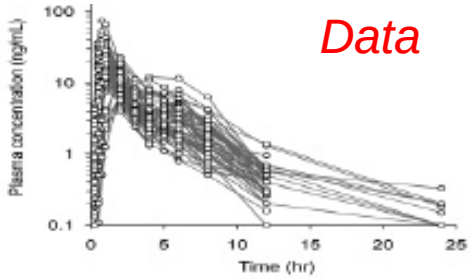
- **Advantages to mathematically model and simulate skin absorption and transport.**
- Historical perspective and state-of-the-art on modeling efforts both in the industry as well as academia.
- Structure based models such as Potts-Guy, MIT model, Wang-Kasting-Nitsche model, etc.
- Compartmental Models, PBPK models. Analytical and computational solutions.
- Permeation models vs. flux models.
- *IVIVC* of *in vitro* and *in vivo* results, and the implications for *in silico* modeling and simulation.



Mathematical Modeling of Skin Absorption and Transport: Foundation Lecture – the challenge!



- To take you on a journey showing what we have learned and the same time, showing you that we have many unresolved questions
- The journey includes two streams:
  - The "top-down" approach, in which **pharmacometrics** (often dominated by statistics) is used to model, interpret both *in vivo* and *in vitro* data, and relate *in vivo*, *in vitro* and *in silico* data in both understanding and predicting in vivo skin absorption and transport for various products,
  - The "bottom-up" approach whereby a **mechanistic understanding of** the interactions and temporal changes in **active-product-skin interactions** and the processes of topical absorption can be used to explain and predict skin absorption and transport, and
  - **A bringing of the two streams together.**
- In doing so, I want to reiterate two old sayings that really underpin this lecture:
  - *It is better to be approximately right than absolutely wrong – Brian Barry*
  - *Every model is wrong – it is just that some are useful - Anon*



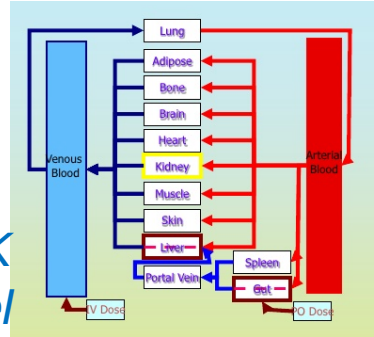
Data

Assume no model or use simple PK compartment

Analyse

Predict

Convolute with skin PK model

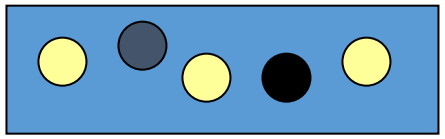


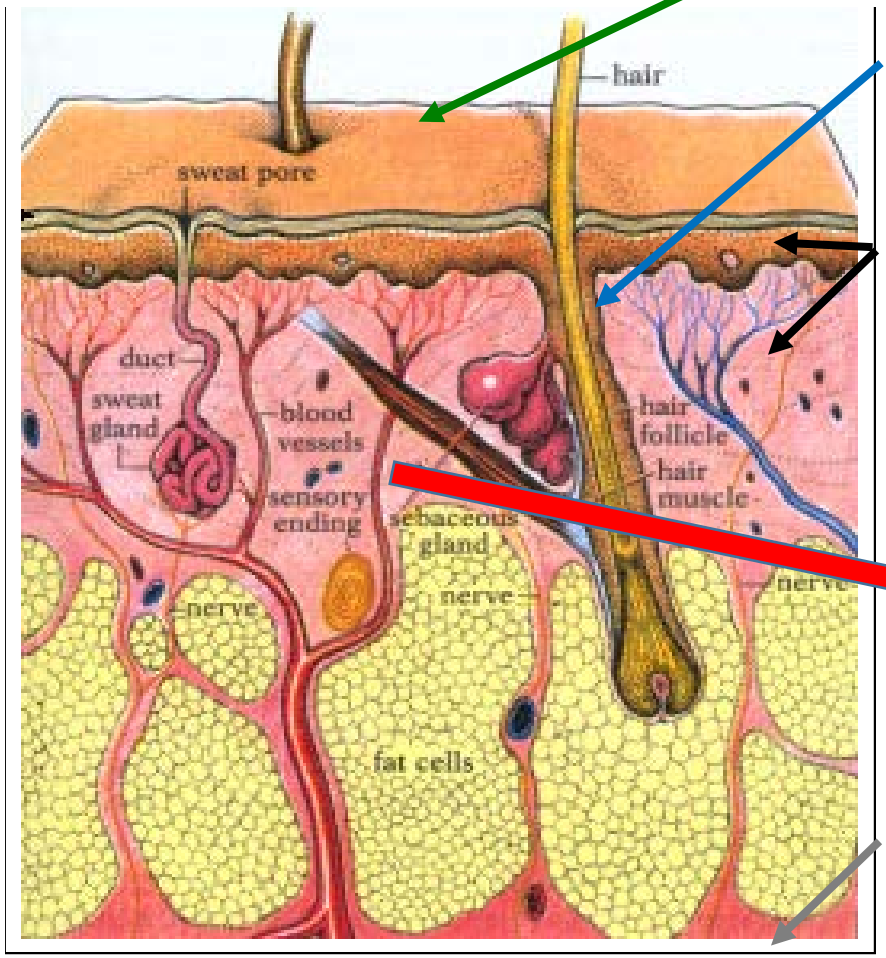
PBPK Model

Feldmann RJ, Maibach HI. *J Invest Dermatol.* 1967; **48:**181-3.

Our key goal is adequate & consistent product delivery to the following topical delivery target sites

Product





Superficial – ***retention & action***

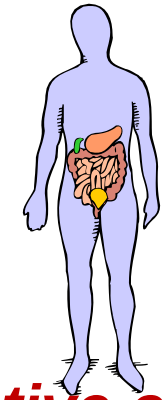
Barrier products, sunscreens, insect repellents, cosmetics

Appendageal – ***targeting, adequate concentration, retention***

Anti-acne, anti-perspirants, hair restorers

Epidermal/ Dermal ***– effective concentration to modulate keratinocytes, immune/inflammatory & other cells;***

Steroids, anti-histamines, local Anaesthetics, ant-infectives



Systemic

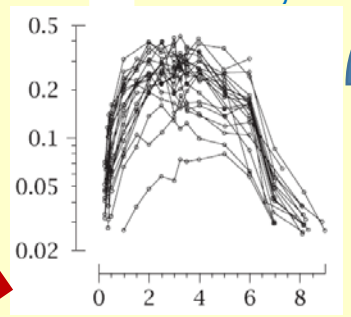
Nitroglycerin, scopolamine nicotine, HRT, long duration, avoid git first pass, manage nausea etc

Deep Tissue – ***effective concentration to modulate muscle inflammation***

Analgesics anti-inflammatories

Top-down & bottom up approaches

Patient, volunteer data



Statistical analysis

Covariates, bioequivalence

Use recommendations

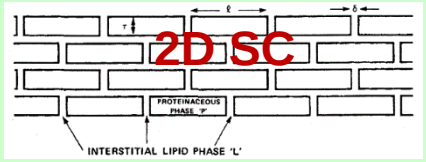
Predict *In vivo*

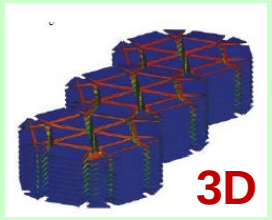
IV PK model

*

SC Flux, lag time

Convolution

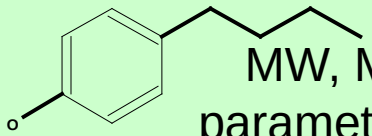




3D SC

Predict

\+



MW, MV, log P, MP, solubility parameters, PSA, H bonding, etc

Top - down

- Collect *In vivo* human exposure & response data
- Use ‘mixed model” or other analyses to identify key co-variates in topical drug exposure & response
- Analysis by non-parametric, by a plausible pharmacokinetic &, if population data, population pharmacokinetic - pharmacodynamics model

Focus on confirming and defining clinical usage conditions

Focus on predicting, learning and translation

- Link predictions to systemic blood/local levels & effects
- Physiologically based pharmacokinetic (PBPK) model for skin, target & disposition to predict *in vivo*
- PBPK model (s) for skin to predict *in vitro* absorption
- *In vitro* physiochemical data of solutes, product formulation & skin morphology

Bottom - up

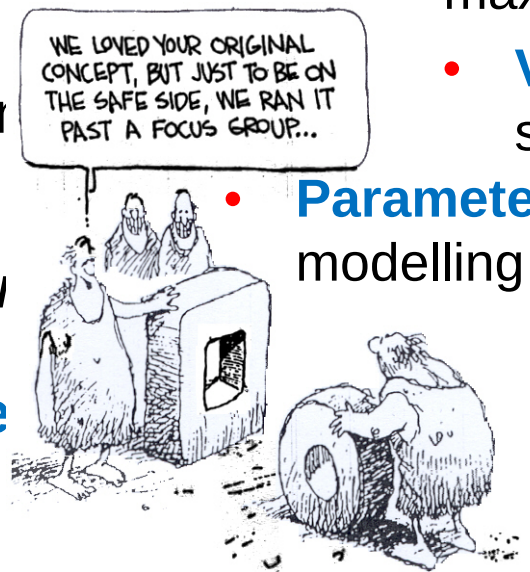
Roberts MS. *J Pharmacokinet Pharmacodyn.* 2010, **37**::541-73.

My thoughts on advantages & dangers in modelling skin absorption

- ✓ Growth of computer science & *in silico* modelling means **low cost & fast** outcomes
- ✓ Able to use known, rich morphology & pharmacology to **predict effects in inaccessible topical action sites**
- ✓ Avoid *in vivo* studies
- ✓ Prediction accuracy by *in vitro-in vivo* extrapolation (IVIVE) methods
- ✓ Virtual models yield robust statistical analysis eg bootstrapping
- ✓ **Predictive performance** of formulation design & release profiles
- ✓ **Translation of data** to predict local PKPD at a target site using IVPT and *in vivo* sampling from another body site
- ✓ Modelling to take into account **disease effects** & abnormal kinetics

Dangers

- **Model** is **plausible** in biology & thermodynamics
- Poor **structural identifiability** (eg can an unknow parameter be identified by experiment is assumption that corneocyte wall offers no barrier resistance real!!
- **Lack of sensitivity** due to limited data or in PBPK model predictions – PBPK sensitivity analyses with varying parameters critical
- **Correlation between PBPK parameters**, eg half life = 0.693 Vd/clearance; permeability coefficient kp = maximum flux/saturated concentration
- **Variability** – in skin type, disease, study design, environment, genetics
- **Parameter uncertainty** (experimental, modelling & assumption errors) – Bayesian best!
- **Extrapolating beyond** data,
- **Group think –** permeability coefficients, normal SC, lipid pathway, transcellular pathway etc



Brief history of topical *in vivo* absorption

- We have known from Ancient Egyptian and Babylonian skin medicine (around 3000 BC) and, later, from Galen (131-201AD) that variations in topical formulations, including salves, ointments, potions and even patches consisting of plant, animal or mineral extracts, have been used topically to meet different therapeutic needs.
- **Ibn Sina (Avicenne, 980-1037AD), a Persian physician**, preached that topical products:
  - Have two spirits or states and it is the soft spirit that crosses skin – the hard part does not!
  - Act locally, immediately beneath skin, in joints (regional effects) & in remote areas (systemic effects)
  - With a systematic action are preferred when oral dosing is not possible.
  - May be applied like patches – plaster applied to the skin and covered by paper backing material.

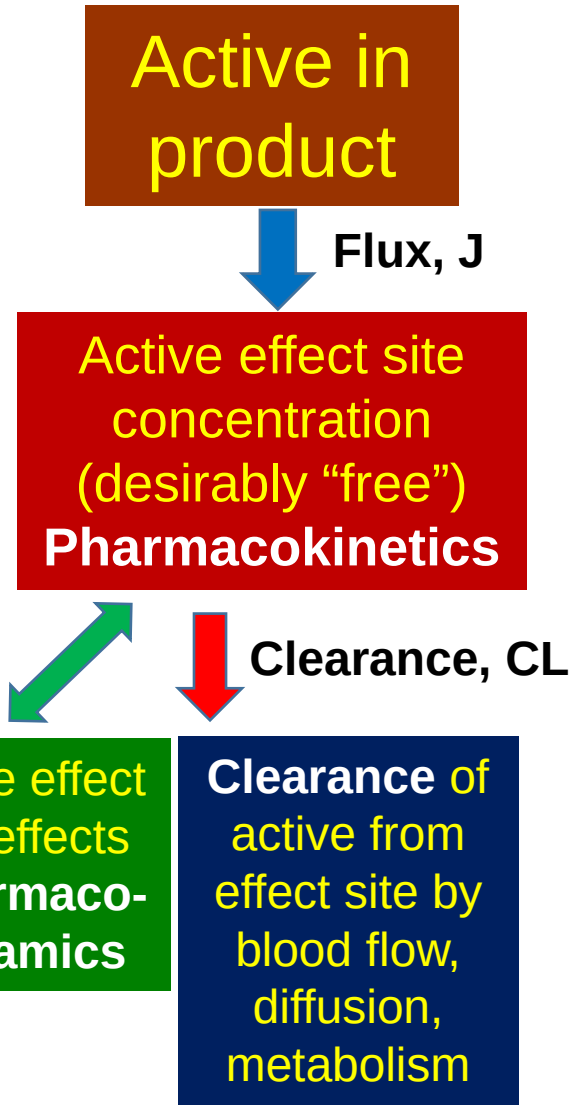
- Earliest **quantifiable** skin absorption was **poisoning** after topical application, e.g.
  - After belladonna plaster, liniment and lotion (*British Medical Journal* - Morgan, 1866; Harrison, 1872).
  - Exposure to nitrobenzene and aniline dyes in dyed clothing (early 1900s)
  - 'Nitroglycerin head' on explosive manufacture exposure (Laws, 1898; 1910; Evans, 1912).
  - From nicotine used as a topical insecticide (Wilson, 1930; Faulkner, 1933; Lockhart, 1933).
- **First quantitative** measurements of topical absorption of therapeutic active through **analysis of active in urine**:
  - Dog – Iodine by redox titration with sodium thiosulphate (Nyiri and Jannitti, 1932)
  - Human - Methyl salicylate by colorimetric assay of ferric - salicylate metabolite complex (Brown and Scott, 1934).
  - Human - Spectrometry of a p-chloro-m-xylenol after reaction and ether extraction (Zondek, 1943)
  - Human - phenolsulfonphthalein by colorimetry (Nadkarni et al., 1951).
- Pharmacological effect (steroids,alkaloids) & radioactivity [131I]diiodofluorescein in rat blood - (Hadgraft, 1956)
- Effect of skin temperature and hydration on human skin absorption of aniline and other organic solvents (Dutkiewicz et al, 1957; Piotrowski et al 1957, Meigs et al 1954)
- **Pharmacokinetics of urinary excretion** after topical absorption & intravenous dosing (Wurster & Kramer, 1961)

Pastore et al *Brit J Pharmacol* (2015) **172** 2179–2209

General pharmacokinetic principles often apply in topical delivery, but with incomplete release

- Two key goals in topical drug delivery are to:
  - Quantify the **extent and rate of absorption** of an active drug to a topical target site (bioavailability) and
  - Express topical delivery in terms of its **target site effect** (may be local or use blood level as a surrogate) and unwanted absorption and potential toxicity (may be systemic).
- Quantification of **extent and rate**
  - **Extent** is best expressed an **amount absorbed over a time period**
    - % absorption, although commonly used, can be misleading as amount absorbed often not proportional to dose applied
    - Area under the curve for a blood concentration –time or response –time (eg vasoconstrictor test) often used as surrogates
  - Rate can be defined as continuous or as a peak rate/ concentration & peak time
    - Continuous rate defined as steady state flux (*Jss*)
    - Maximum flux (*Jmax*) is that obtained under thermodynamically stable conditions for the equivalent of a saturated solution.
  - Effect is usually expressed in terms of "unbound" or "free" effect and toxic site concentrations

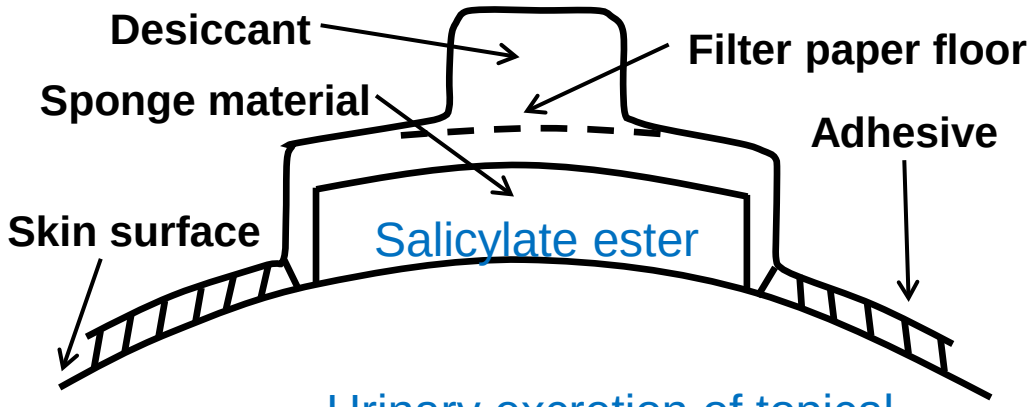
$$Steady\ state\ concentration\ at\ a\ given\ site\ C_{ss} = \frac{Rate\ of\ delivery\ to\ that\ site\ (flux)}{Clearance\ from\ that\ site\ (CL)}$$



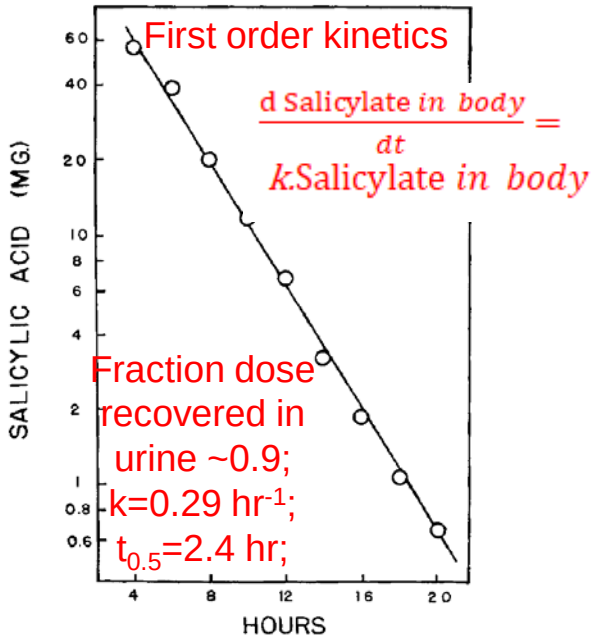
Topical absorption kinetics is often “flip-flop”

In their classical in vivo topical salicylate ester study, Wurster & Kramer in *J Pharm Sci* (1961) **50:** 288-293 illustrated concepts of:

- Extent of absorption
- Rate of absorption
- **“Flip-flop” kinetics**, i.e. terminal slope due to absorption as slower than elimination
- Deconvolution using intravenous data



Urinary salicylate excretion after **intravenous dose** of sodium salicylate



Urinary salicylate excretion after **topical** glycol salicylate

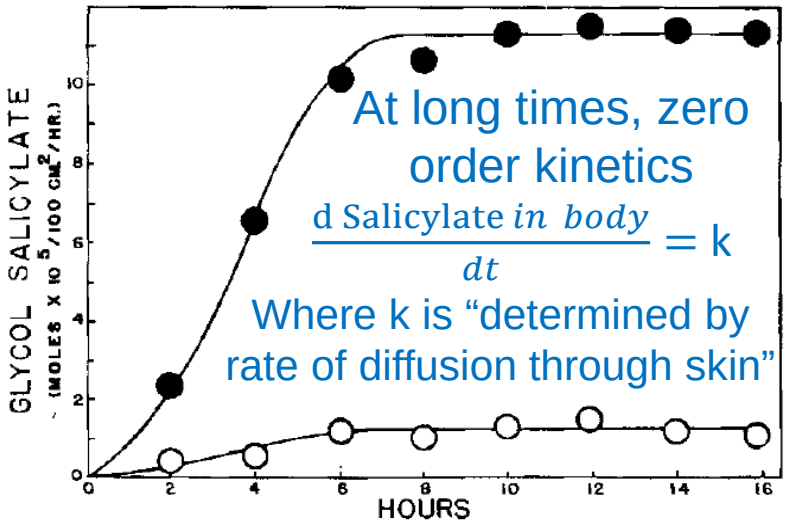
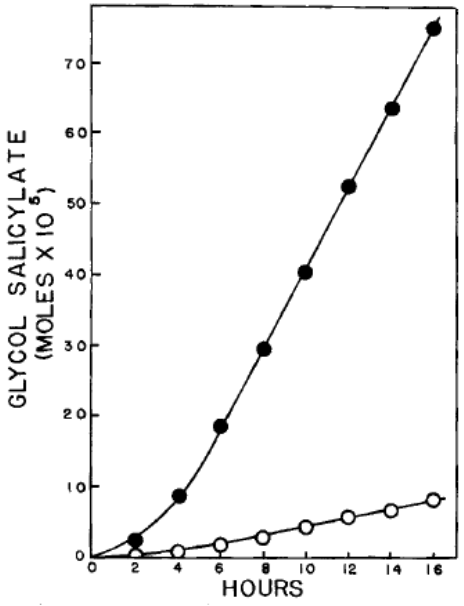


Fig. 6.—Urinary excretion data showing the influence of moisture on the percutaneous absorption rate of glycol salicylate. ● Hydrous system rate, 11.7 (plateau level); ○ anhydrous system rate, 1.3 (plateau level).

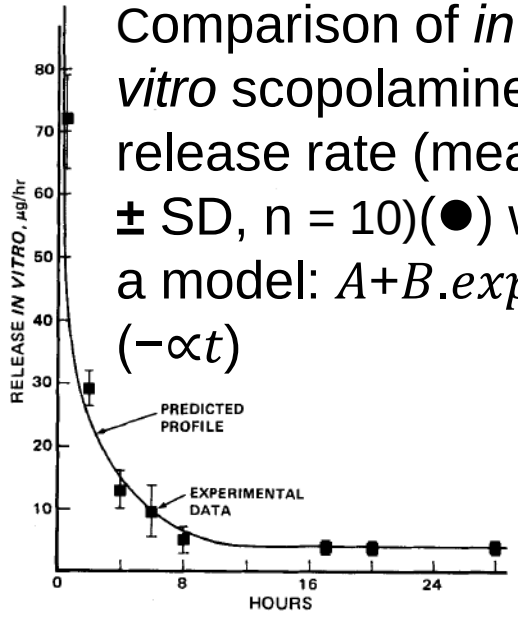
Urinary excretion of topical glycol salicylate as a **cumulative amount absorbed** versus time plot



Advances in our mathematical modeling of skin absorption & transport post 1960s – key role of industry eg ALZA

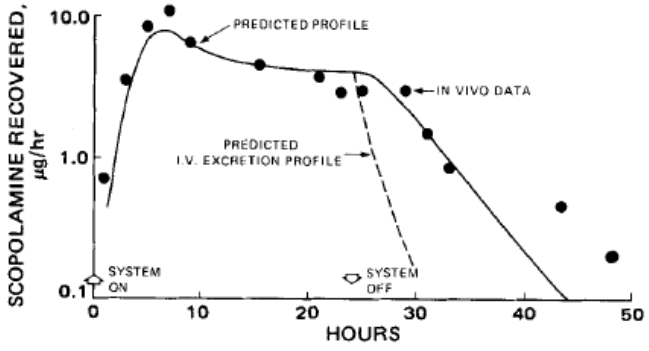
- **Non-parametric.** A graphical description in which skin permeation and absorption data is related to time or to a physicochemical property of the solute or a change in product or skin condition
  - Non parametric analysis to derive area under the curve (AUC), peak concentration (Cmax) and peak times (Jmax)
- **Regression** - A representation of observed relationships by an empirical model derived data by a known model
  - Linear regression for steady state portion of cumulative amount permeated across skin versus time for a constant donor concentration & sink receptor conditions
  - Nonlinear regression of compartmental or diffusion models for skin permeation and absorption using analytical and numerical Laplace inversion & finite difference methods
  - Mixed model (population) analysis to account for sparse data and covariates
  - In vitro –in vivo relationships & correlations
- **QSAR** - Quantitative structure permeation and response relationships in which data is explained in terms of the physicochemical properties of the solute, the delivery system and the skin barrier, and
- **In silico** - A mechanistic approach in which permeation is expressed in terms of both the known morphology of the delivery system and the skin as well as the physicochemical properties of the solute, the delivery system and the skin barrier
- Combination of all of the above

Chandrasekaran *J Pharm Sci* (1978) **67:** 1370-1374



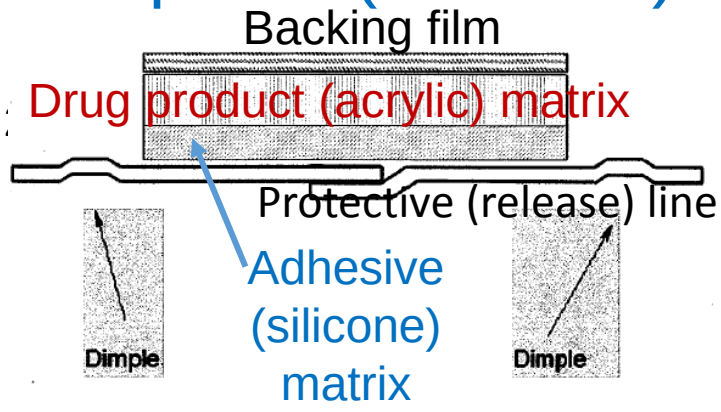
Comparison of *in vitro* scopolamine release rate (mean ± SD, n = 10)(●) with a model: $A+B.exp(-\propto t)$

To quite complex equations & profiles - scopolamine urinary excretion rate (●) vs prediction



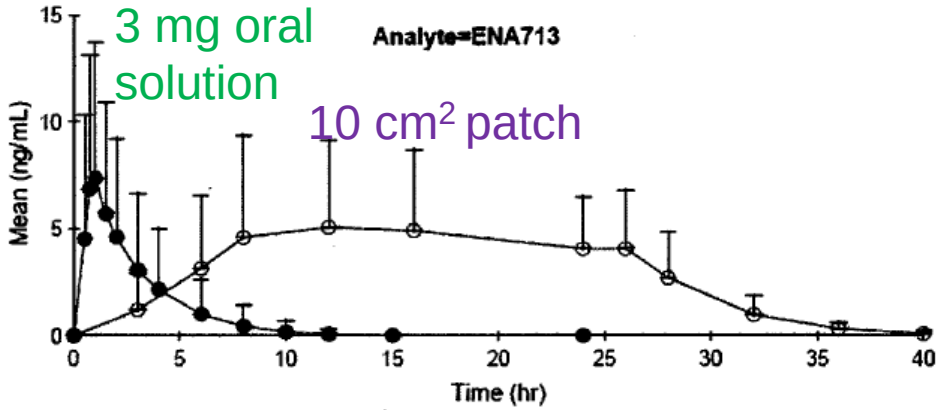
Much of FDA's approval process now appears to emphasise a pharmacometric approach

Centre for Drug Evaluation & Research -Clinical Pharmacology & Biopharmaceutics Review # 22-083 Exelon^{R} transdermal patch (Novartis)



- Extension of oral products; doses of 5 cm^2 (9mg) and 10 cm^2 (18mg) with a 50% bioavailability for symptomatic treatment of Alzheimer's & Parkinson's disease dementia
- Once a day without food to improve caregiver & patient convenience & as an alternative with swallowing difficulties

Figure: Rivastigmine plasma concentrations (mean +/- SD) following single dermal (o.d.) patch application (open circles)

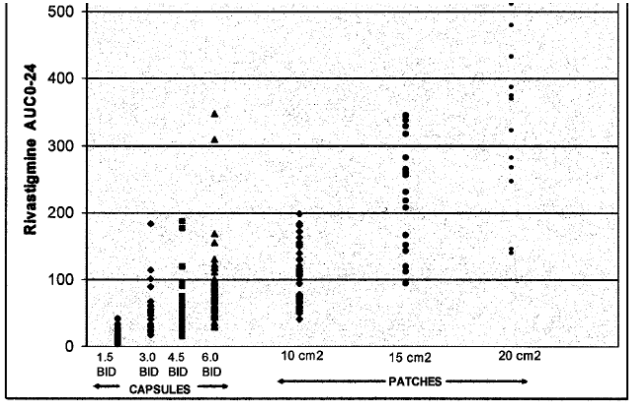


○—10 cm^2 (FMI) transdermal patch ●—single 3 mg Exelon oral solution

Studies in 440 volunteers & 1374 Alzheimer's patients

Measure AUC_{0-24}; Cmax; tmax; $t_{1/2}$; V/F; CL/F for different doses & with BW adjustment

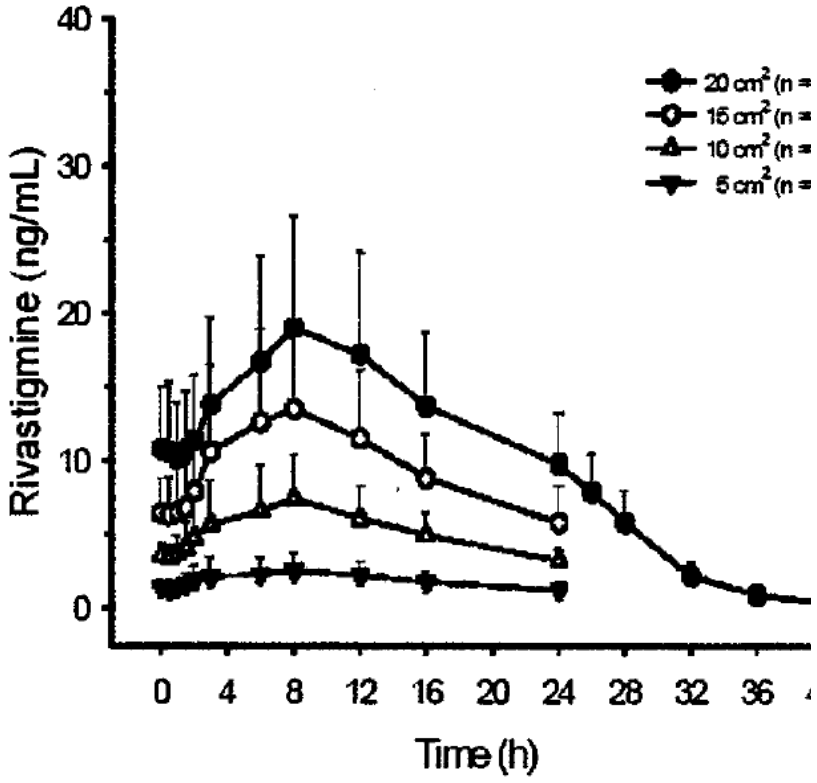
AUC 0-24 for bid capsule vs different patch size dosing



Rivastigimine transdermal human 022083s000_ClinPharmR_P1

Exelon^{R} transdermal patch (Novartis) contd

Plasma levels for a dosing interval after multiple dosing for 14 days



Inter and intrasubject variability in C_{max} and AUC values for rivastigamine and its metabolite NAP226-90 in volunteers

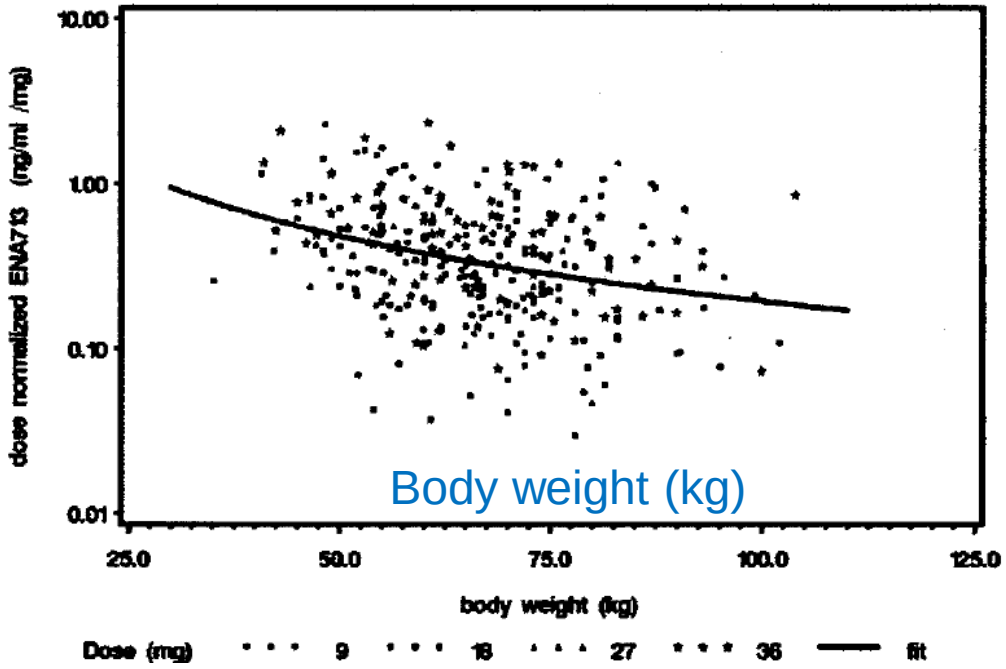
PK parameter	Study No.	Patch size (loaded dose)	Rivastigmine (%CV)[1]		NAP226-90 (%CV)[1]	
			Intra-	Inter-	Intra-	Inter-
C_{max}	ENA713DW159	10 cm² (18 mg)	19%	60%	-	-
	713D2332	10 cm² (18 mg)	42%	59%	37%	37%
	713D2338	10 cm² (18 mg)	34%	44%	-	-
AUC_{0-t}	ENA713DW159	10 cm² (18 mg)	18%	62%	-	-
	713D2332	10 cm² (18 mg)	56%	80%	31%	34%
	713D2338	10 cm² (18 mg)	42%	52%	-	-
AUC_{∞}	ENA713DW159	10 cm² (18 mg)	-	-	-	-
	713D2332	10 cm² (18 mg)	53%	77%	30%	33%
	713D2338	10 cm² (18 mg)	35%	45%	-	-

-: not available ; [1] CVs obtained from the multiplicative model.

Exelon^{R} transdermal patch (Novartis) contd 2

Population PK analyses of steady state plasma rivastigmine concentrations after patch application

- Renal - no clear effect of creatinine clearance
- Hepatic - no clear effect of SGOT and SGPT
- Age – Study 2320 showed not affected by age (p=0.72)
- Gender – 107 males and 203 females not affected (p=0.73)
- **Body weight – yes p=0.0003**
- Race? P=0.05 but if exclude 2 black patients, p=0.38
- Drug interactions – mainly metabolised by esterase hydrolysis; limited affinity for major CYP450 enzymes



Conclusion: No dose adjustment needed except when titrating low body weight patients with patch doses >10cm^2

Pharmacometrics also used in bioequivalence assessment – 80-125% confidence interval

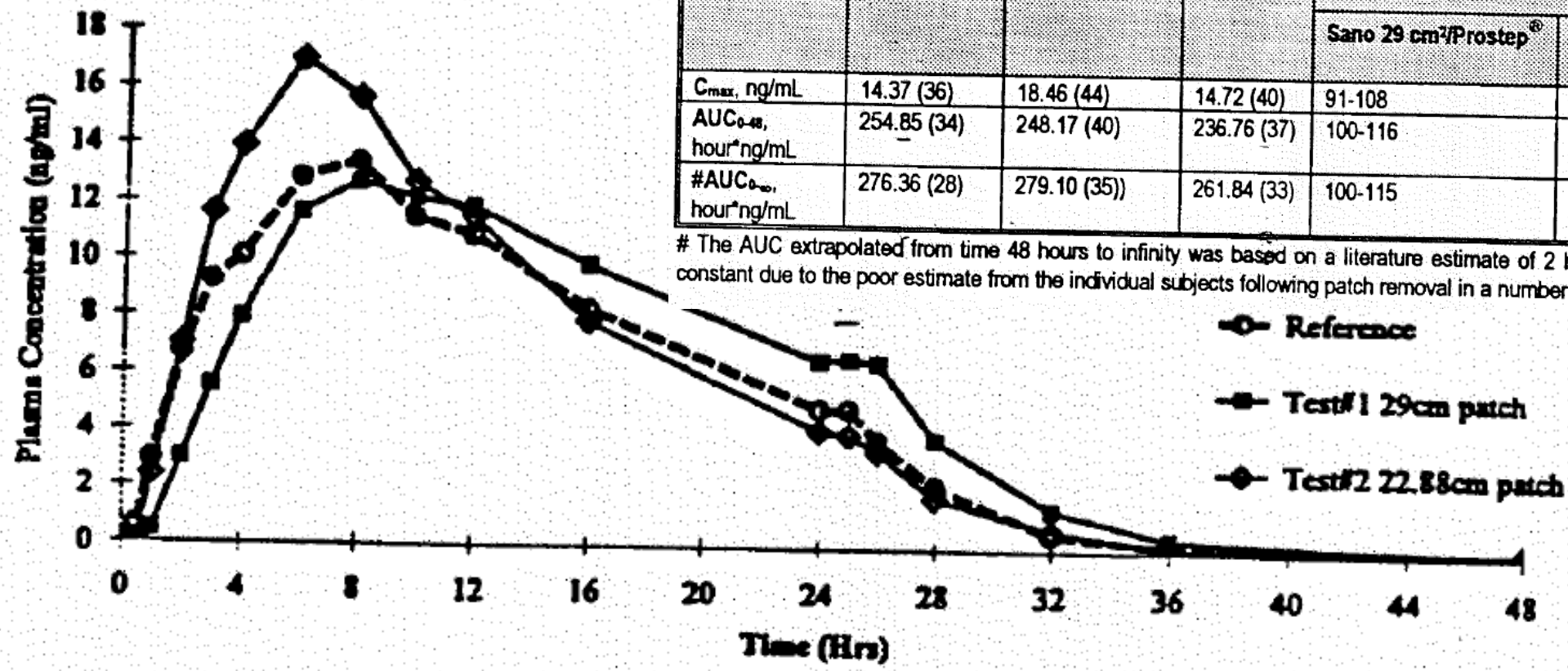
Centre for Drug Evaluation & Research Clinical Pharmacology & Biopharmaceutics Review NDA 19-1983/S-012 Prostep (Nicotine transdermal 11 and 22 mg/day Elan) – *assessing bioequivalence versus 2 Sano products*

* Not bioequivalent – outside 80-125% limits

Mean nicotine plasma concentrations

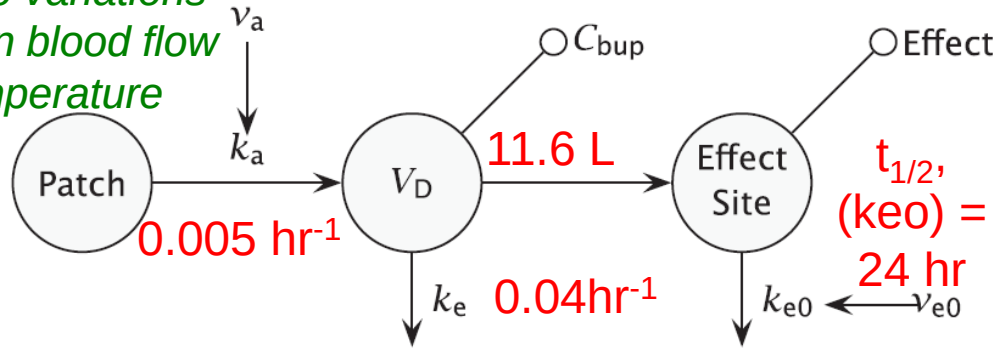
Parameter	Sano 29 cm²	Sano 22.88 cm²	Prostep®	90% Confidence Intervals for Log Transformed Parameters	
				Sano 29 cm²/Prostep®	Sano 22.88 cm²/Prostep®
C_{max}, ng/mL	14.37 (36)	18.46 (44)	14.72 (40)	91-108	114-135 *
AUC_{0-48}, hour*ng/mL	254.85 (34)	248.17 (40)	236.76 (37)	100-116	97-112
#$AUC_{0-\infty}$, hour*ng/mL	276.36 (28)	279.10 (35))	261.84 (33)	100-115	97-112

The AUC extrapolated from time 48 hours to infinity was based on a literature estimate of 2 hours for the elimination rate constant due to the poor estimate from the individual subjects following patch removal in a number of cases.



Pharmacokinetic–pharmacodynamics analysis for a 144-h (6-day) administration of buprenorphine by transdermal patch

Process noise due to variations in skin blood flow & temperature



Population pk analyses with NONMEM's subroutine ADVAN13, with PK and PD data analyzed simultaneously

Stochastic Model for Buprenorphine Absorption

$$dAa(t)/dt = -ka(t)\cdot Aa(t) \quad (1)$$

$$dAd(t)/dt = ka(t)\cdot Aa(t) - ke\cdot Ad(t) \quad (2)$$

$$ka(t) = \exp[Z(t)] \quad (3)$$

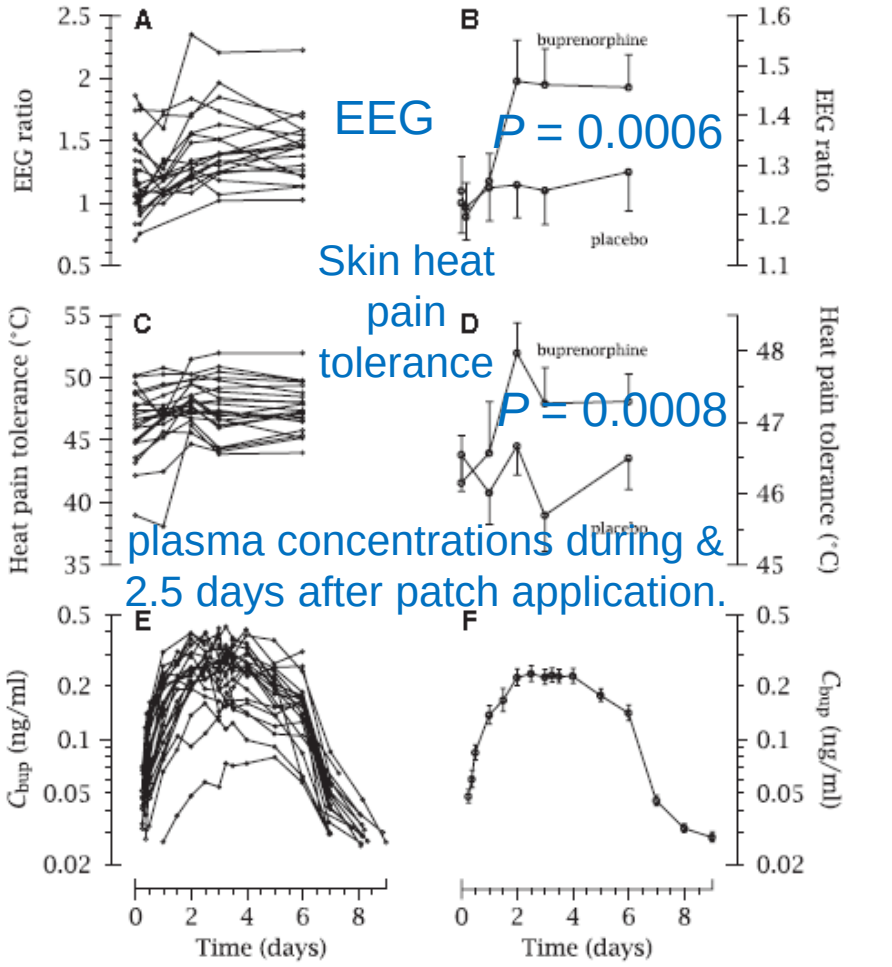
$$dZ(t) = \sigma w\cdot dw(t) \quad (4)$$

Pharmacodynamic (PD) Analysis

$$dCe(t)/dt = ke0[Cd(t) - Ce(t)] \quad (5)$$

$$EF(t) = BLN\bullet\left[1 + \left(Ce(t)/C100\right)^{\gamma}\right] \quad (6)$$

Individual data Mean ± SEM



EEG $P = 0.0006$

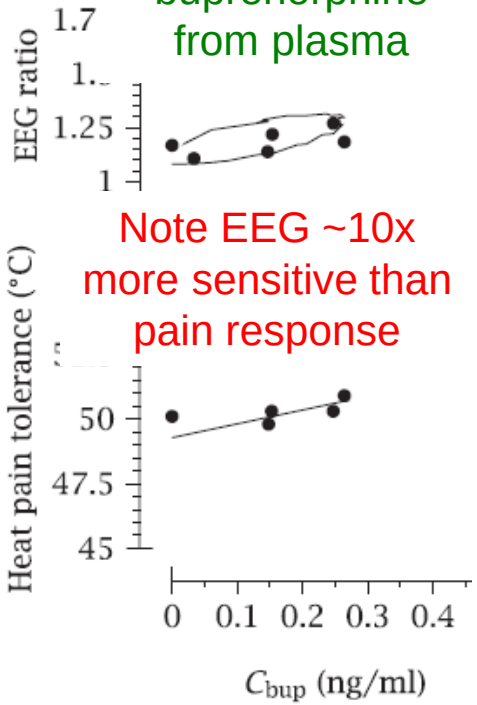
Skin heat pain tolerance $P = 0.0008$

plasma concentrations during & 2.5 days after patch application.

Olesen et al *Anesth Analg* 2015;**121**:1165–75

Effect versus plasma concentration for one subject

EEG hysteriesis = slow distribution buprenorphine from plasma



Note EEG ~10x more sensitive than pain response

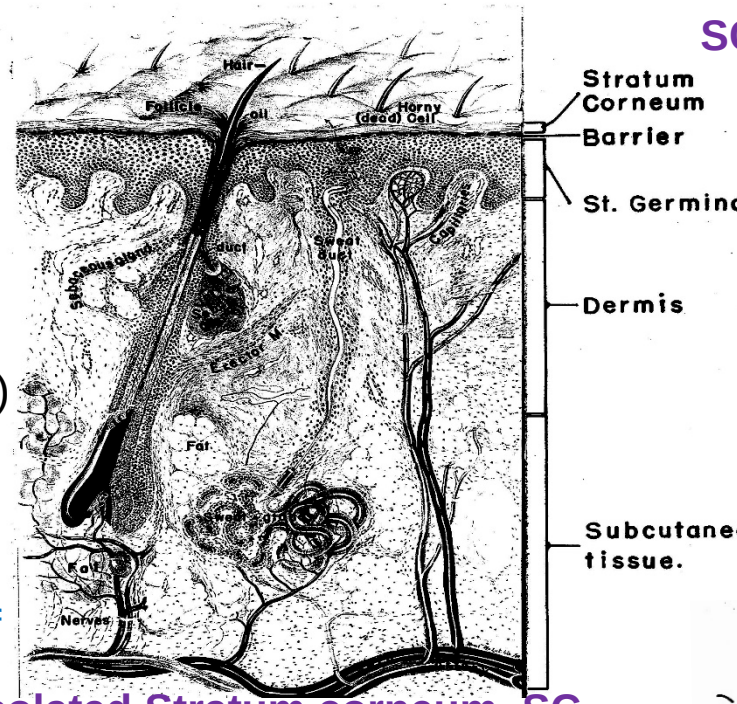
Mathematical Modeling of Skin Absorption and Transport: Foundation Lecture

Topics to be covered:

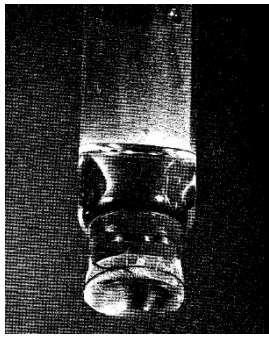
- Advantages to mathematically model and simulate skin absorption and transport.
- Historical perspective and state-of-the-art on modeling efforts both in the industry as well as academia.
- **Structure based models such as Potts-Guy, MIT model, Wang-Kasting-Nitsche model, etc.**
  - Focus predominantly on aqueous solutions
  - Permeation usually expressed in terms of permeability coefficients, kp
  - Many studies based on isolated epidermis or dermatomed skin permeation studies

Historical understanding of **SC** as skin permeation **barrier** layer (-1960)

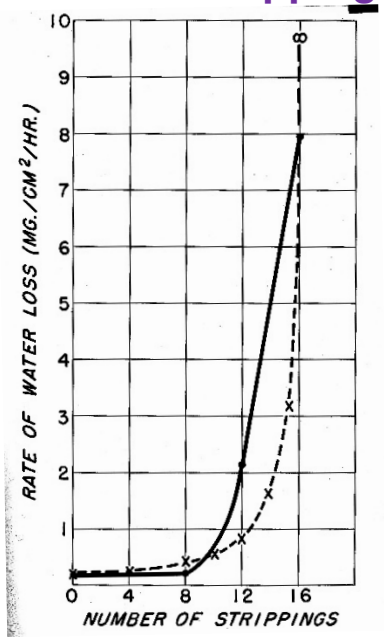
- 1853 Barrier located in epidermis [blister formation] (Homalle)
- 1877 Skin impermeable to all substances……. (Fleicher)
- 1904 Skin slightly permeable to lipid sol. …..(Schwenkenbecker)
- 1919 Barrier at top of epidermis, (SC) [war gas]… (Smith et al)
- 1924 Barrier below the SC (stratum lucidum)…… (Rein)
- 1945 Barrier, the stratum lucidum. [dye location].... (Mackee et al)
- **1951 Diffusion through dead human skin. Am J Trop Med Hyg 31:842-853 Berenson GS and Burch GE**
  - Water penetration through S.C. difficult, strong temp. dependence~ 2.5 fold greater with a 10°C increase in temp. $E^{\#} = 18.5 \times \ln(2.5) = 17$ kcal/mole. Compared to self diffusion for water. $E^{\#} = 4.5$ kcal/mole..
- 1954 SC is a grossly porous membrane, readily permeable to ions and large molecules [text, Review]…….. (Rothman)
- 1956 Barrier is between SC and live stratum spinosum, water permeation involves active transport…… (Mali)
- **1957 Barrier is practically the entire SC…….. (Monash)**
  - Time required for anesthesia to topical anesthetics (xylocaine base) $D=\delta 2/6X\tau = (10\mu)2/ 6hr = 0.5 X10\text{-}11cm2.s\text{-}1$ vs $0.5 X10\text{-}13cm2.s\text{-}1$ for 1.0 μ layer.)
- 1958 Barrier is the (stratum corneum disjunctum) … (Szakall)



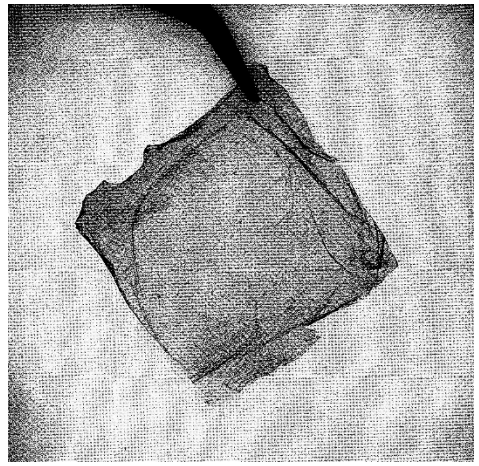
SC impermeability to water



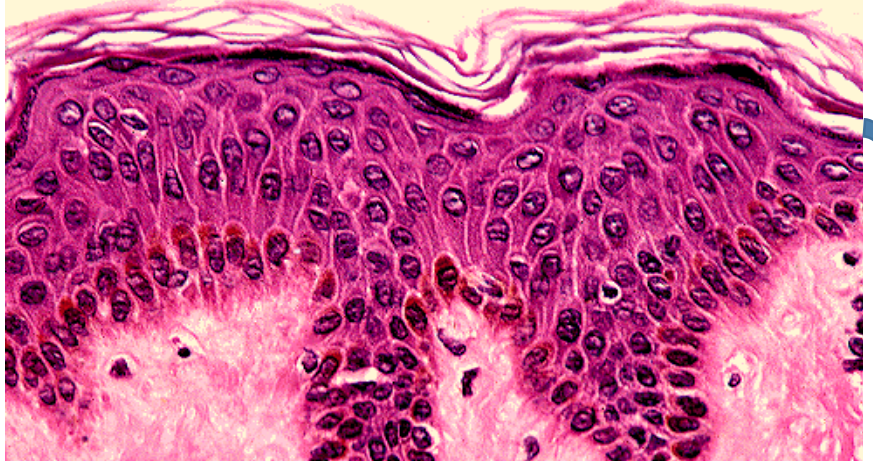
Water loss with SC stripping



Isolated Stratum corneum, SC

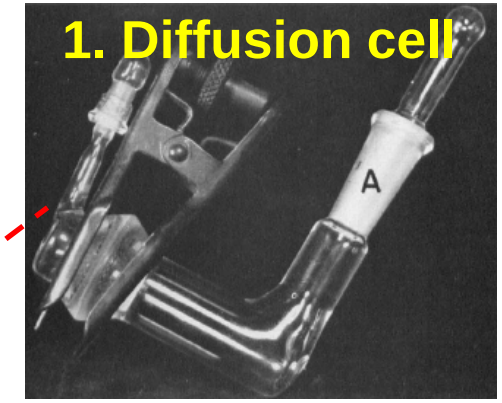


From Scheuplein 2011 Pathfinders Lecture, Boston & *Skin Pharmacol Physiol* 2013; **26**:199–212



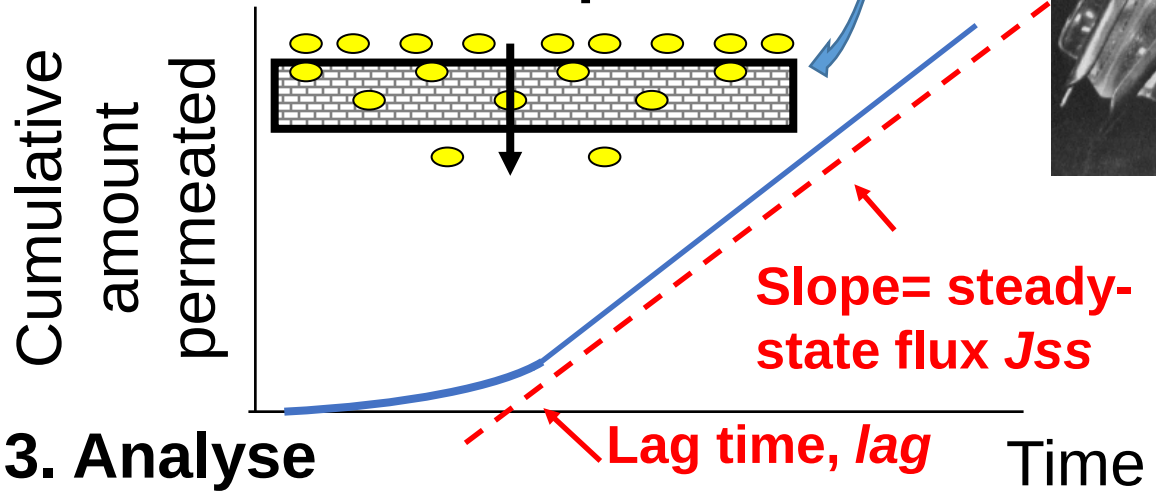
Stratum corneum, SC, is main skin barrier

Blank & Scheuplein pioneered the *in vitro* human skin permeability coefficient *kp* approach to defining skin transport – requires:



- ✓ Stratum corneum rate limiting
- ✓ Steady state conditions
- ✓ Infinite sink
- ✓ Normally, an aqueous vehicle

2. Collect data and plot

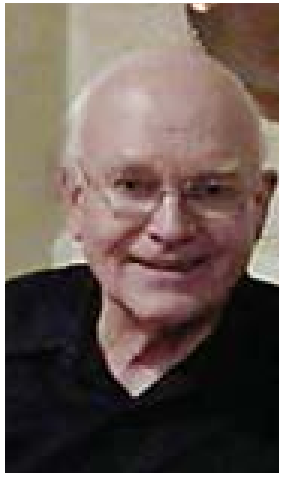


3. Analyse

$$J_{ss} = \frac{Q_{ss}}{A(t - lag)} = \frac{D}{h}(C_{sc,v} - C_{sc,d}) \approx \frac{KD}{h}\Delta C_v = k_p \Delta C_v \approx k_p C_v$$

Note steady state diffusion realises:

1. From a **structural identifiability viewpoint** only **2 unique parameters** kp & lag, which, in turn:
2. Are **highly correlated** - both depend on D, and,
2. Both also have high a **uncertainty**, especially **lag!**

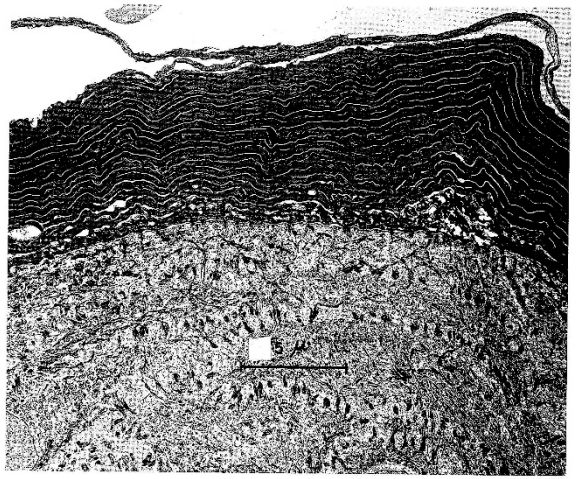


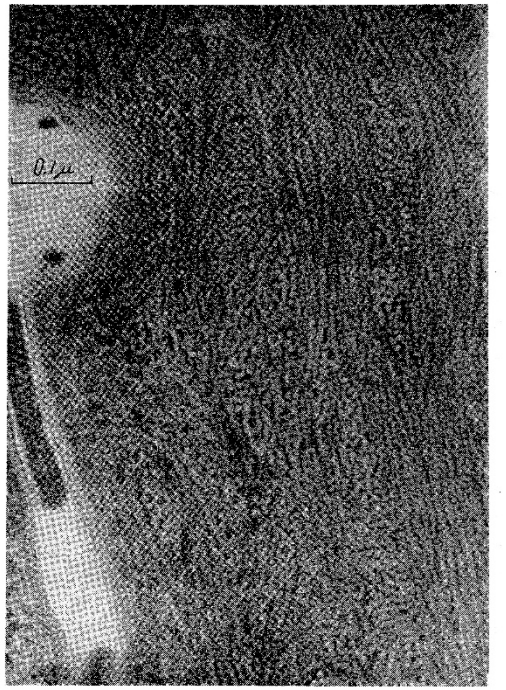
Bob comments, in his recent overview on skin penetration, : "….I hoped that *Jss* would be reasonably proportional to ΔC or, $Jss = kp\Delta C$ and that the permeability constant, *kp*, would be a useful parameter; and so it was". *Scheuplein Skin Pharmacol Physiol 2013;26:199–212*

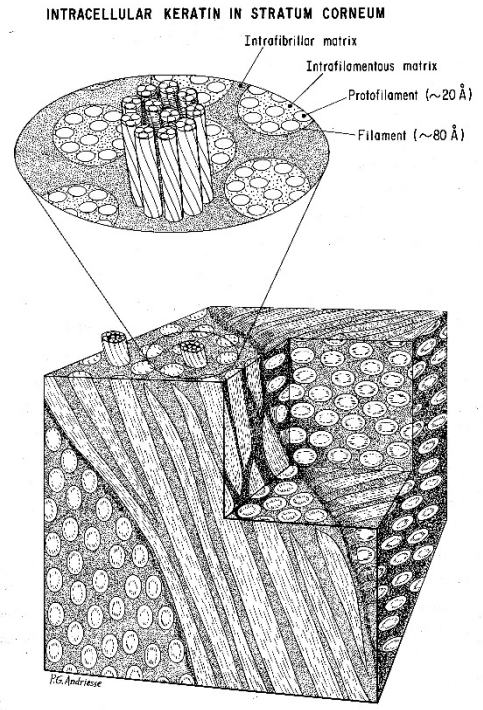
Scheuplein SC **Diffusion** Model in 1971

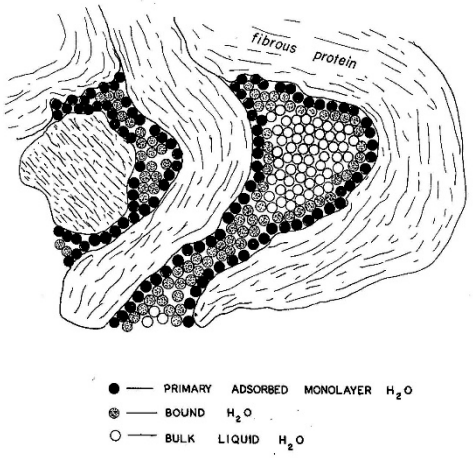
- Transcellular diffusion
- Two parallel pathways, a single phase.
- Bound water in SC provide main diffusional resistance.
- Evidence: Intercellular diffusion too small; Diffusion of both polar and nonpolar substances; Bulk of SC is keratin and water; Evidence for tightly bound water, large activation energies for penetration; keratin fibrils surrounded by lipid, intercellular region apparently amorphous, consisting of both lipid and protein.

From Scheuplein 2011 Pathfinders Lecture, Boston &
Skin Pharmacol Physiol 2013;**26**:199–212









Two phase model for SC transport 1972

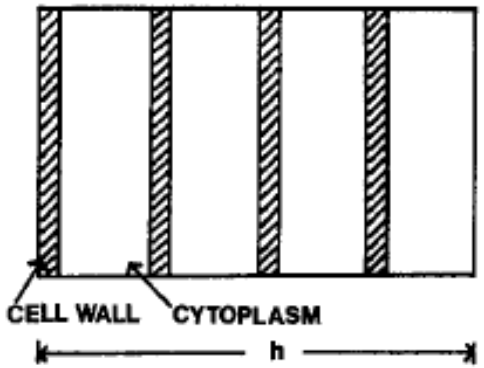
J. Pharm. Pharmac., 1972, **24**, 934–941 *Received June* 8, 1972

A two phase series model for the transport of steroids across the fully hydrated stratum corneum

T. YOTSUYANAGI AND W. I. HIGUCHI

College of Pharmacy, University of Michigan, Ann Arbor, U.S.A.

A two phase series model for the permeability behaviour of the fully hydrated stratum corneum has been examined using Scheuplein's data on steroids, since these strongly encouraged the investigation of possible heterogeneous diffusion models that showed the dependence of the effective diffusion coefficient, D_e, upon the effective partition coefficient, K_e. The model described can be characterized by V_c and V_w, the volume fractions for the "cytoplasm" and the "cell wall" phases, K_c and K_w, the solute partition coefficients for the "cytoplasm" and the "cell wall" phases and D_c and D_w, the respective diffusion coefficient for the two phases. Reasonable correlations were found



- ✓ Corneoycte (C)
- ✓ Cell wall + lipid (W)
- ✓ SC 20 cells,
- ✓ 40 µm thick;
- ✓ cell wall phase vol 0.01 to 0.1

The effective permeability coefficient, P_e, for this system is given by

$$P_e = \frac{1}{\frac{V_w}{P_w} + \frac{V_c}{P_c}} \qquad (1)$$

where P_w and P_c are the permeability coefficients for the cell wall and the cytoplasm phases, respectively, and are given by

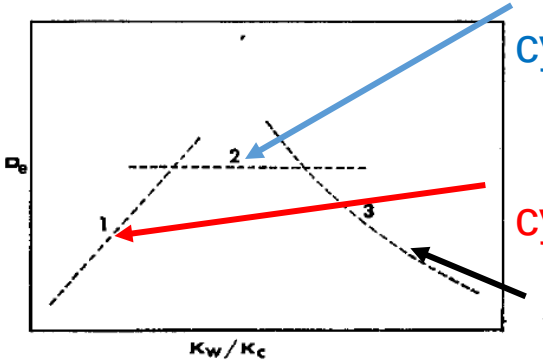
$$P_w = K_w D_w \qquad (2)$$

$$\text{and } P_c = K_c D_c \qquad (3)$$

where the K's and D's have already been defined.

- ➢ Cell wall + lipid (W) main diffusional barrier
- ➢ Steroids: Kw ~hexadecane, then D_w~ 3 X 10^{-12} cm^2/s for V_w =0.01 and 3 X 10^{-11} cm^2/s for V_w =0.1;
- ➢ $K_c D_c$ ~ 10^{-6} cm^2/s

Effective diffusion coefficient, D_e



Alcohols affinity: cytoplasm << lipids

Steroids affinity: cytoplasm >> lipids

Small MW highly lipophilic solutes

Michaels et al "brick-and-mortar' model 1975

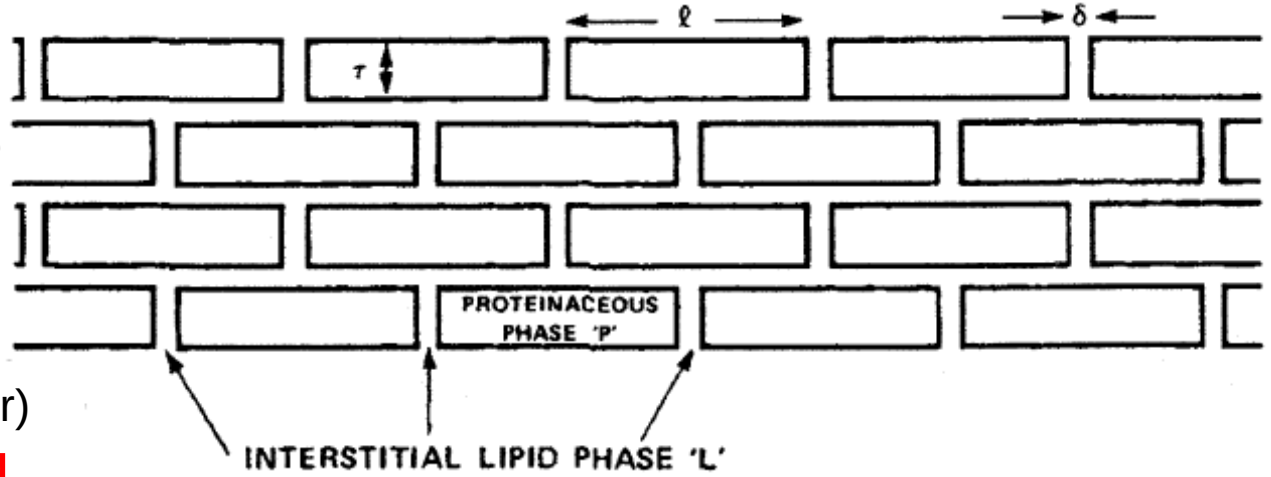
AICHEJ (1975) 21: 985-996

Model Components

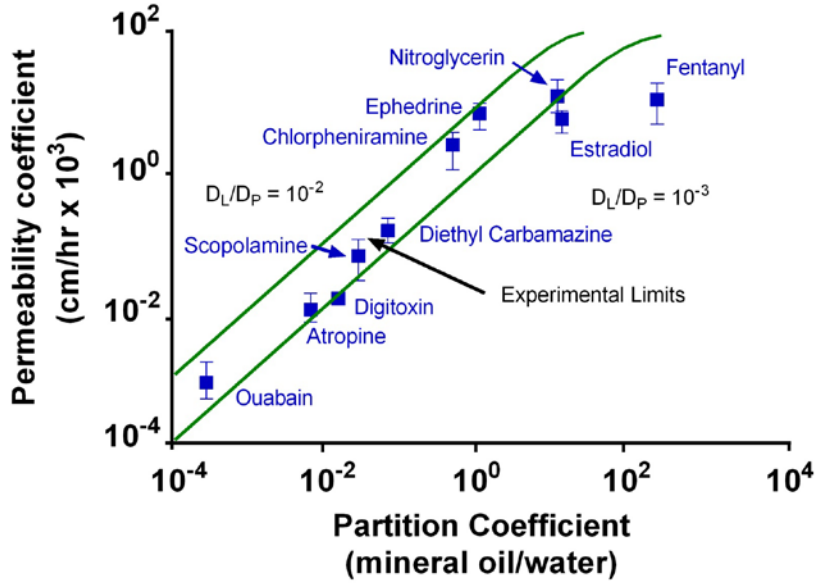
- Two Phases (lipid and aqueous protein)
- Multicellular geometry (cellular & intercellular dimensions)
- 2 diffusion constants, 2 partition coefficients & 2 plausible diffusion pathways (intercellular; transcellular)
- Permeability of SC to any solute determined by only 2 physicochemical parameters:
  - K D_p = specific permeability of SC protein phase, where for a solute MW 300 to 500, K is similar to volume fraction of water in corneocyte & D_p is about 1/10 that in water = 2 X 10^{-7} cm^2/s
  - σ D_L/D_p = product of solute partition coefficient between lipid and protein phases & ratio of diffusivities in 2 phases.
- Two geometric parameters
  - $\propto$ = SC thickness/ single corneocyte cell thickness: ~20
  - β = interstitial lipid layer thickness /corneocyte thickness: ~0.16
- Assumes no corneocyte wall barrier

Theoretical envelope of the actual data suggests D_L/D_p (diffusion in lipids/corneocytes is 0.01 to 0.001

Idealized model of the stratum corneum

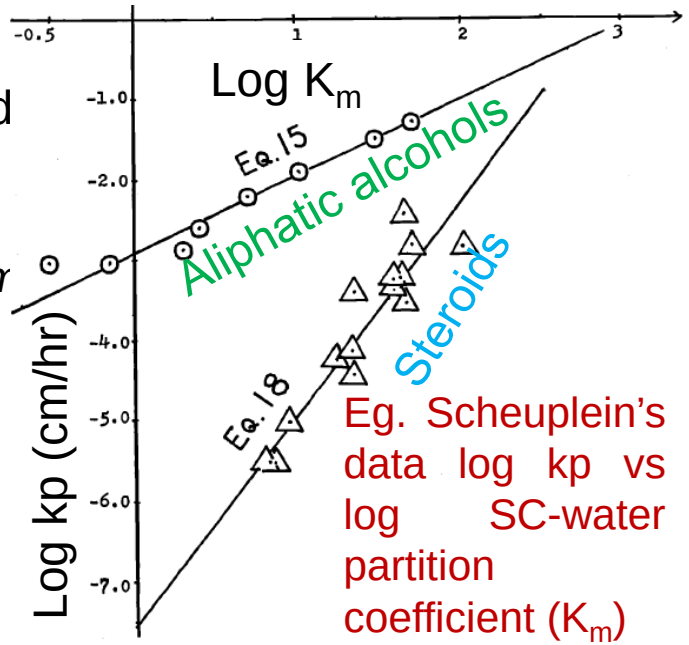


Experimental normalised flux (kp) & estimated flux (with D_L<<D_p) vs partitioning



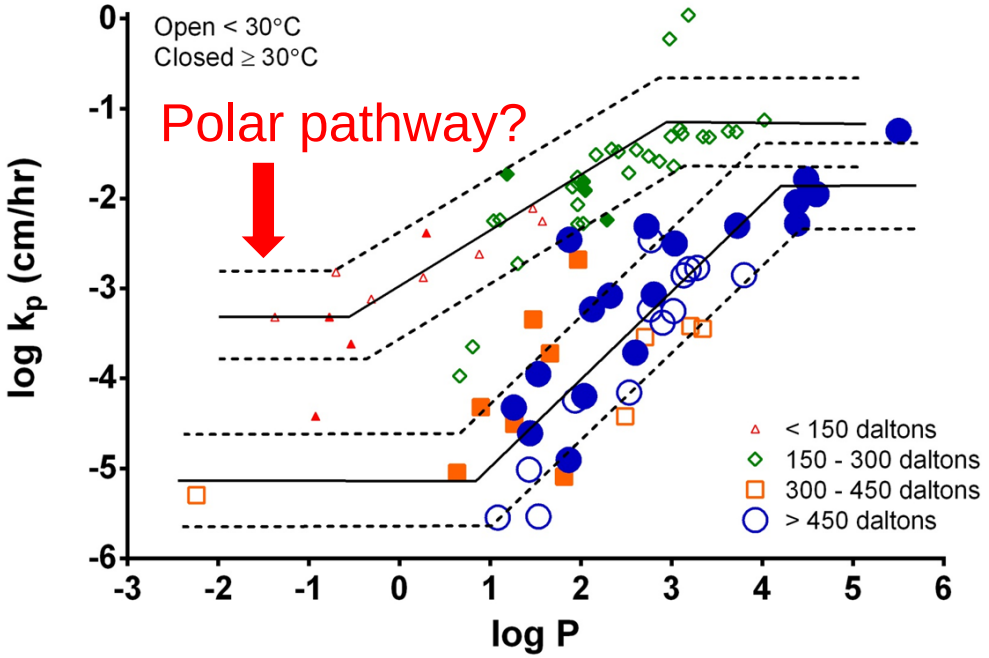
Translation: experimental human epidermal kps generated for many solutes & related to their physicochemical determinants

Early work summarised by Lien & Tong *J Soc Cosmet Chem* (1971) **24:** 371-384

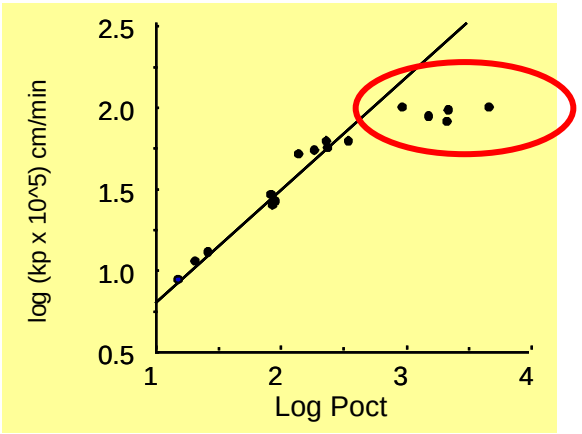


Eg. Scheuplein's data log kp vs log SC-water partition coefficient (K_m)

Gordon Flynn brought most of the data sets together with the realisation that both solute lipophilicity and size mattered



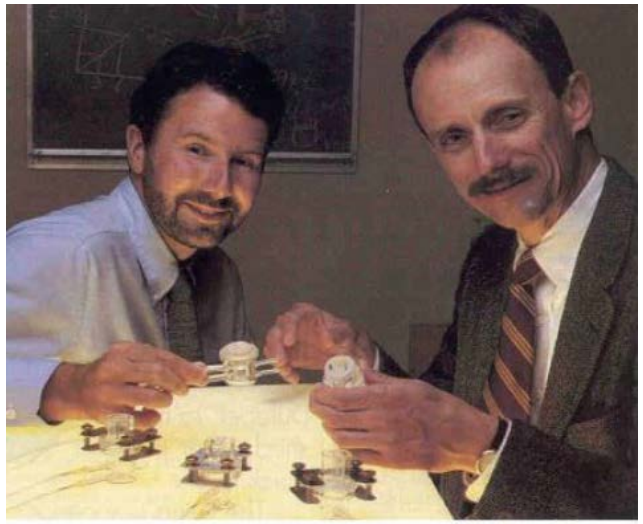
Phenolic solutes – Roberts et al *J Pharm Pharmacol* (1977) **29:** 677-683

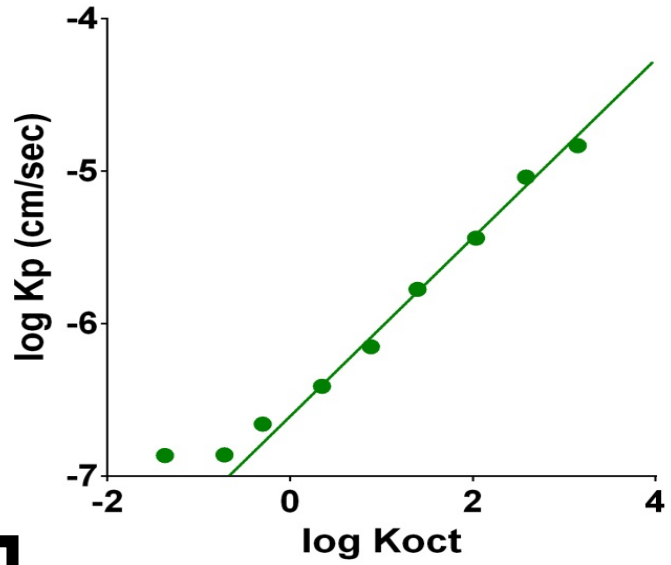


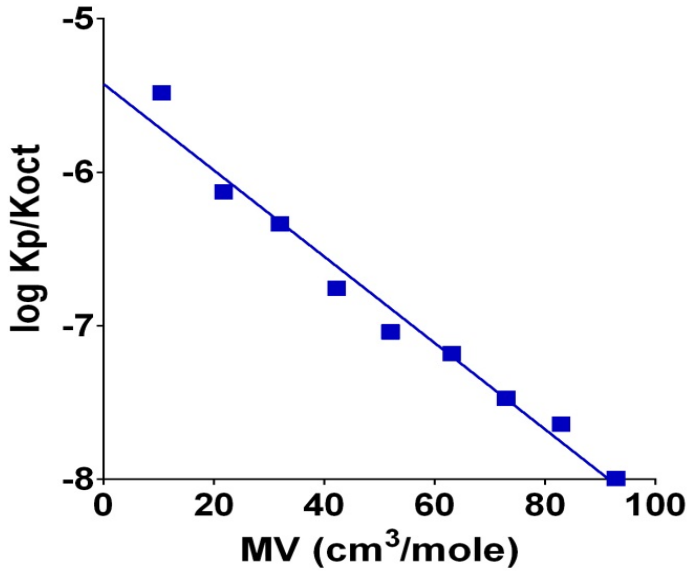
He & others attributed the higher than predicted kps for polar & ionized solutes as arising from a "**polar pathway**", possibly the same one by which iontophoresis facilitates their enhanced absorption

Adapted from: Flynn GL: Physicochemical determinants of skin absorption; in Gerrity TR, Henry CJ (eds): Principles of Route to Route Extrapolation for Risk Assessment. New York, Elsevier, 1990, pp 93–127. – **Please note our undergrad text details in my bio**

Flynn's data set (including Scheuplein, my and other work) was then expressed in the now famous Potts-Guy equation relating human epidermal kp to solute lipophilicity and size







Pharmaceutical Research, Vol. 9, No. 5, 1992

Predicting Skin Permeability

Russell O. Potts[1,3] and Richard H. Guy[2]

Highly Cited

Potts-Guy: solutes *MW* 18 to >750 Da & *log P* -3 to +6, the permeability coefficient *kp* is given by:

$$\log kp\ (cm\ sec^{-1}) = -6.3 + 0.71 \log P - 0.0061.MW$$

$$r^2 = 0.67;\ n = 93$$

They also showed that viable tissue only affected solute kin penetration for MW~100 when log P>4 & for MW>200 when logP >5

Complex models - Volsurf applied to skin maximum flux

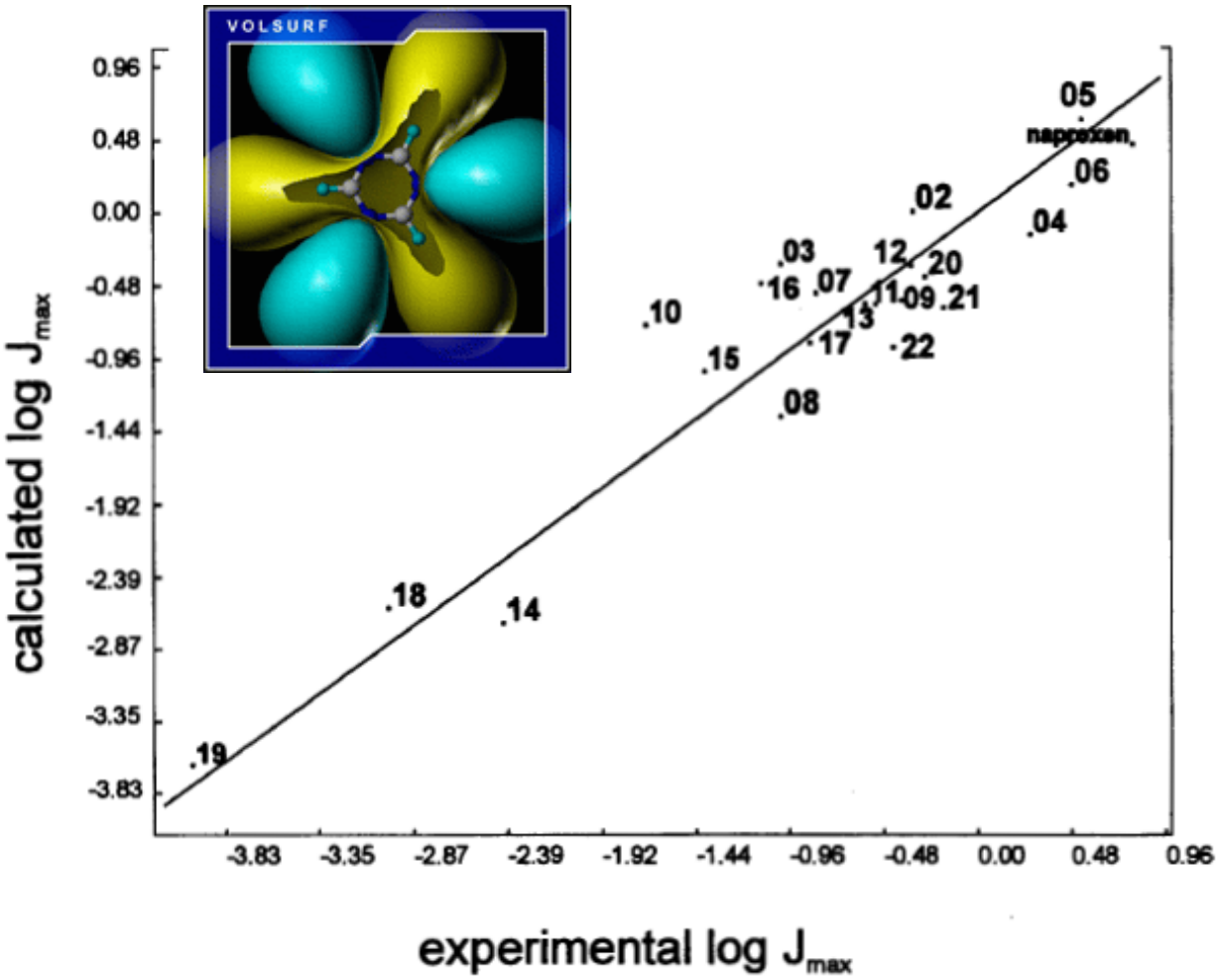


Fig. 1. Plot of experimental skin permeation data (log J_{max}) versus the corresponding calculated data.

Ngawhirunpat et al 2001, 2002

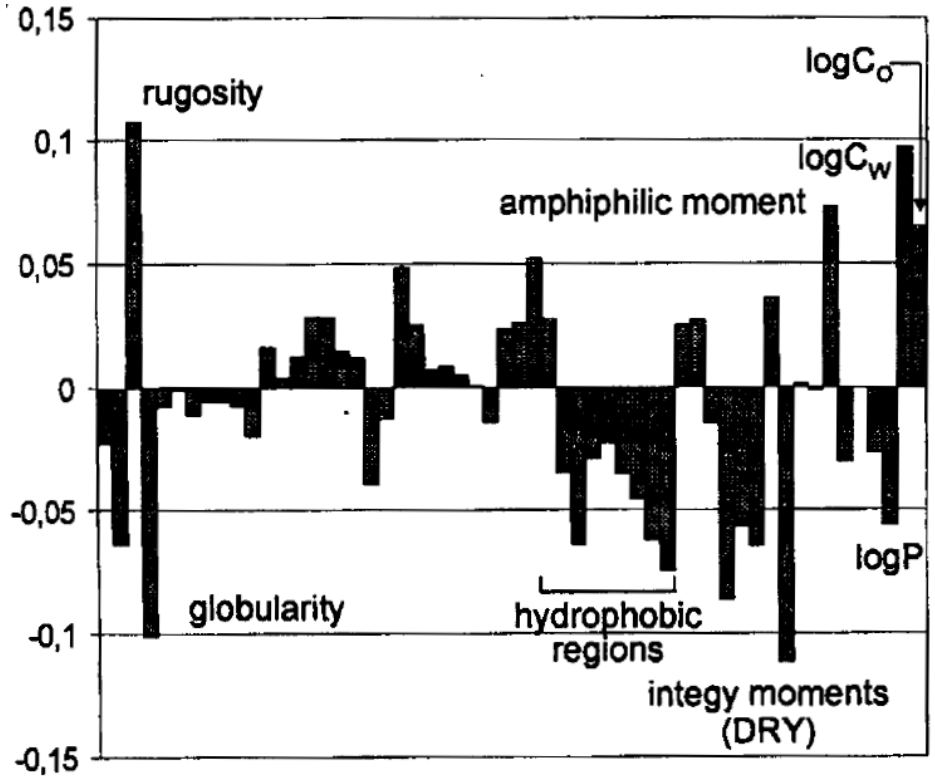
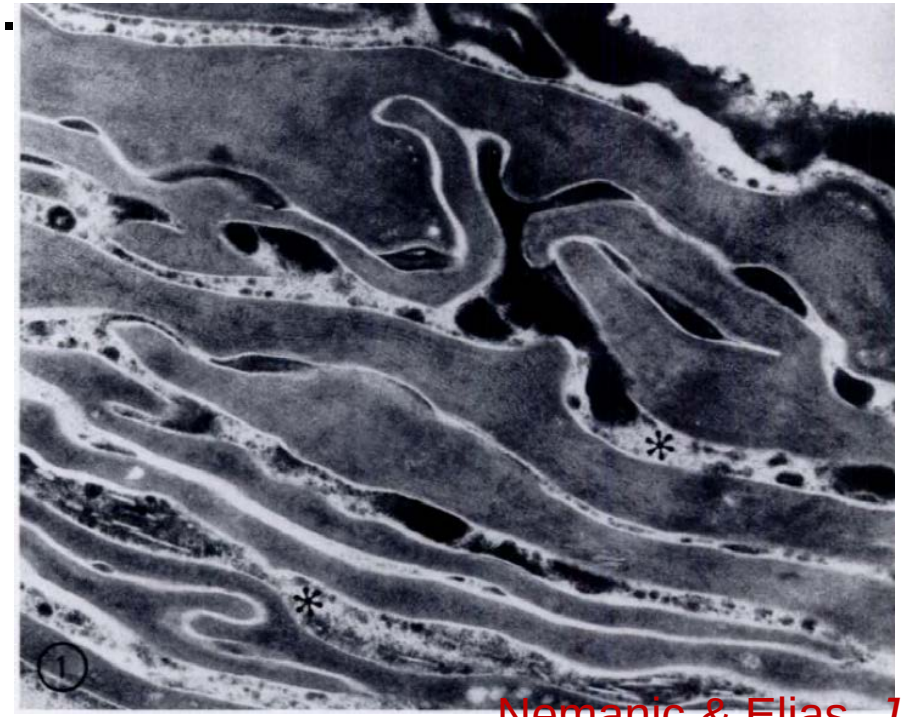


Fig. 2. Coefficient plot expressing the individual contribution of physicochemical descriptors: large bars indicate an important and small bars a slight contribution, positive directions represent a positive and negative ones an inverse correlation. The meaning of the bars— from the left to the right—is identical to the sequence of the VolSurf descriptors listed in Table II: e.g., rugosity (nr 3), globularity (nr 4), hydrophobic regions (nrs 32-39) hydrophobic integy moments (nrs 40-47), and amphiphilic moment (nr 50). Additionally, log P (nr 54), log C_w (nr 55), and log C_o (nr 56) are given.

An experimental observation can call into question theories not based on actual data

- SC “comprises a heterogeneous layer of corneocytes embedded in expanded, neutral, lipid-rich intercellular domains.”
- “One might predict, therefore, that **lipophilic substances should preferentially traverse the stratum corneum between cells rather than through them.**”

In situ precipitation of n-butanol after osmium vapor treatment for human stratum corneum exposed to n-butanol for 2 hr, then to osmium vapor for 60 min. x45,600;
Note the extensive flocculent, but irregular, pattern of intercellular deposition (asterisks).



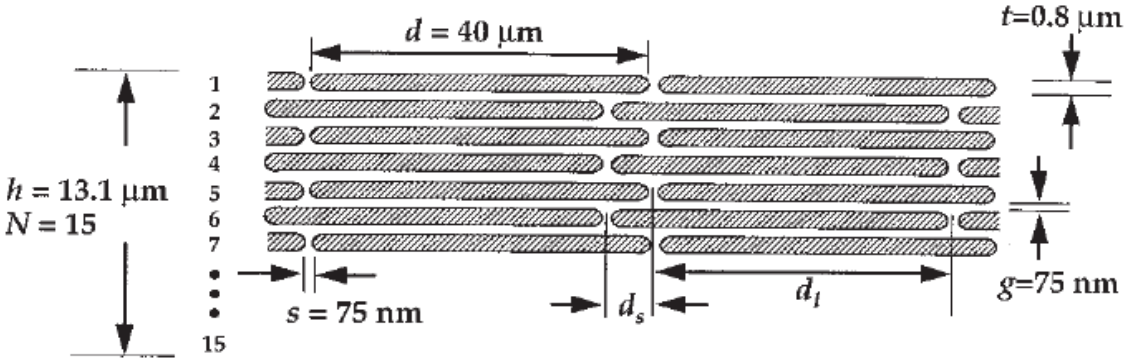
- **~8X more osmium in intercellular domains of n-butanol-treated samples vs controls by** EDAX.
- ~3X more osmium precipitate in the interstices than in the cytoplasm in n-butanol perfused tissues by scanning densitometry.
- Results suggest that the stratum corneum intercellular spaces may serve as a preferential transport pathway for certain lipid-soluble substances

Nemanic & Elias. *J Histochem Cytochem* (1980) **28**: 573-8

Evaluation of Solute Permeation through the Stratum Corneum: Lateral Bilayer Diffusion as the Primary Transport Mechanism

1162 / Journal of Pharmaceutical Sciences
Vol. 86, No. 10, October 1997

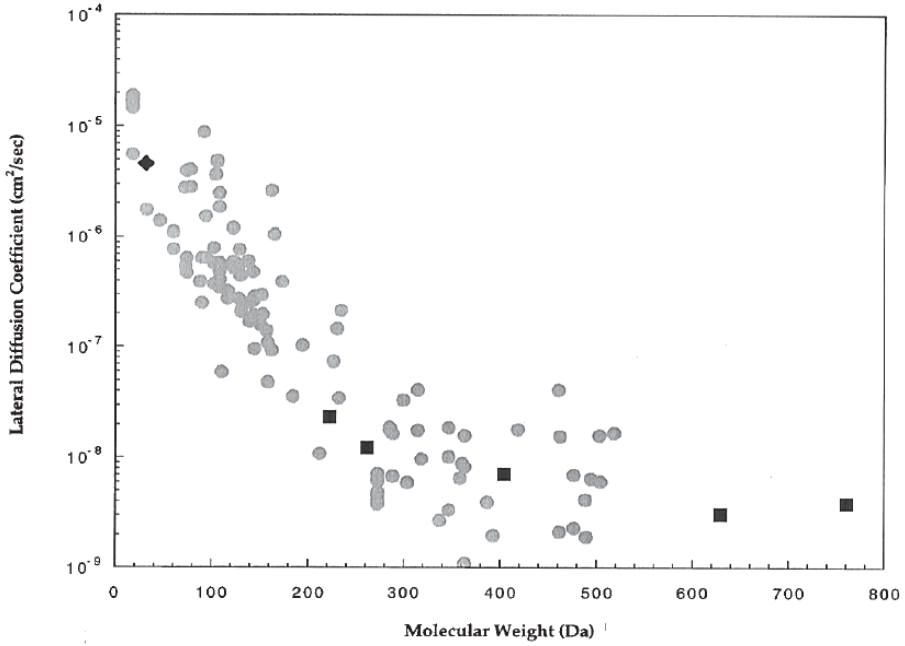
MARK E. JOHNSON, DANIEL BLANKSCHTEIN[x], AND ROBERT LANGER[x]



- Used dimensions in Fig. to estimate an *effective tortuosity* (ratio diffusive flux through SC without & with impediment) of *2490*.
- Human epidermal permeabilities of radiolabeled n-decanol, n-hexanol, 2-napthol, and n-octanol measured in side-by-side diffusion cells into PBS receptor
- Comparison of experimental video-FRAP ■ and EPR spectroscopy ◆ human skin permeabilitiy calculated ● lateral diffusion coefficients.

Nonionic solute diffusion occurs mainly in SC lipids with corneocytes effectively impermeable

- First enters top-most bilayer from aqueous solution
- Then in SC diffuses through a series of segments of lateral diffusion and intramembrane transbilayer transport to cross *n* bilayers internally and diffuses laterally over a total distance, *l*.
- Lastly, leaves bottom-most bilayer into viable epidermis



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Journal of Controlled Release 86 (2003) 69–92

journal of controlled release

www.elsevier.com/locate/jconrel

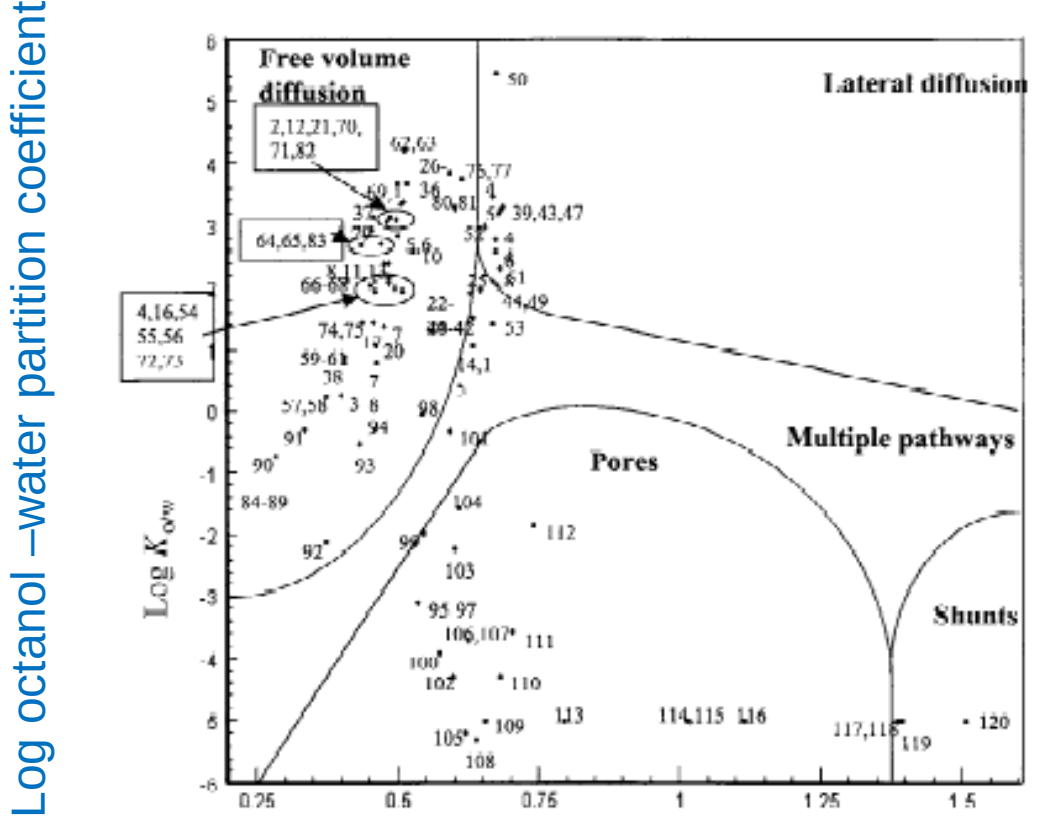
Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways

Samir Mitragotri*

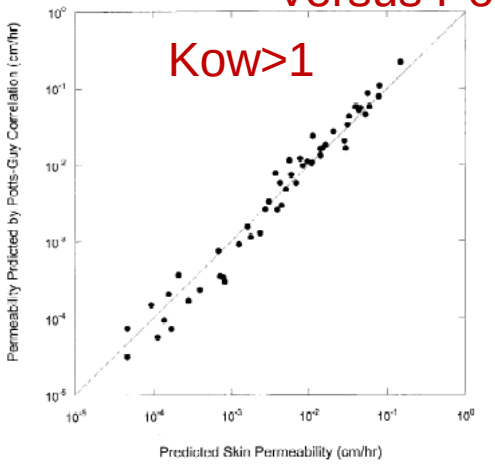
Solute permeation through SC by:

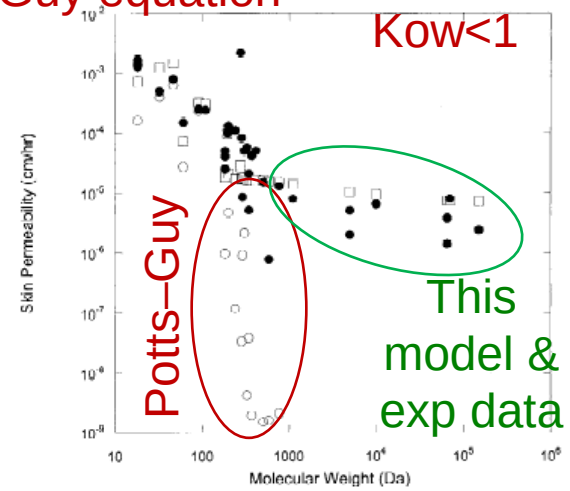
- free-volume diffusion through lipid bilayers by Scaled Particle Theory - dominant for low-molecular weight hydrophobic and moderately hydrophilic solutes.
- lateral diffusion along lipid bilayers – for large lipophilic solutes.
- diffusion through pores – for small excessively hydrophilic drugs, and
- diffusion through shunts - for large hydrophilic solutes

$$K_p = K_p^{fv} + K_p^{lateral} + K_p^{pore} + K_p^{shunt}$$



Versus Potts–Guy equation

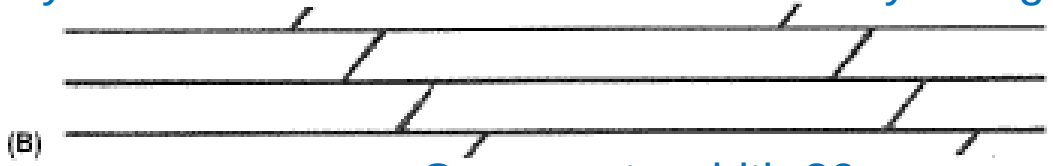




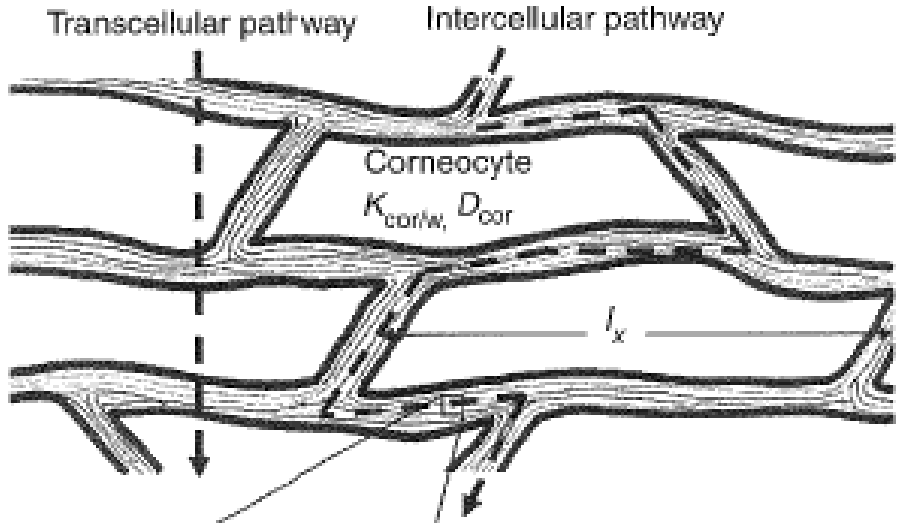
Wang-Kasting-Nitsche holistic multiphase SC model

Partially hydrated brick-and-mortar model of SC by Wang et al

Fully hydrated brick-and-mortar model of SC by Wang et al



Corneocyte width 30 µm



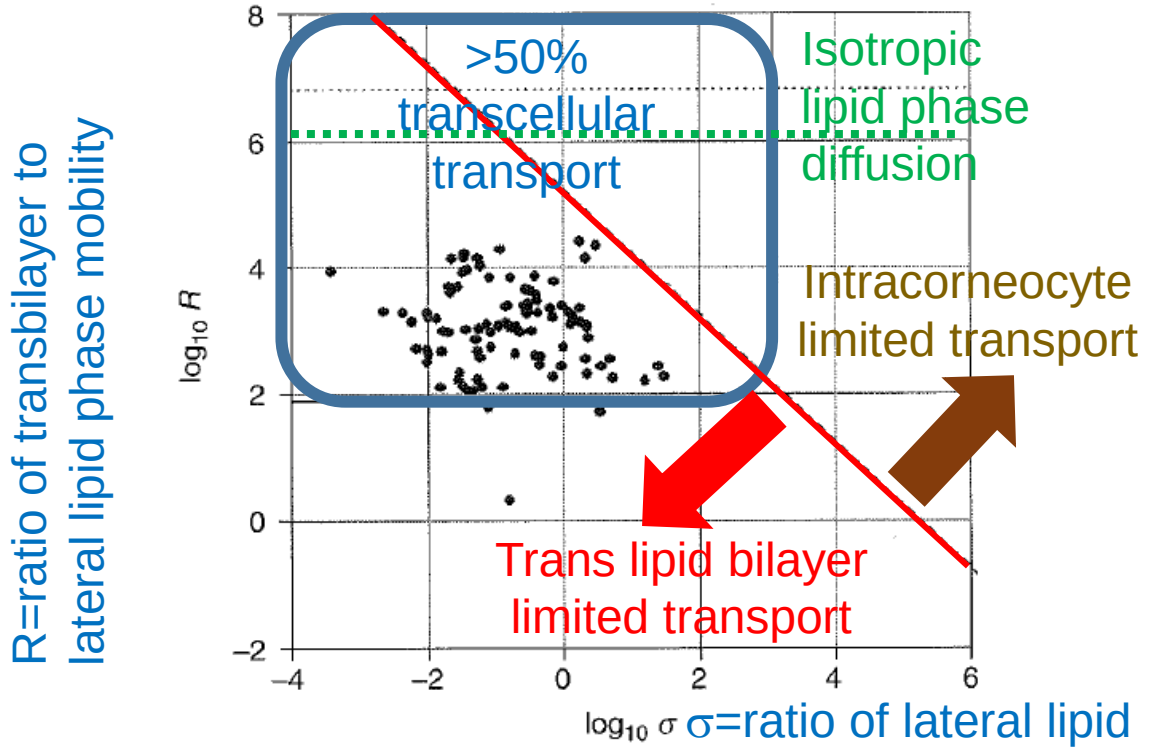
Lateral diffusivity

Lipid bilayer thickness 13 nm

Transbilayer mass transfer coefficient

$R = k_{trans}\, l_x^2 / (\delta\, D_{lip})$ Trans to Lateral lipid transport

$\sigma = D_{lip} K_{lip/w} / (D_{cor} K_{cor/w})$ Lateral lipid to corneocyte transport



σ=ratio of lateral lipid phase to corneocyte phase mobility

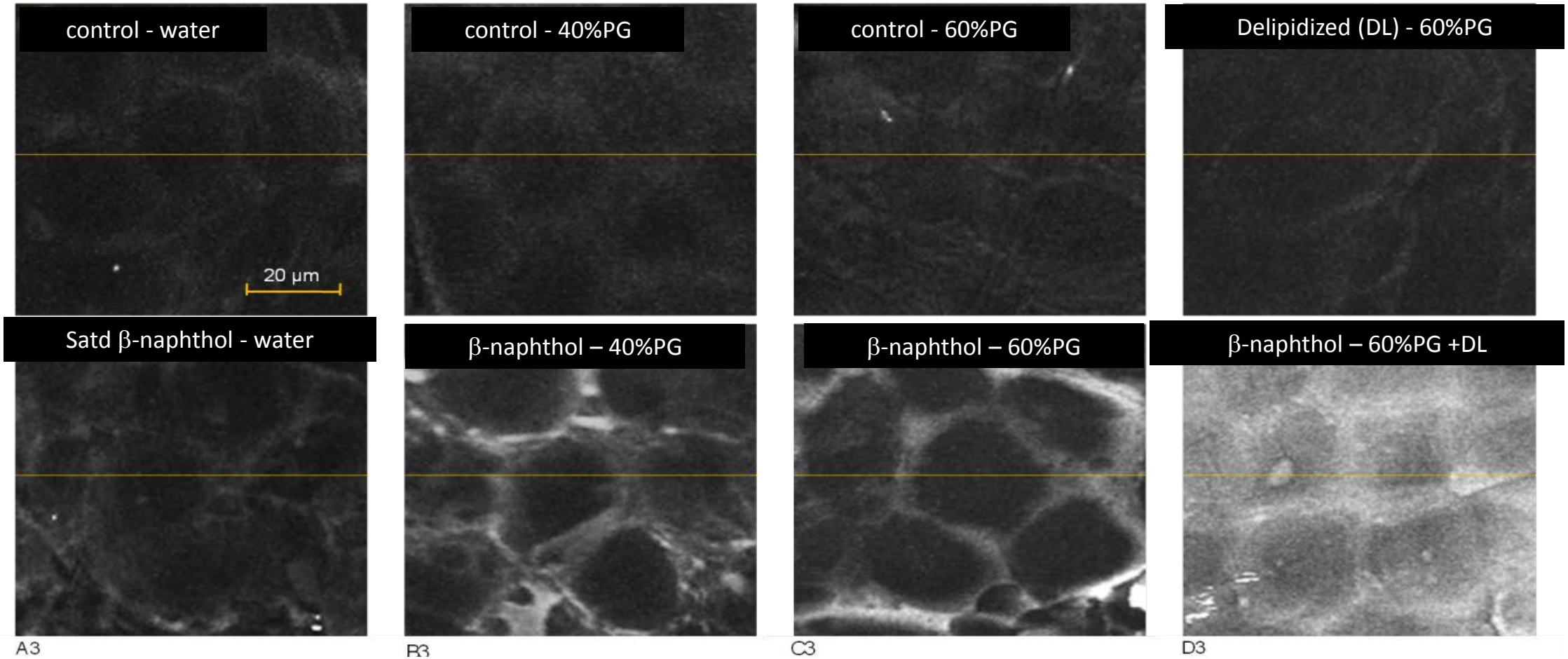
Kasting & Nitsche. Biophysical Models for Skin Transport & Absorption. Ch 13 in Dermal Absorption & Toxicity Assessment 2nd ed Roberts & Walters, Marcel Dekker, New York, June 2008.

Noted that

- Lipid diffusion only requires high D_{lipid} & unrealistically short lag times
- 97% solutes a dominant transcellular pathway where solute binds to keratin/ lipid & dissolves in corneocyte water

Does our imaging work on epidermal transport of β - naphthol support Johnson et al (MIT) or Wang-Kasting-Nitsche?

Note phenols strong keratin binding & so Johnson's theory only applies when solvents do not affect corneocyte wall

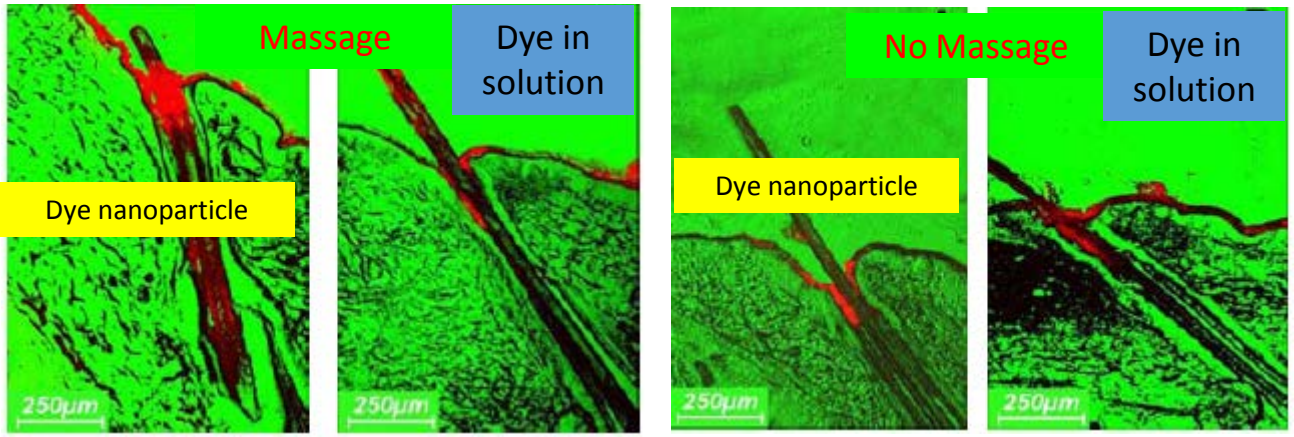


Zhang et al. *J Control Rel* (2011) **154** 50–57

Should we dismiss other pathways so quickly?

Appendageal & polar pathway a long history of rapid effects

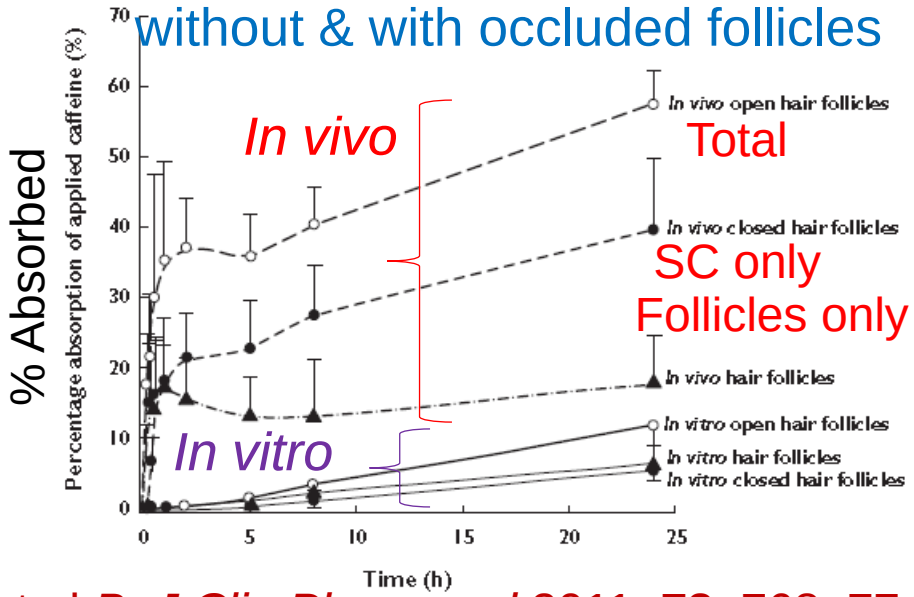
- **Shelley and Melton (1949)** observed perifollicular wheals 5 min after the application of 10 % histamine free base in water.
- Histologic studies by **Mackee et al. (1945)** have also demonstrated follicular diffusion occurring within 5 min.
- Formulation will really matter in depth of follicular deposition



- Viable epidermis & dermis can also matter
  - Significant barriers for more lipophilic solutes
  - Viable epidermal metabolism
  - Diffusion, carriage away by blood supply & shunting to deeper tissues for highly plasma protein bound drugs

Our data with open & closed appendages *in vivo* also suggests it occurs at early times for solvent deposited solids & >> *in vitro*

Human *in vivo* and *in vitro* after solvent deposited solid of caffeine without & with occluded follicles



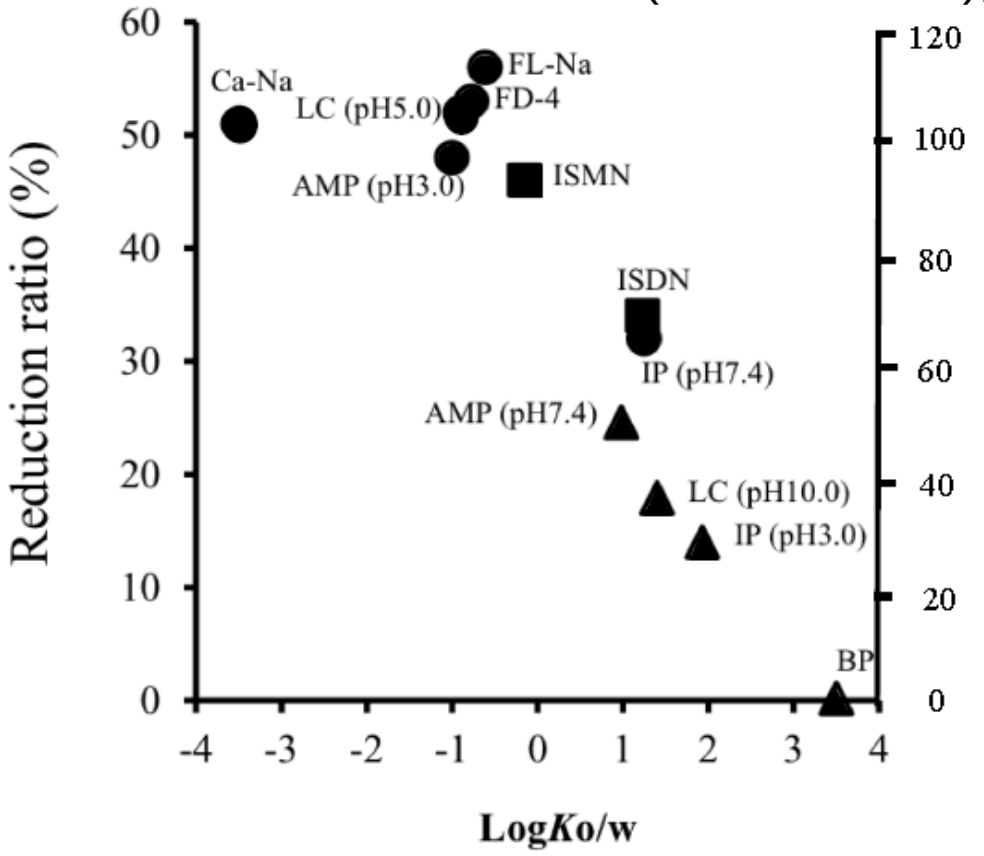
Liu et al *Br J Clin Pharmacol* 2011: **72**: 768–774

Porcine skin *in vitro*: Lademann et al 2006, 2009

In vitro appendageal transport

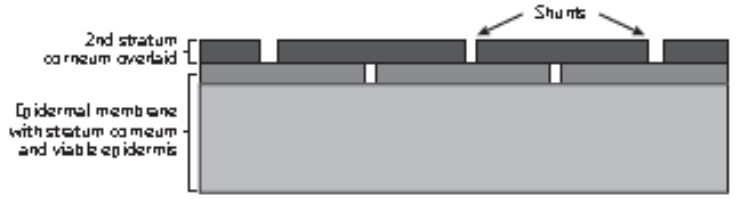
Paltzelt's hair follicle plugging method

% reduction in permeation by for solutes with Log $K_{o/w}$. ●: ionized form (acidic or basic); ▲: non-ionized form (acidic or basic); ■: neutral

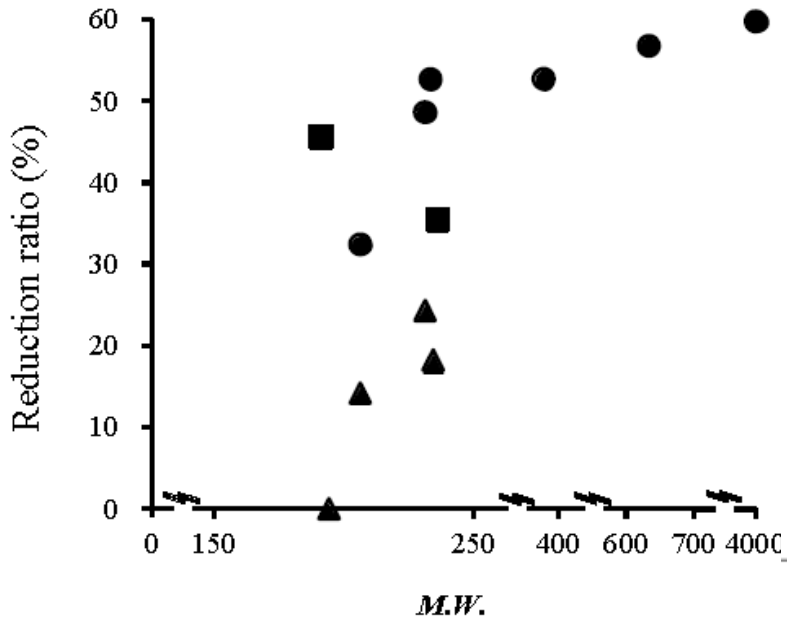


Mohd et al Pharmaceutics **2016**, 8, 32

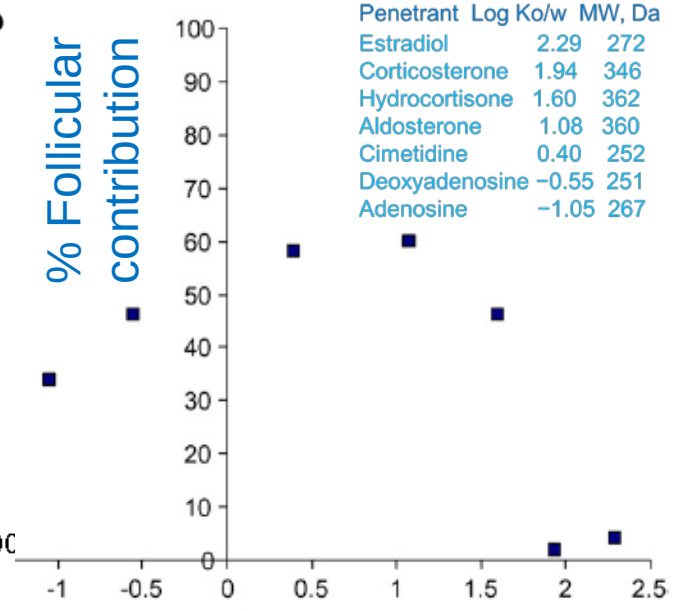
Brian Barry's sandwich method



Williams *Skin Pharmacol Physiol* 2013;**26**: 234–242



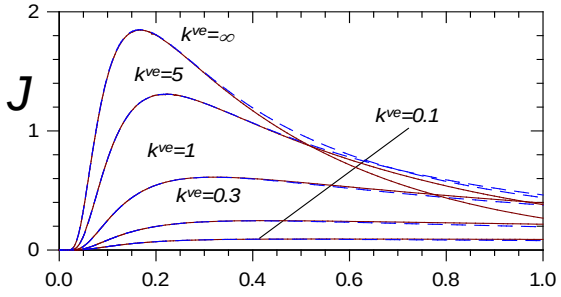
Frum et al Eur J Pharm Sci (2007) 30: 280–287



Log $K_{o/w}$

Compartmental Models, PBPK models Analytical and computational solutions.

- The diffusion model is also an infinite number of compartments & can be so represented
- We used a series of compartments to represent various skin tissues and integrate with body to show deep tissue penetration & recirculation (Singh & Roberts)
- Diffusion although precise are partial des and often difficult to express in analytical form (Bunge) & we have used Laplace solutions (Anissimov) – challenge is doing non-linear regression in this domain. We overcome using Scientist[R]. Others have used finite differences (Frasch)
- But not good for population pharmacokinetics – here compartments are the best established for NONMEM, ADAPT, Berkeley Madonna etc
- Computational solutions require expertise & software



Kv is ratio of epidermal to stratum corneum resistance

$$J_{max} = 185\frac{D_m h_v C_{v0}}{h_m^2}$$

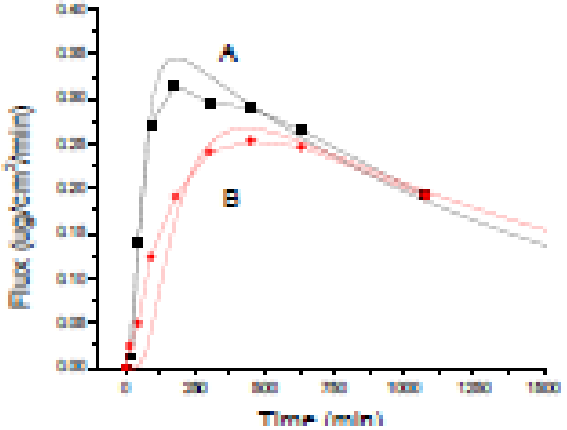
$$t_{max} = \frac{h_m^2}{6D_m}$$

$$\hat{J}(s) = \frac{dose}{A}\frac{1}{\left(1+\frac{V_{dN}st_d}{\kappa_{ve}}\right)\cosh\sqrt{st_d} + \left(\frac{1}{\kappa_{ve}}+V_{dN}\right)\sqrt{st_d}\sinh\sqrt{st_d}}$$

Anissimov & Roberts 2001

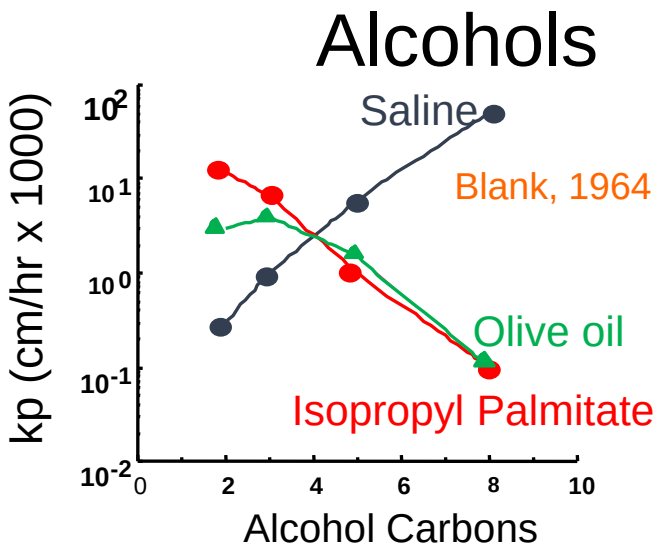
Lidocaine

In vitro finite dose percutaneous absorption data (symbols) with overlaid model fit (solid line) for different products. (Lehmann, 2014)

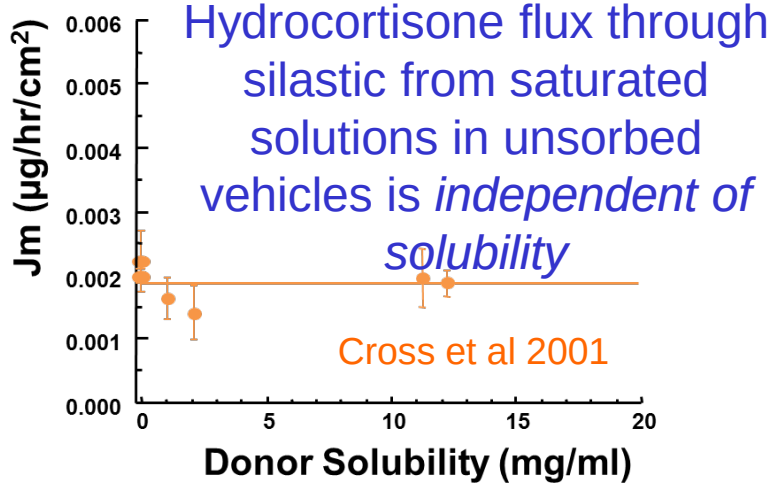


Is kp the right paradigm for delivery of actives from products?

kp paradigm



Max flux paradigm



- Impact of solvents on kp
  - It is evident here that the more lipophilic solutes have a higher kp in water where they are less soluble than more polar solutes but the converse applies in oils.

- **So, what is the alternative paradigm?**

- Back in 1960 in the J Soc Cosmet Chem, Tak Higuchi noted that the thermodynamic activity of a saturated solute in different solvents or in solid form is identical & maximal, unless supersaturated.
- The impact of that finding is that the solute should have the same saturated flux from all solvents, providing that solvent does not affect the skin.
- Note: k_p = Saturated flux/ solubility

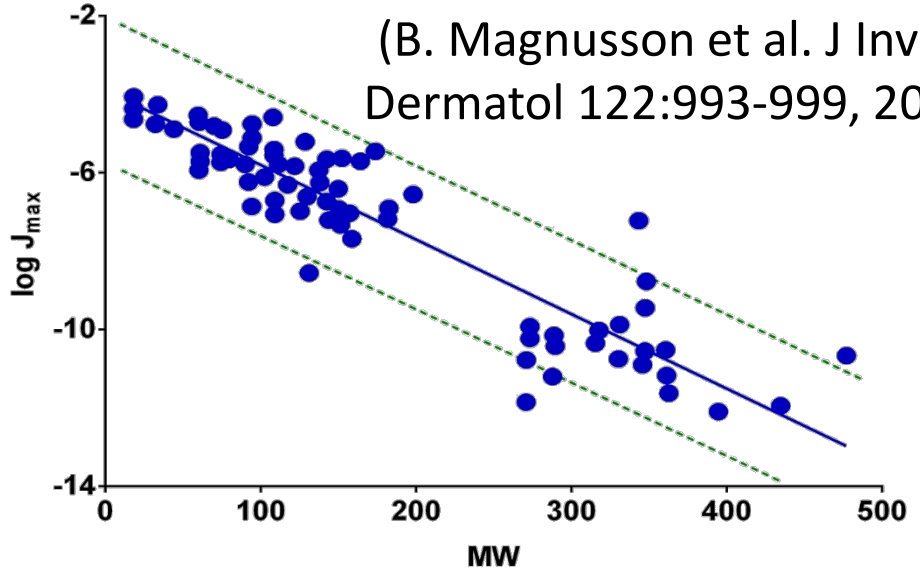
Permeability coefficient or flux ?

- **Permeability coefficients**
  - Relate to dilute solutions
  - Transport through biological membranes – water
  - ***But estimated from concentration in vehicles & therefore is fundamentally determined by the thermodynamic activity in that vehicle***
  - ***Dependent rather than independent variable***
- **Topical products**
  - Often non-aqueous
  - Often high concentrations
- **Flux**
  - Is the actual delivery to the site of action
  - It can be expressed as a time variant quality
  - It can be directly measured
- **Maximum flux advocated by T Higuchi - 1960s**
  - Defined by stratum corneum - diffusivity & solubility
    - ***Jmax ~D.Ssc/hsc***
  - Can have equilibrium between solids & solutions
  - ***In principle, same maximum flux, irrespective of vehicle***

To our surprise, solute molecular weight was its main determinant of available maximum flux data

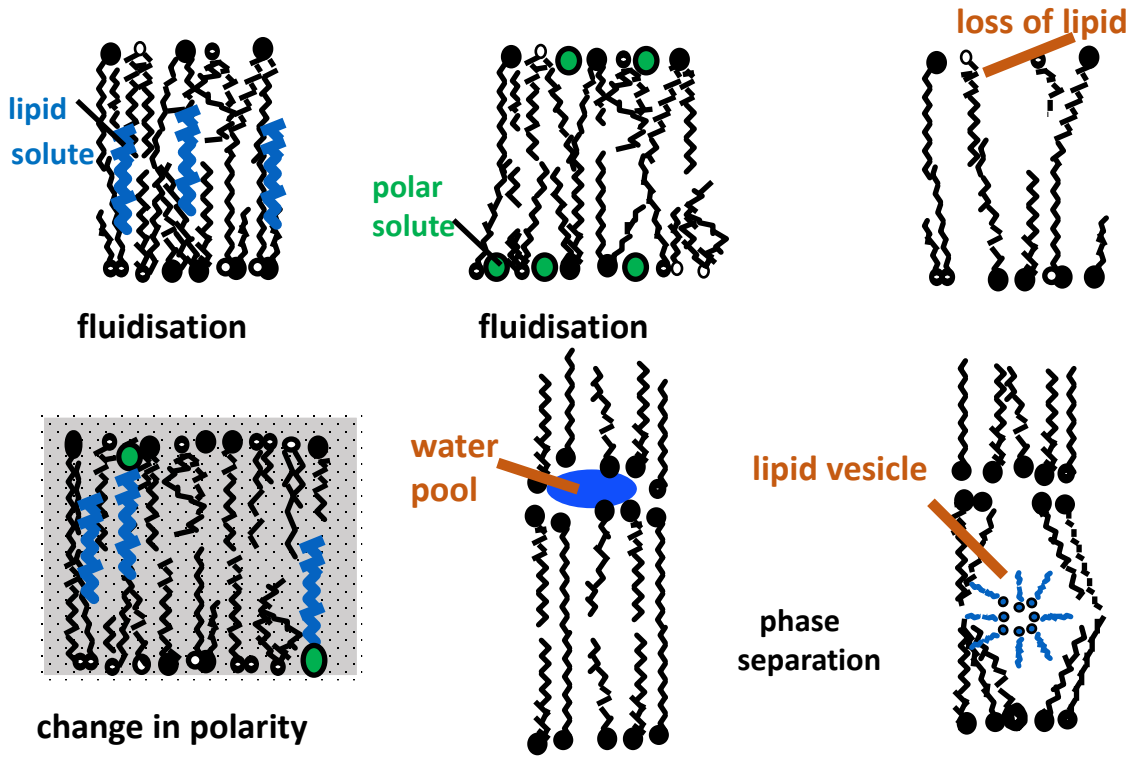
Log J_{max} = -3.90 – 0.0190MW;
P<0.01, R^2 = 0.847, N=87

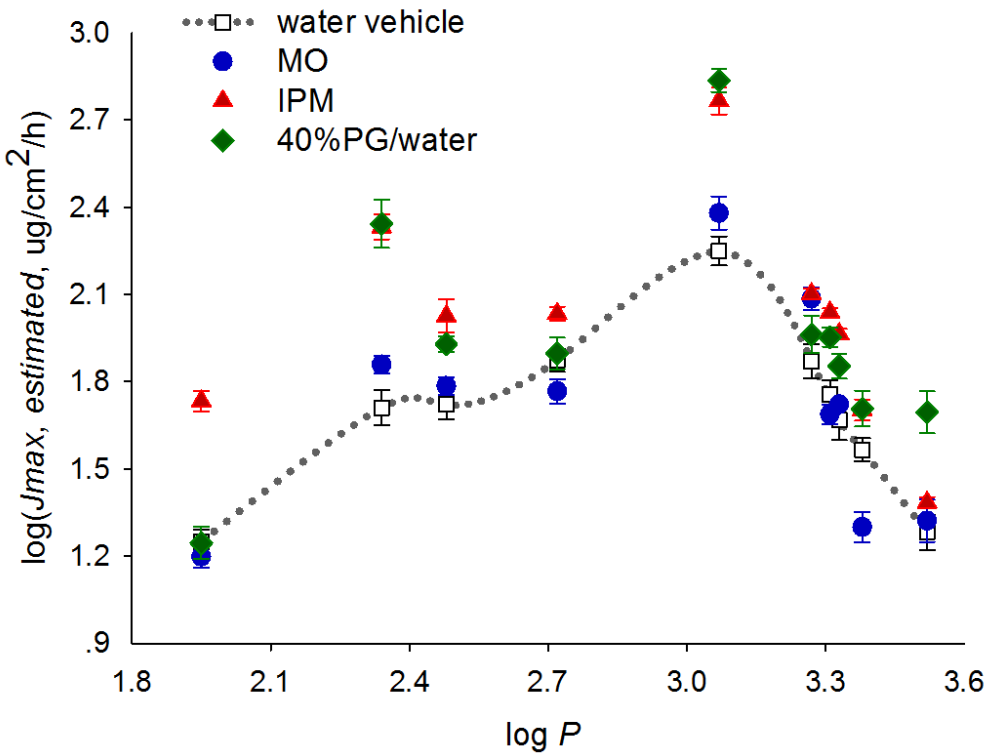
(B. Magnusson et al. J Invest Dermatol 122:993-999, 2004)



Solute- vehicle – skin interactions

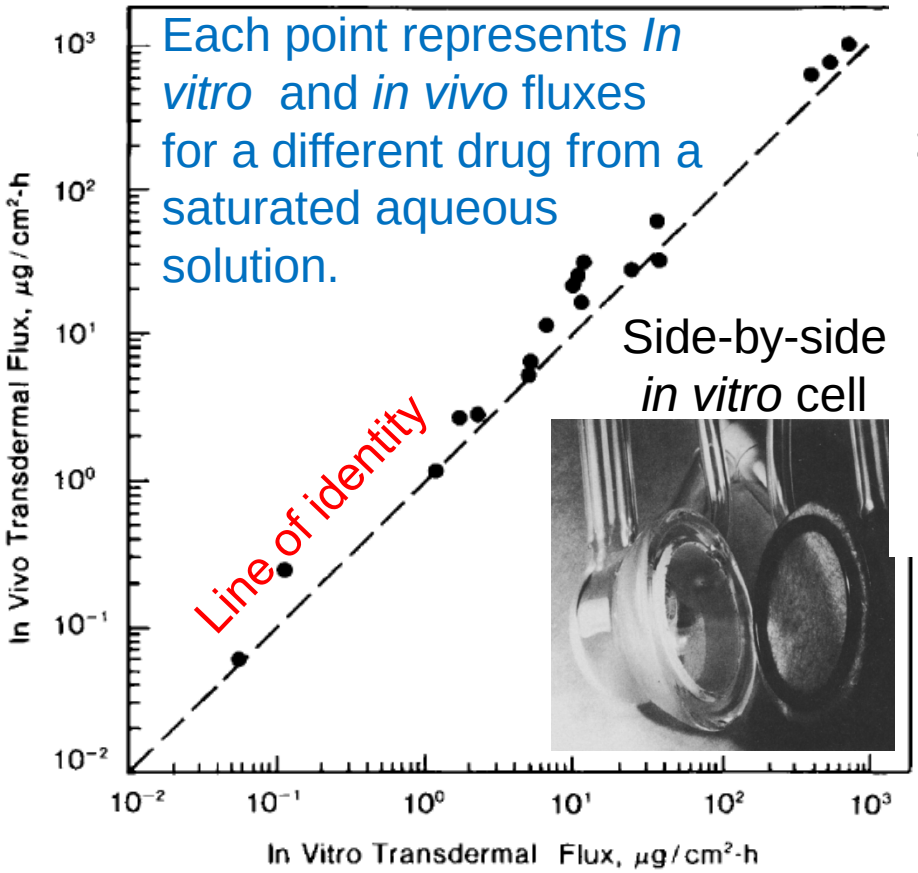
Phenols *Jmax* for mineral oil (MO), isopropyl myristate (IPM) & 40% propylene glycol - water





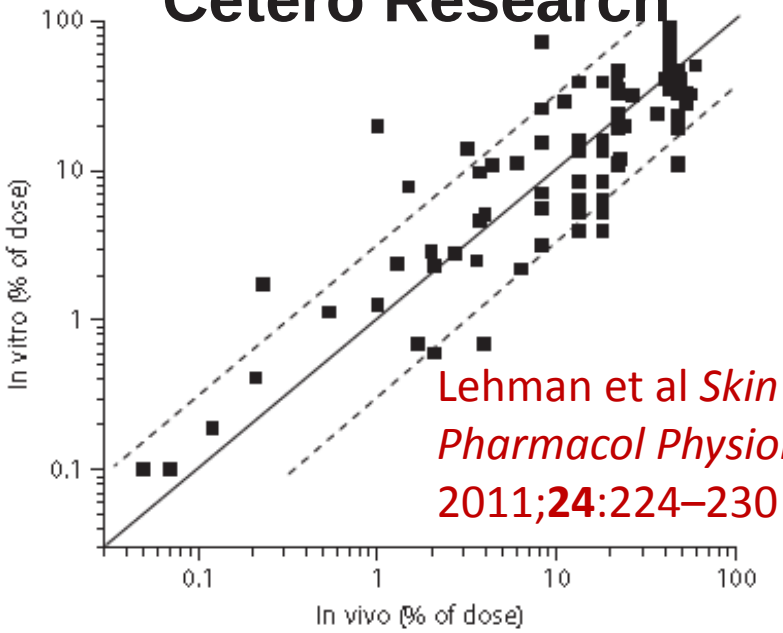
In vitro – in vivo established for a long time but there are issues!

Early work by ALZA

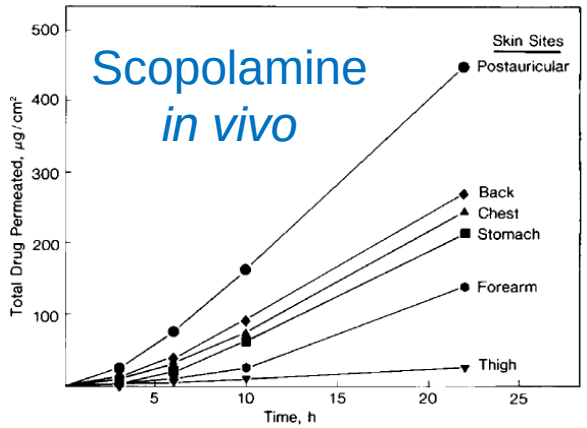


Shaw et al *Arch Dermatol* 1987;**123**:1548-1556

Cetero Research



Lehman et al *Skin Pharmacol Physiol* 2011;**24**:224–230



- Lehman *IVIV* 20X difference reduced to <2X with harmonised sets, notably in body sites & product content
- Point-to-point (Level A) with internal & external validation preferred – using *in silico* for skin temperature, metabolism & blood flow, desquamation effects

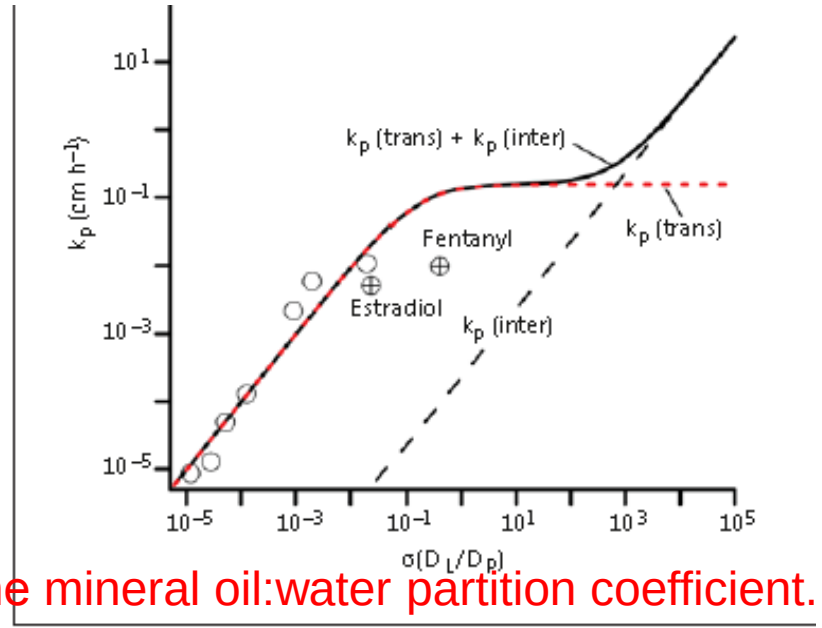
www.fda.gov/downloads/drugs/guidances/ucm070239.pdf

Conclusion - wise final comments from Bob Scheuplein

Skin Pharmacol Physiol 2013; **26**:199–212

- Most current models of skin permeation emphasize intercellular diffusion, e.g. Johnson et al. [30] and others [33–35] .
- Some of these models are extremely detailed but are inconsistent with existing permeation data and with one another, but virtually all claim a good fit with some permeation data.
- Some go into extraordinary detail regarding the architecture of the SC and its consequences for permeation.
- To me, many of these complicated models seem unverifiable.
- Broad agreement, within 1 or 2 orders of magnitude with collected data from several different investigators is predictable and not compelling.
- Given the inherent variability in most permeation data and the number of adjustable parameters in many of the new models, such a level of agreement is almost assured. In the quantitative sciences there is the notion of ‘significant figures’.
- In skin permeation modeling there should be something analogous, like ‘unjustified complexity’ or ‘irrelevant embellishment’.

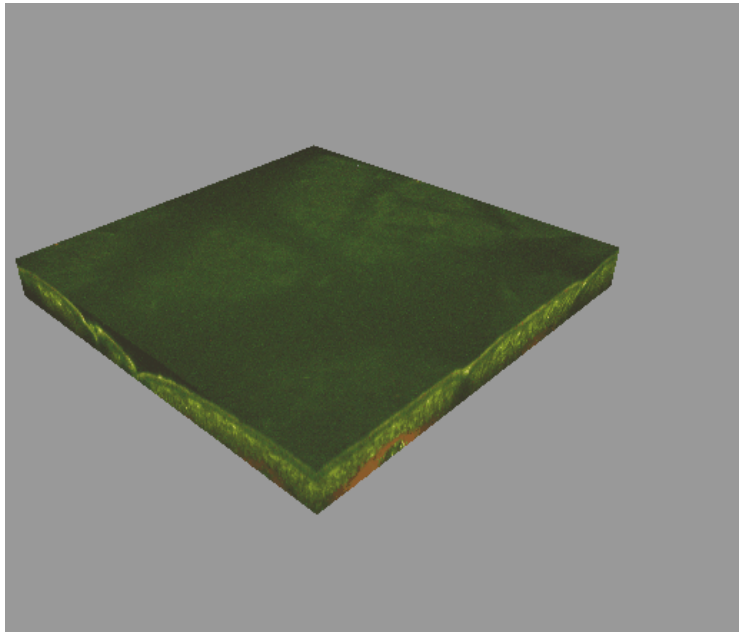
Logarithmic plot of experimental permeability constants (kp) for 10 compounds compared with ALZA predictions by the MCS brick-and-mortar model for the transcellular (- - - -), intercellular (– – –) and combined (———) paths for ratio of lipid to protein diffusion D_L/D_P and lipid to protein partition coefficients (σ).



Best fit with $D_L/D_P = 2 .10^{-3}$ using σ as the mineral oil:water partition coefficient.

Conclusion

- Measuring skin transport is a challenge
- Permeability coefficient is useful for solute structure - skin penetration relationships for low concentrations in aqueous solutions
- Max flux, Jmax, applies to high concentrations & complex vehicles - key determinant is solute size
- Its usefulness is extended to various formulations when interpreted in terms of changes in its components: D/h and Solubility
- Unresolved challenges are:
  - conflicts between theoretical models & observations,
  - the effects of formulations on skin &
  - IVIVCs
- The real solution is a **Middle Out approach** where
  - we combine surrogate models for in vivo skin eg SC tape stripping, dermal microdialysis/open flow dermal perfusion, IVPT, *in vivo* skin imaging with
  - *In silico* modelling and QSAR data, and
  - Compare to *in vivo* data/Extrapolate to other sites and skin conditions



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