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AAPS Topical and Transdermal Community

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# Mathematical modelling of skin absorption and transport


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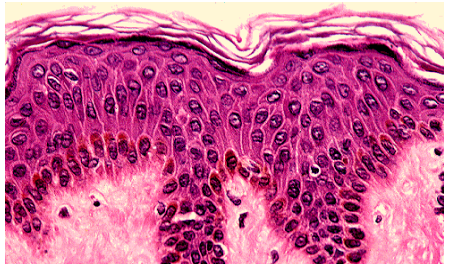
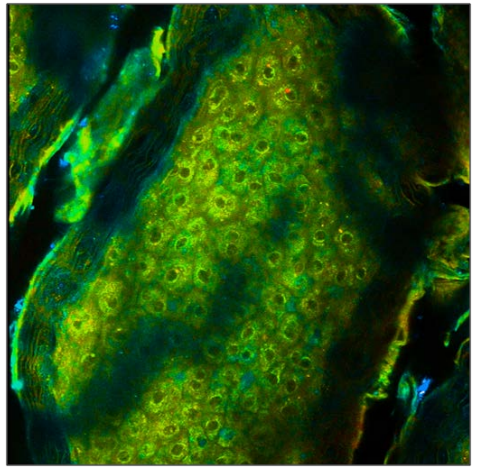
# Learning objectives

## Outline

- Why do we need mathematical modelling in skin absorption & transport?
- Understand limitations of top down, bottom up & middle out approaches to studying skin drug absorption & subsequent effects
- Apply mathematical modelling principles to transdermal & topical absorption

H& E histology of skin





Multiphoton image of skin

Applying product to skin

# Why do we need mathematical modelling in skin absorption & transport?

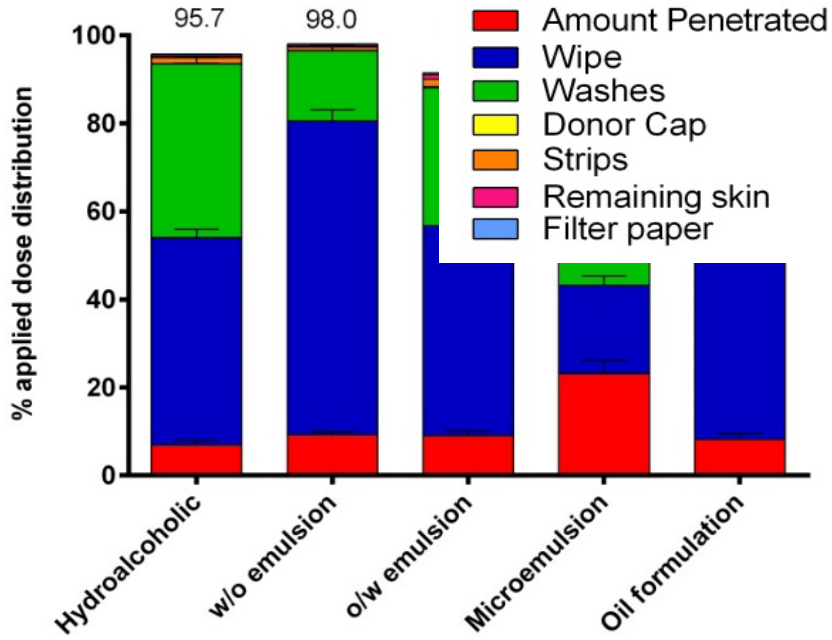
- As one example, a graphical representation of concentration versus time or, as shown on right, of mass balance of *IVPT* finite dose testosterone data is the simplest way of summarising & visualising actual data
- A mathematical model may be a simple or complex representation of what may be occurring and may have the additional benefit of being able to predict and be extrapolated beyond the data available to other situations,
- However,
- *All models are wrong, but some are useful*

Box, G. E. P. J Amer Stat Assoc, 71 (356): 791–799, (1976)

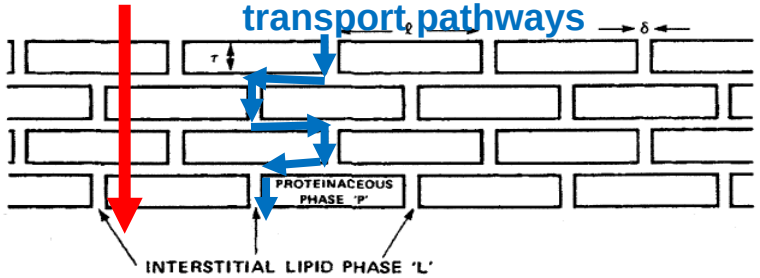
**BUT**

*Everything should be made as simple as possible, but not one bit simpler.*

Attributed to Albert Einstein,1879 – 1955




**Idealized model of stratum corneum & transport pathways**

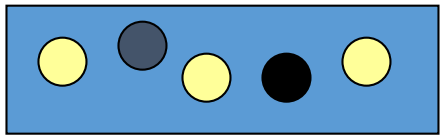


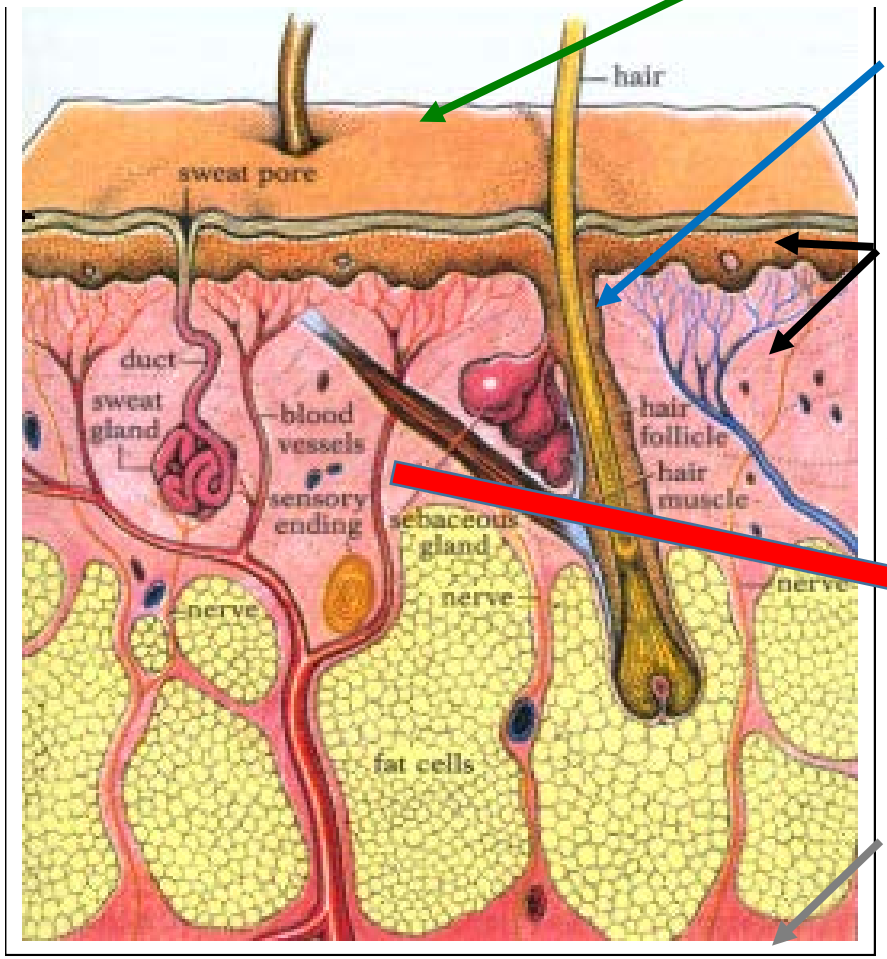

Intercellular localisation of n-butanol in intercellular SC lipids

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

# Our focus here is using models to assess delivery to our target sites with topical or transdermal products

Product






**Superficial** – ***retention & action***

Barrier products, sunscreens, insect repellents, cosmetics

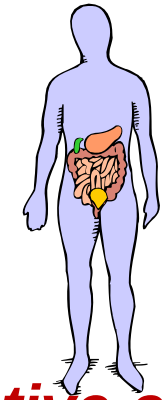
**Appendageal** – ***targeting, adequate concentration, retention***

Anti-acne, anti-perspirants, hair restorers

**Epidermal/ Dermal**

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

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



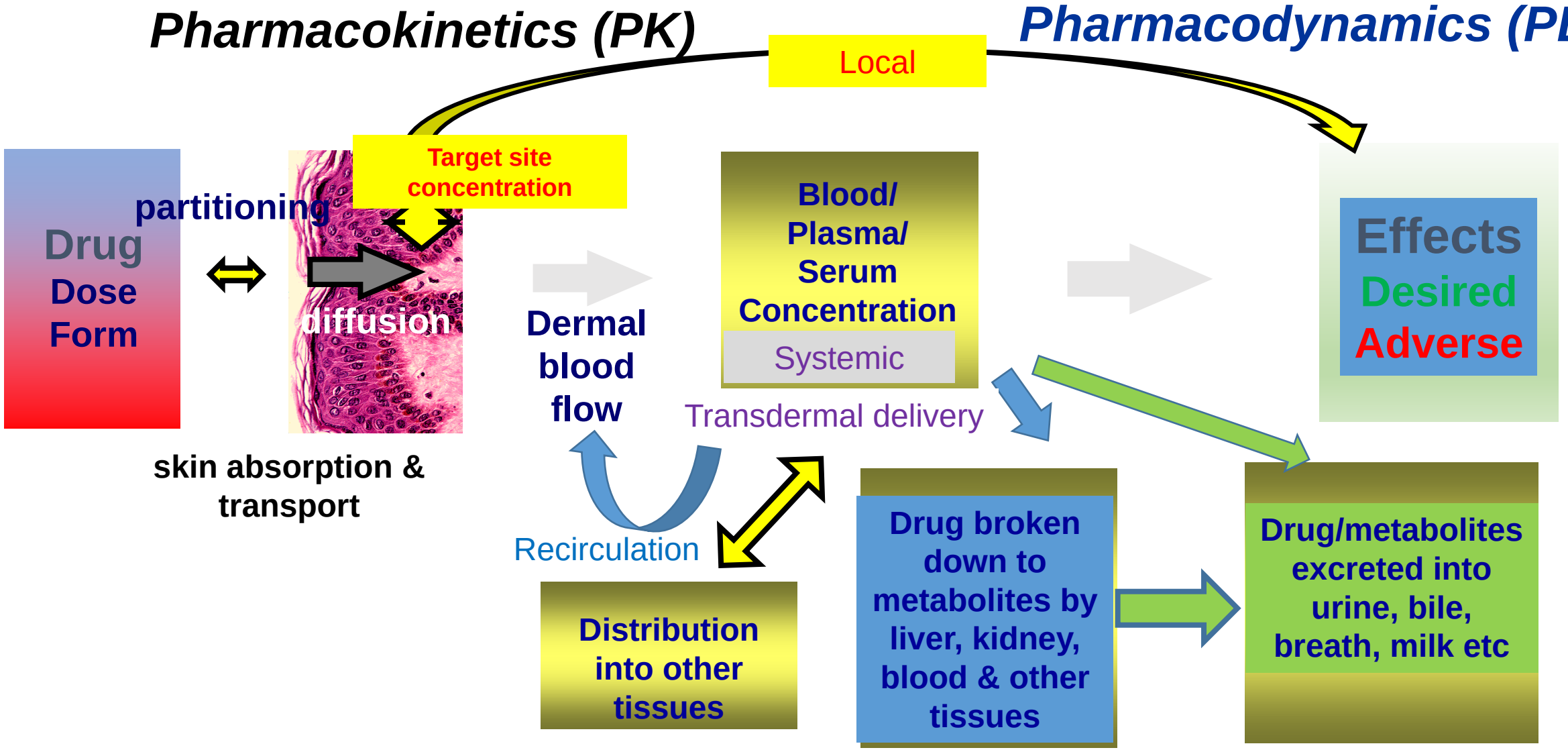
**Systemic**

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

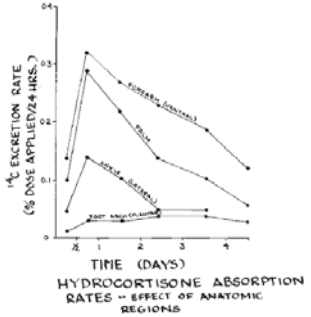
**Deep Tissue** – ***effective concentration to modulate muscle inflammation***

Analgesics anti-inflammatories

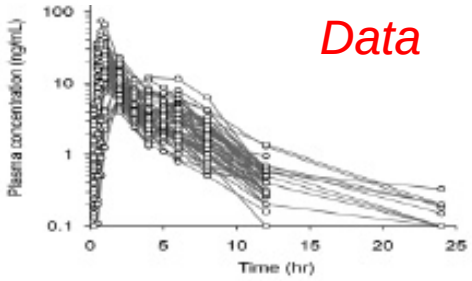
# Framework for mathematical modelling in skin absorption & transport



# An over-riding considering in assessing whether we can achieve targeted delivery is appropriate modelling




- Currently three data driven approaches:
  - 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 & 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 – the middle out approach.**
- In doing applying these models, we need to keep in mind an old saying that really underpins our work:
  - *It is better to be approximately right than absolutely wrong – Brian Barry*



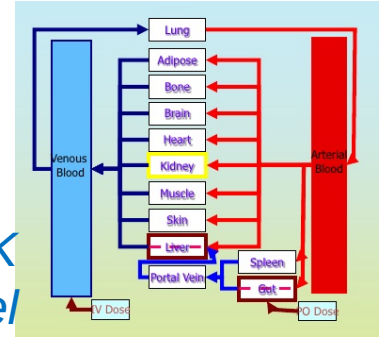

*Data*

Assume no model or use simple PK compartment

**Analyse**

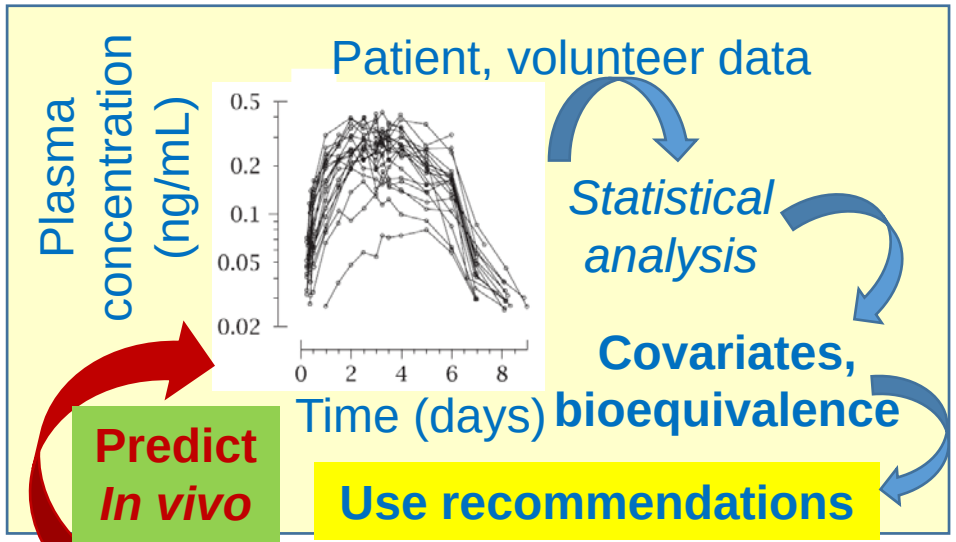
**Predict**

Convolute with skin PK model




*PBPK Model*

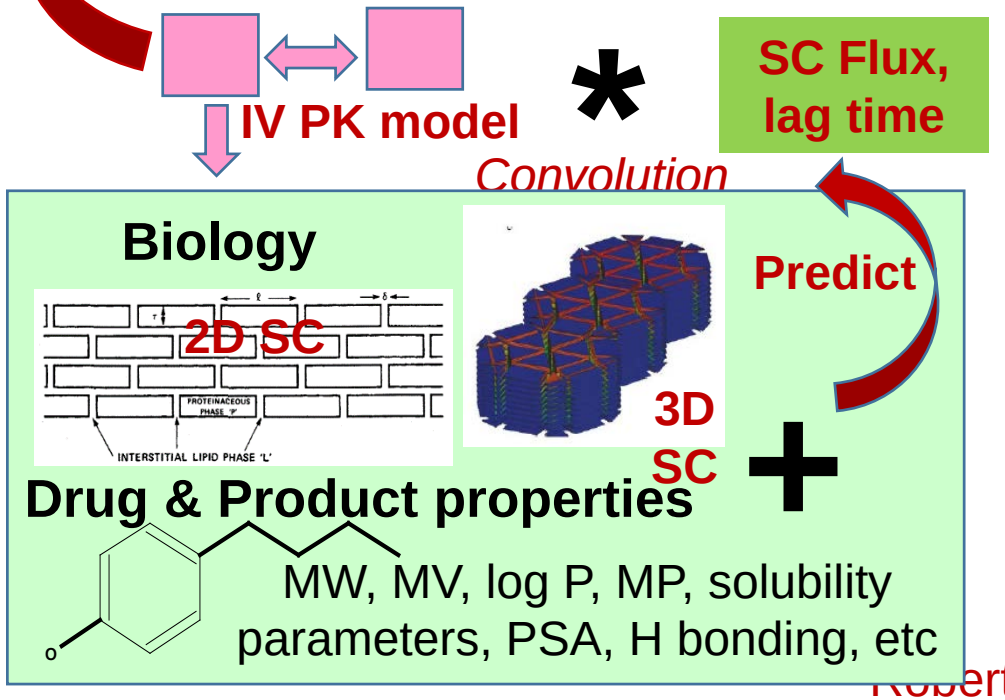
# Top-down & bottom up approaches




## 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.

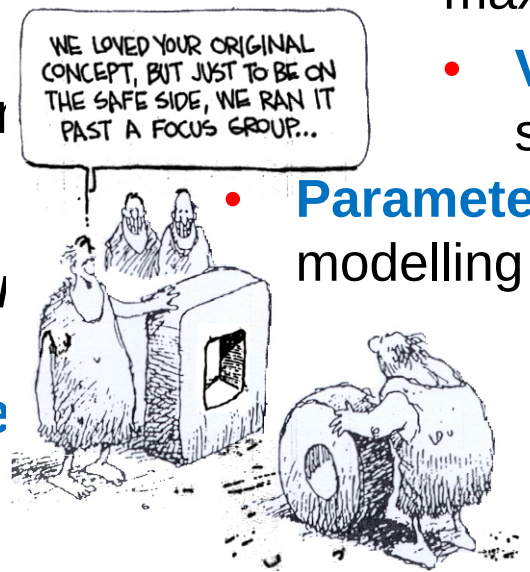
# My thoughts on advantages & dangers in modelling skin absorption

## Advantages

- ✓ 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

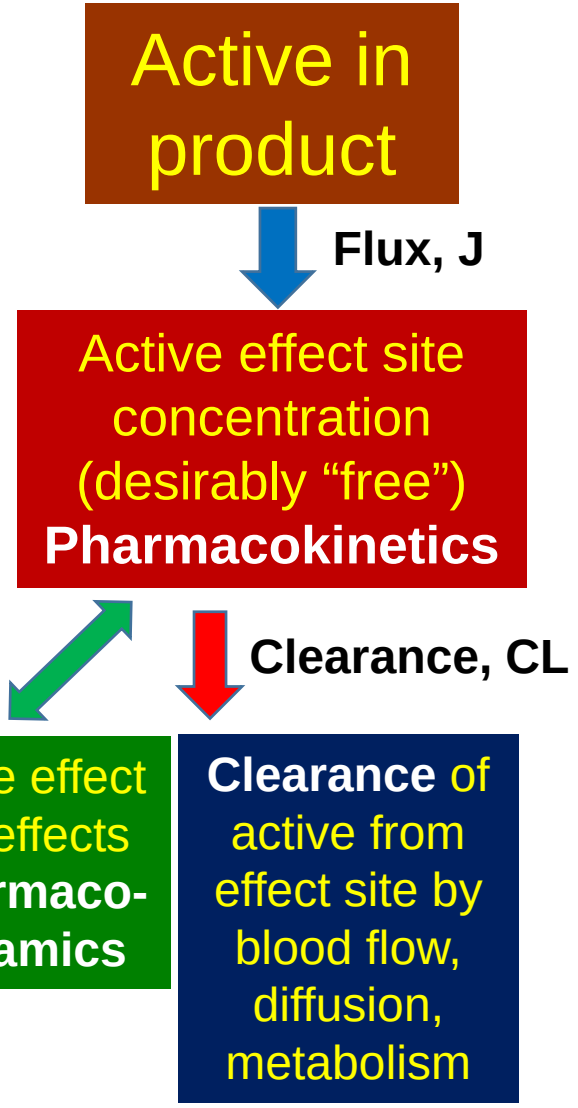



- **Variability** – in skin type, disease, study design, environment, genetics
- **Parameter uncertainty** (experimental, modelling & assumption errors) – Bayesian best!
- **Extrapolating beyond** data,
- **Group think –** permeability coefficients, normal SC, lipid pathway, transcellular pathway etc

# 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

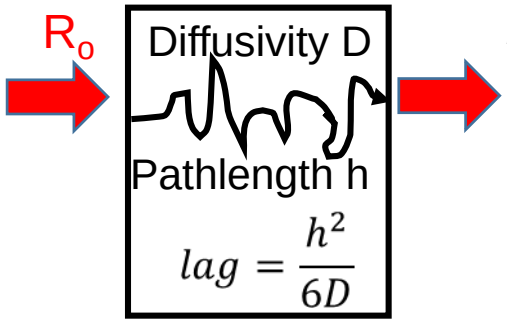
$$Steady\ state\ concentration\ at\ a\ given\ site\ C_{ss} = \frac{Rate\ of\ delivery\ to\ that\ site\ (flux)}{Clearance\ from\ that\ site\ (CL)}$$



# Additional general mathematical modelling (PKPD) principles applying to topical & transdermal product delivery

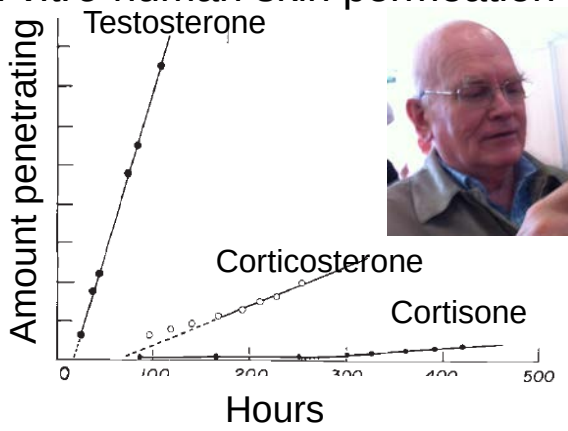
- There is a **lag time** for drugs diffusing across the quite effective SC barrier
- Usually the absorption rate of a drug is faster than its elimination


*Absorption* *Clearance*



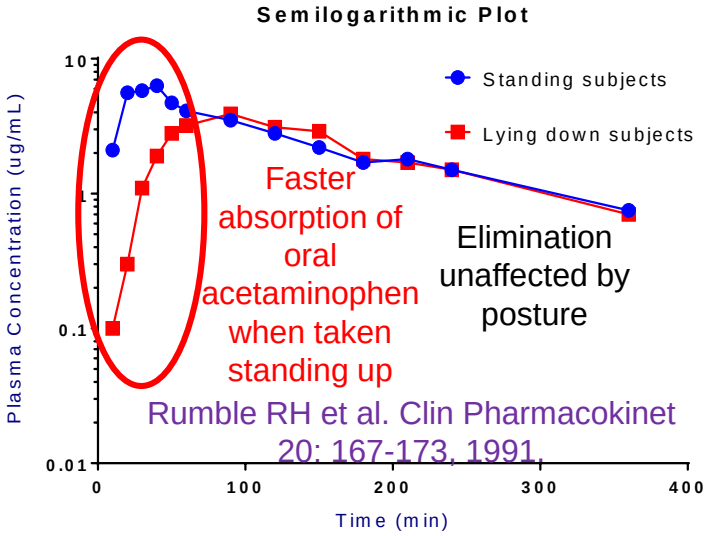

*Scheuplein RJ et al J Invest Derm 52(1): 63-70, 1969*

*In vitro* human skin permeation

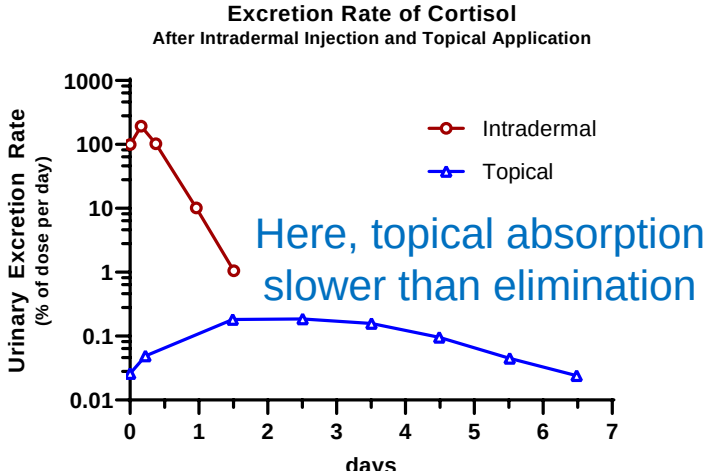





- In contrast, absorption across the skin is usually slower than its elimination from the body – the so-called **flip-flop effect**!




Rumble RH et al. Clin Pharmacokinet 20: 167-173, 1991.




*Riegelman S. Clin Pharm Ther 16: 873- 883, 1974*

# Transdermal delivery

Steady state plasma drug concentrations can be described by a simple input – elimination model

Drug in transdermal patch → Plasma concentration → Drug eliminated as metabolites or in urine

*Rate (t) & in simplest case constant rate $R_o$ after a lag time;*

*Clearance CL*

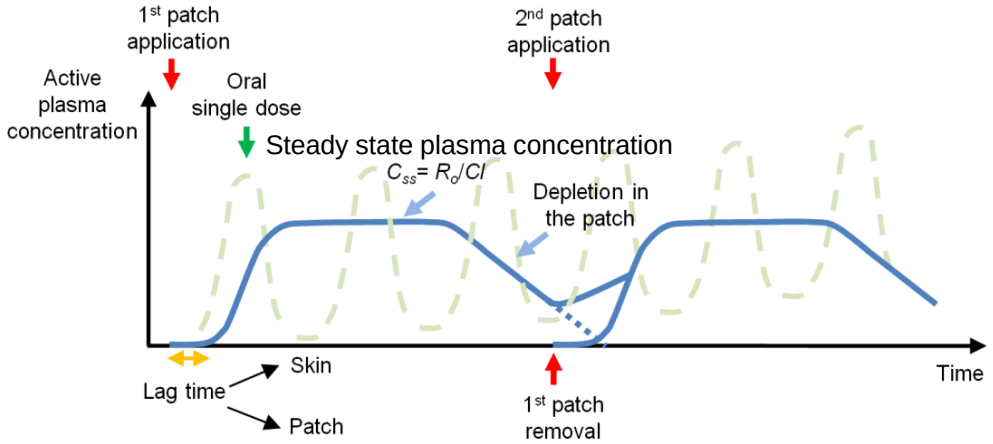
$$\text{In multiple dosing, } R_o = \frac{\text{Dose delivered per patch}}{\text{Dose interval between patches, } \tau}$$

**Transdermal products popular as:**

- Avoid first pass, plasma level fluctuations & gastric distress associated with some oral products
- Are easily removed should there be any toxicity
- In some cases, cause systemic toxicity

As the target steady state plasma concentration $C_{ss}$ to be effective and safe is defined by: $C_{ss} = \frac{R_o}{CL}$

**The desired transdermal delivery rate, $R_o = CL.C_{ss}$**



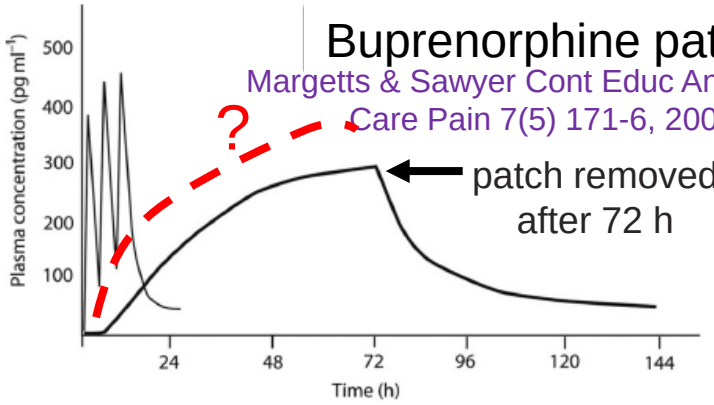

Pastore et al BJP 172(9):2179-209, 2015

**Actives must be**

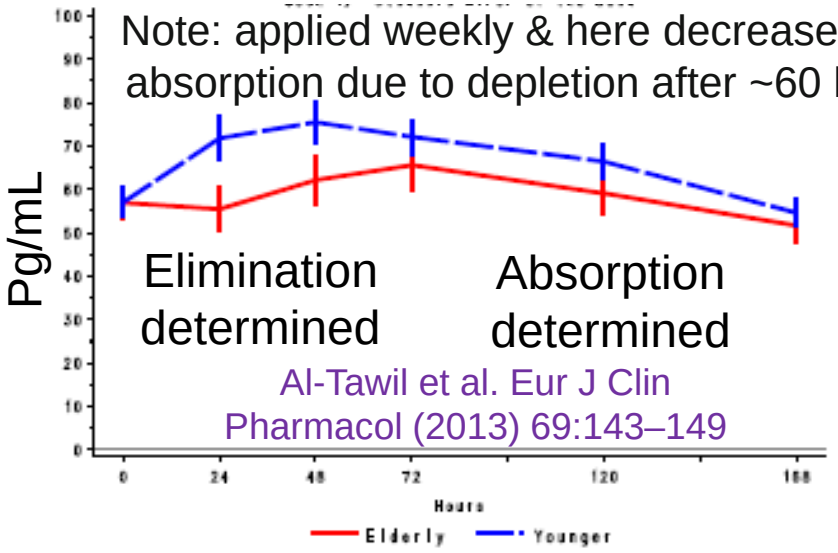
- Potent
- Have an adequate skin absorption rate ( the upper rate defining skin reactions)
- Not be cleared too rapidly

Note: more complex model needed to describe full profile

# Buprenorphine patch PKPD mathematical modelling



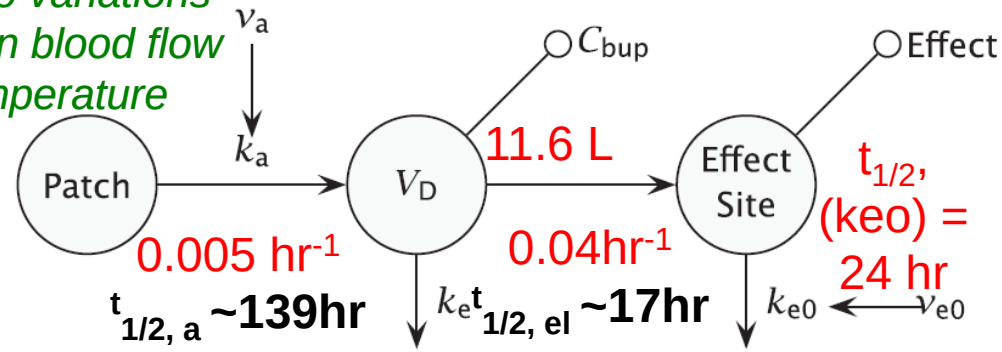

**Transdermal buprenorphine patch plasma levels (mean ± se) in elderly & young**




## Flip-flop kinetics

- At first glance, the sublingual looks like fast absorption & fast elimination
- So that the patch profile reflects a short lag and then patch depletion over time.
- But, look more closely – is there accumulation arising from a long elimination half life?
- Buprenorphine has a half life ($t_{0.5}$) of 24 - 48hr in various patients.
- Its patch should take 3.3 half lives (i.e. 80 – 158 h) to get to 90% $C_{ss}$ with constant $R_o$

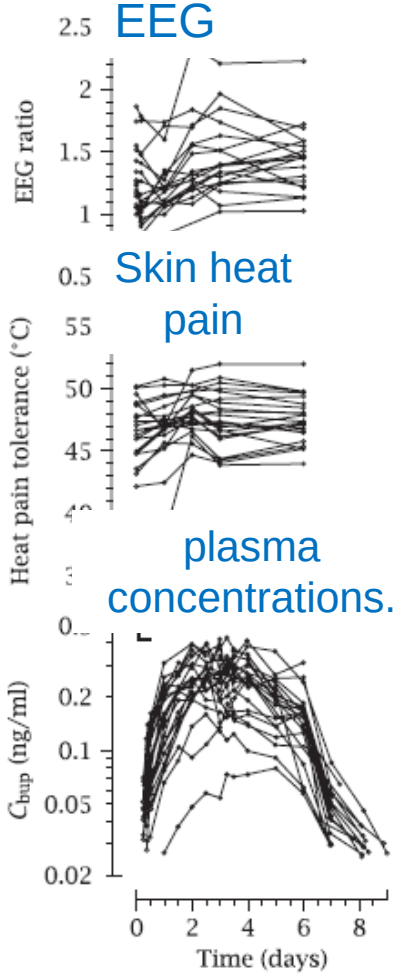
*Process noise due to variations in skin blood flow & temperature*




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

## PKPD modelling of 144-h (6-day application) data

Individual data



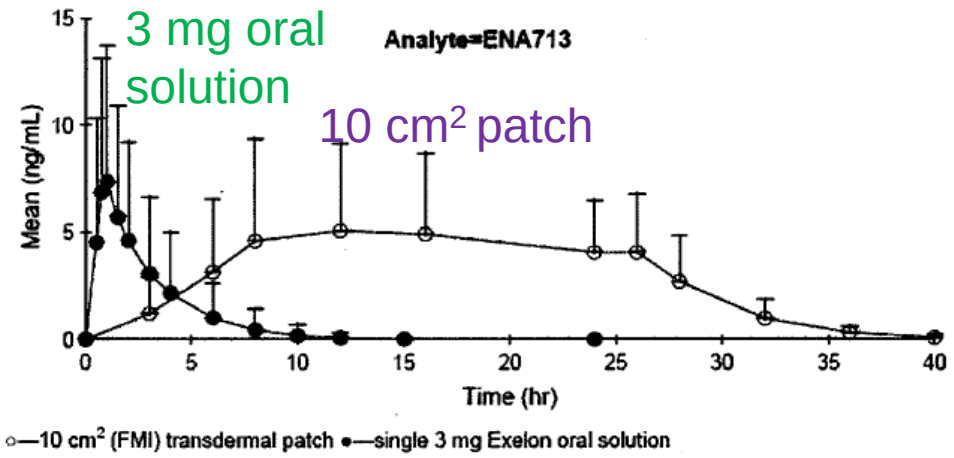

Olesen et al *Anesth Analg* 2015;**121**:1165–75

# As another example, let us consider the PKPD of rivastigmine approved by the FDA

## 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

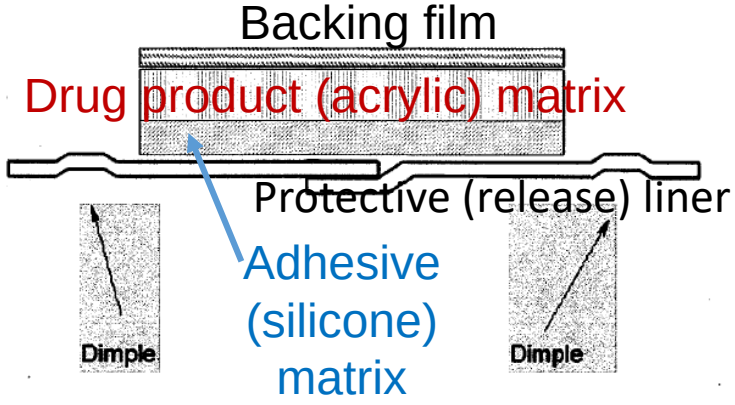
**Figure: Rivastigmine plasma concentrations (mean +/- SD) following single dermal (o.d.) patch application (open circles)**




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

*Studies in 440 volunteers & 1374 Alzheimer's patients*

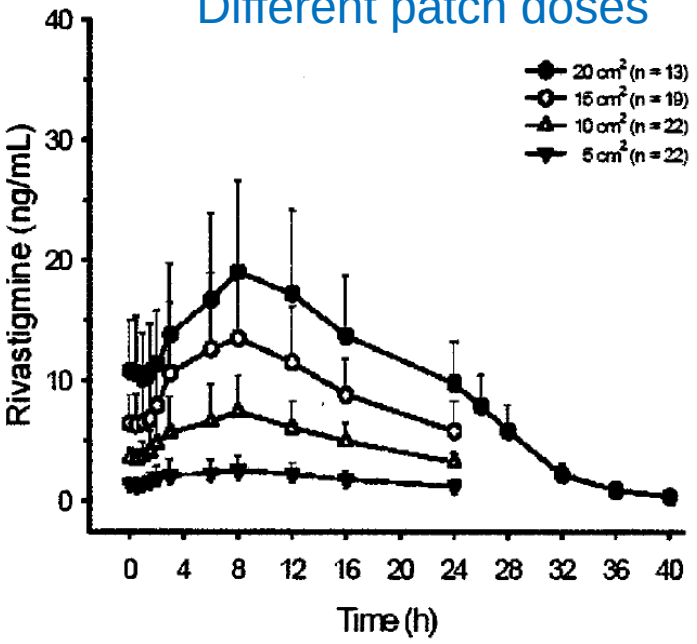
Measure $AUC_{0-24}$; Cmax; tmax; $t_{1/2}$; V/F; CL/F for different doses & with BW adjustment




Rivastigimine transdermal human 022083s000_ClinPharmR_P1

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

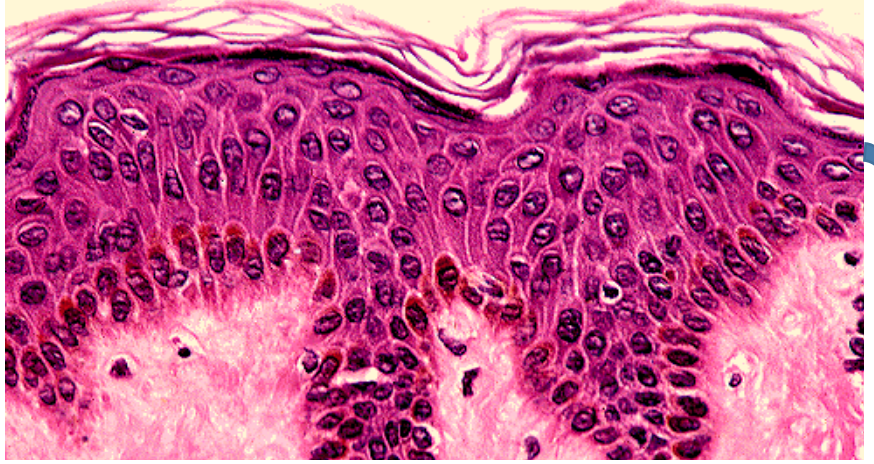
Different patch doses




**Conclusion: No dose adjustment needed except when titrating low body weight patients with patch doses >10cm²**

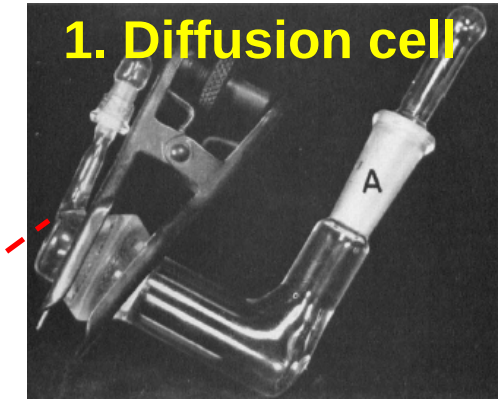
## Population PK analyses of steady state plasma rivastigmine concentrations after patch application

- 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



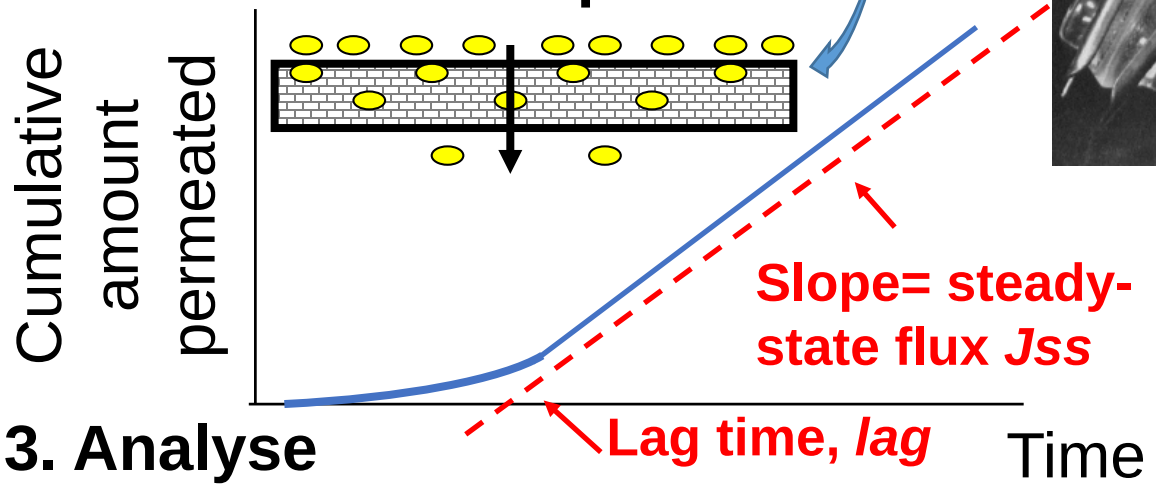
Stratum corneum, SC, is main skin barrier

# Prediction of human skin permeability of topical & transdermal products using *in vitro* permeation tests (*IVPT*)




Focus on deriving permeability constant, *kp*, *Scheuplein Skin Pharmacol Physiol 2013;26:199–212*

**2. Collect data and plot**




**3. Analyse**

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

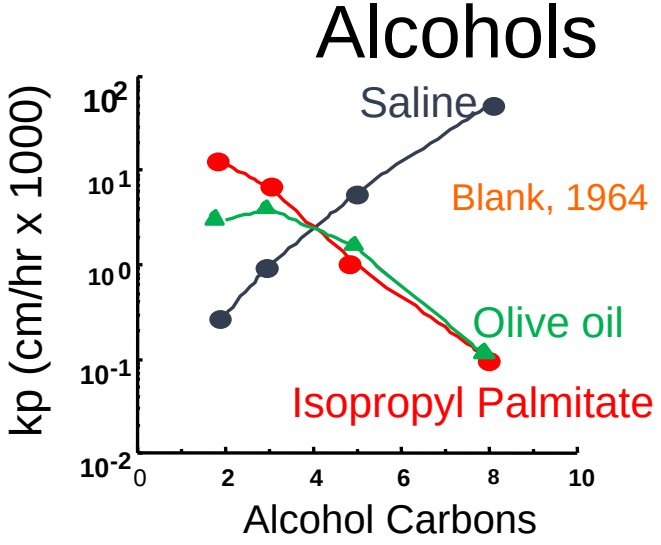
- ✓ Stratum corneum rate limiting
- ✓ Steady state conditions
- ✓ Infinite sink
- ✓ Normally, an aqueous vehicle

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!**

# Personally, I think that kp is the wrong paradigm to be using in describing the delivery of actives from products?

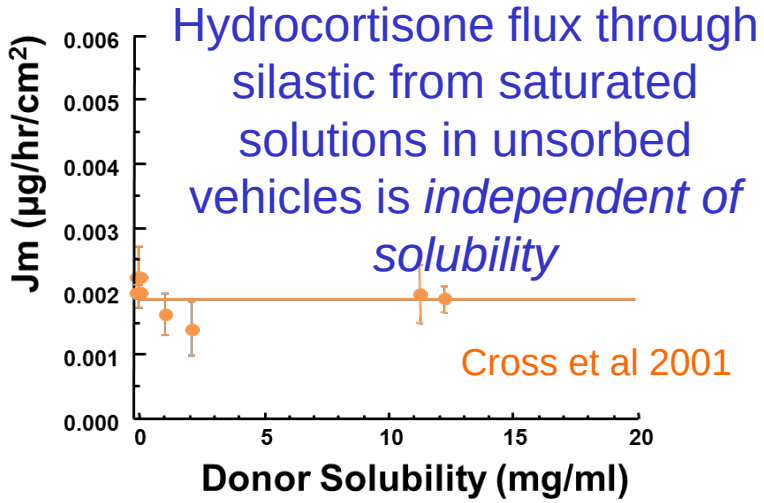
**kp paradigm**




## Impact of formulations 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.

**Max flux paradigm**

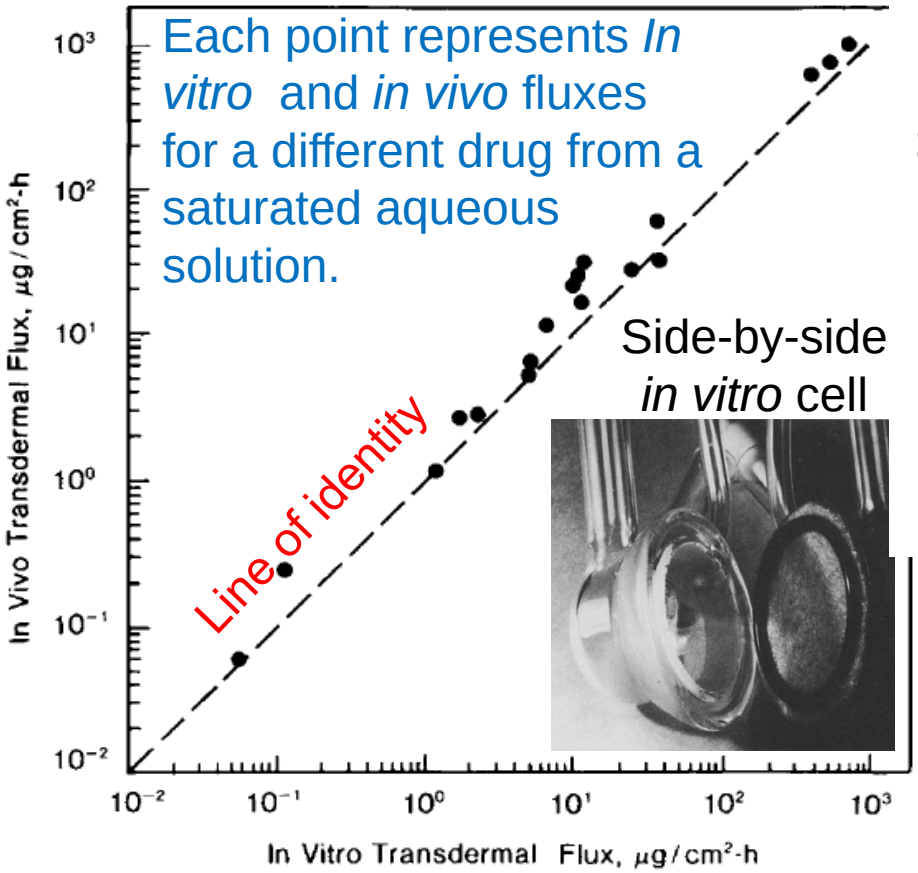



## So, what is the alternative paradigm?

- 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.
- Accordingly, an active should have the same flux for a given fractional solubility in all vehicles, providing that vehicle does not affect the skin & behaves ideally.
- Note: $k_p$ = Saturated flux/ solubility

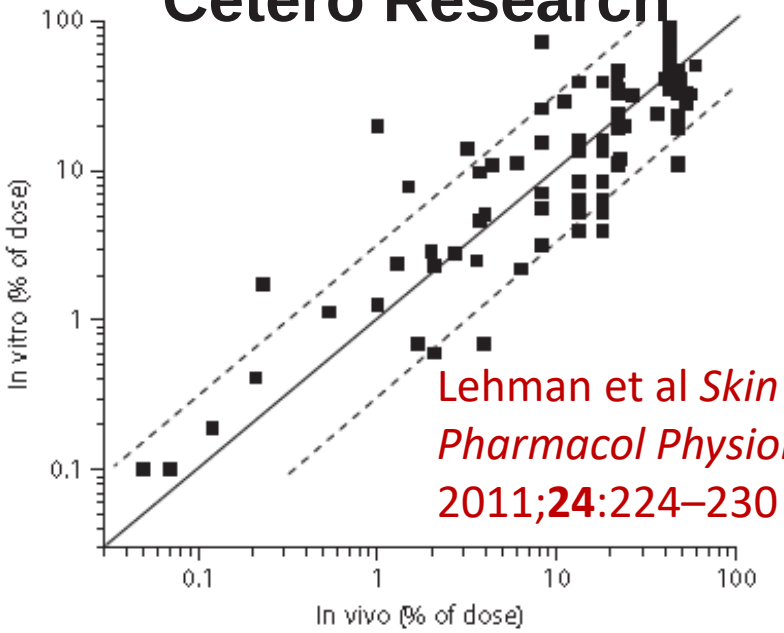
# Principles well established that we can use *IVPT* data to predict *in vivo* relationships - but with issues!

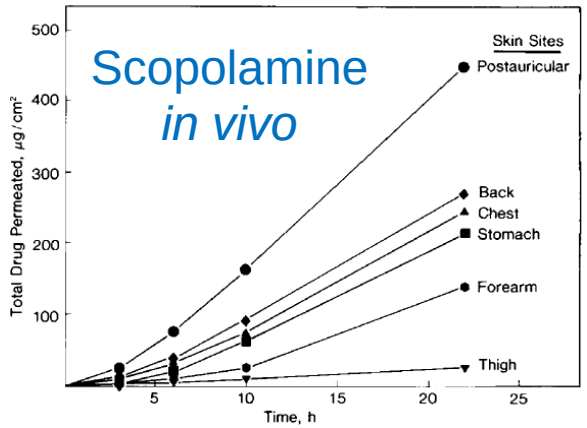
## Early work by ALZA




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

## Cetero Research



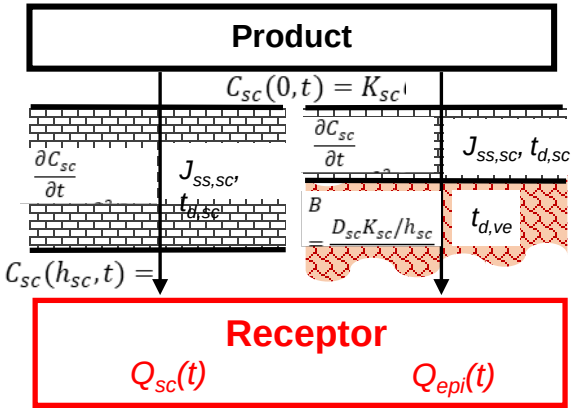




- Lehman *IVIV* 20X difference reduced to <2X with harmonised sets, notably in body sites & product content
- Point-to-point (Level A) with internal & external validation preferred – using *in silico* for skin temperature, metabolism & blood flow, desquamation effects

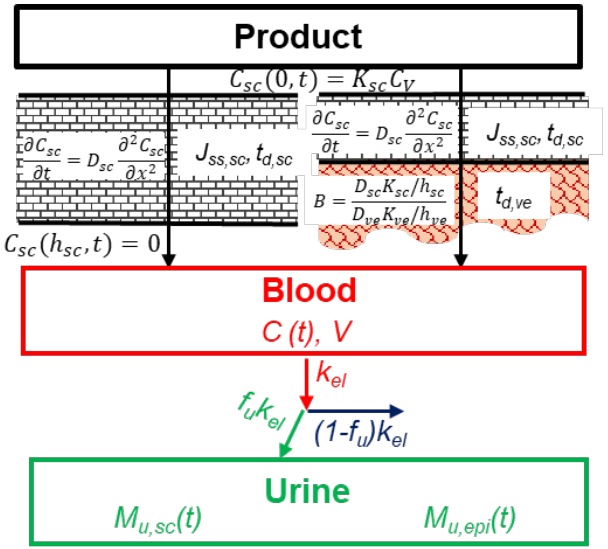
www.fda.gov/downloads/drugs/guidances/ucm070239.pdf

# Some examples of PBPK modelling to successfully predict *in vivo* pharmacokinetic profiles from *in vitro* permeation tests (*IVPT*)

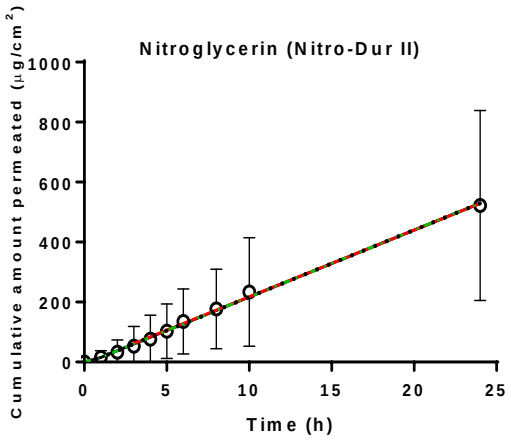
**A. SC and epidermal *IVPT* diffusion model**

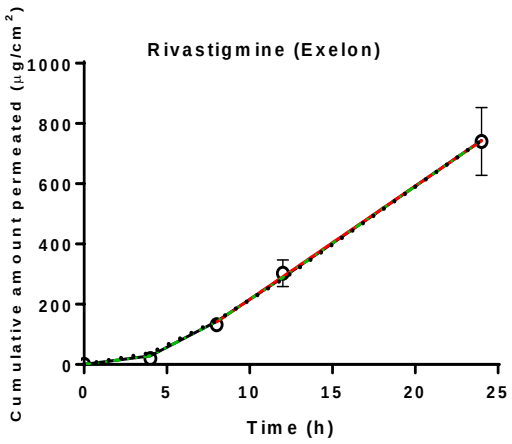



**B. SC and epidermal *in vivo* diffusion model**

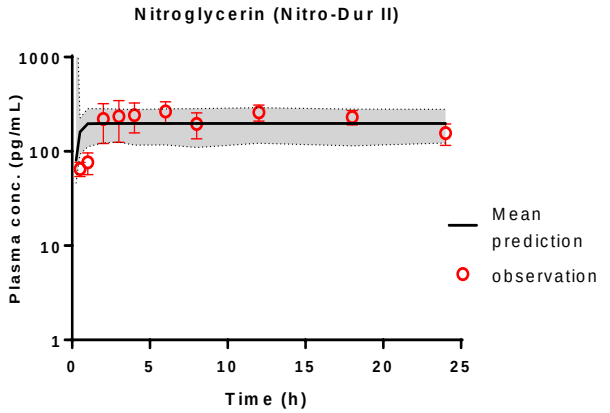


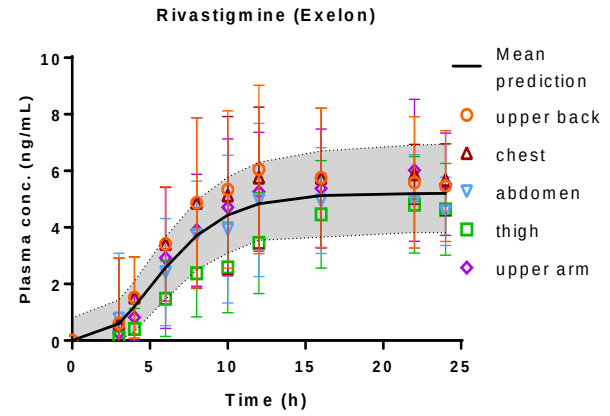

**A. *In vitro* skin permeation test (*IVPT*)**



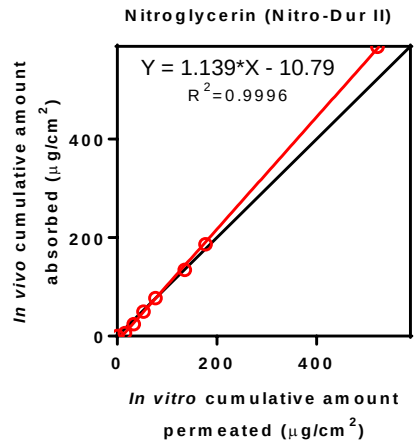



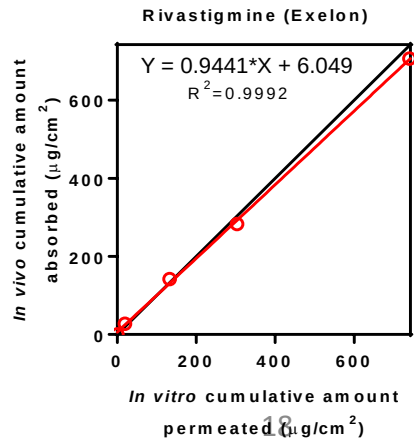

**B. 1 stage *IVIVR*,** *IVPT* convoluted with intravenous pharmacokinetics to predict plasma levels for dose form.




**C. 2 stage *IVIVR*,** 1. Deconvolution of plasma data to estimate absorption profiles that are 2. Compared with *IVPT* data.



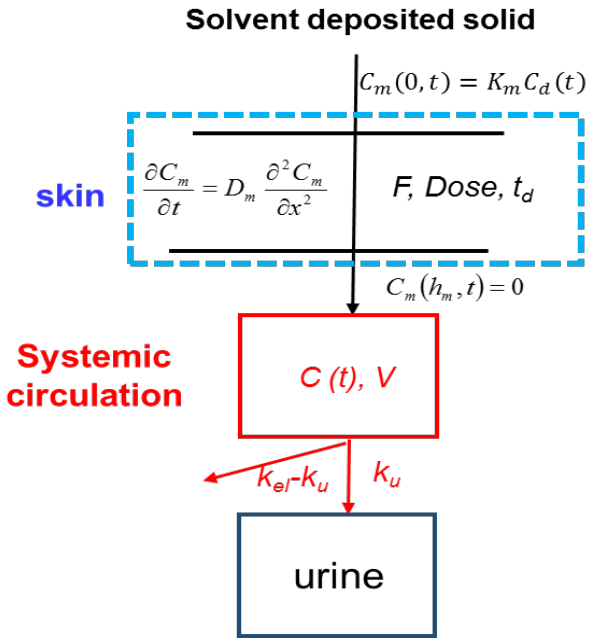



# Case study: In practice, we can also model *in vivo* PBPK of topical products applied as a finite dose. Consider the urinary excretion data for 3 drugs in 3 dose forms, courtesy of Tom Franz

## Experimental

- Radiolabelled compounds ($^{14}$C-benzoic acid, $^{14}$C-caffeine, $^{14}$C-testosterone) were formulated in vehicles: petrolatum, ethylene glycol gel, and water gel
- Formulations were applied to an area of 20-60 cm$^2$ using a flat metal spatula to spread a layer of uniform thickness on abdomen.
- Urine was collected throughout the course of experiment until background levels of radioactivity were approached

***In vivo PBPK* model- Finite dose application, SC diffusion to systemic circulation & excretion into urine**




- **Modelling.** 2-stage analysis using a convolution of a finite dose SC diffusion model for skin absorption with a single exponential intravenous disposition phase using Scientist (Micromath) (analysing individual subject data first)

$$\widehat{M_u}(s) = \frac{k_u}{s(s+k_{el})} \frac{F \times dose}{\cosh\sqrt{st_d}}$$

- $k_{el}$ – elimination rate constant (2.37, 0.075, 0.314 h$^{-1}$ for benzoic acid, caffeine and testosterone, respectively) – obtained from literature data after intravenous dosing
- $k_u$ – urinary elimination rate constant (2.27, 0.055, 0.27 h$^{-1}$ for benzoic acid, caffeine and testosterone, respectively) – obtained from literature data after intravenous dosing
- $F$ – bioavailability (%) (model parameter)
- $t_d$ – diffusion time (h) (model parameter)

# Urinary excretion of benzoic acid, caffeine & testosterone for 3 topical dose forms

## First part of 2- stage *PBPK* analysis using diffusion model

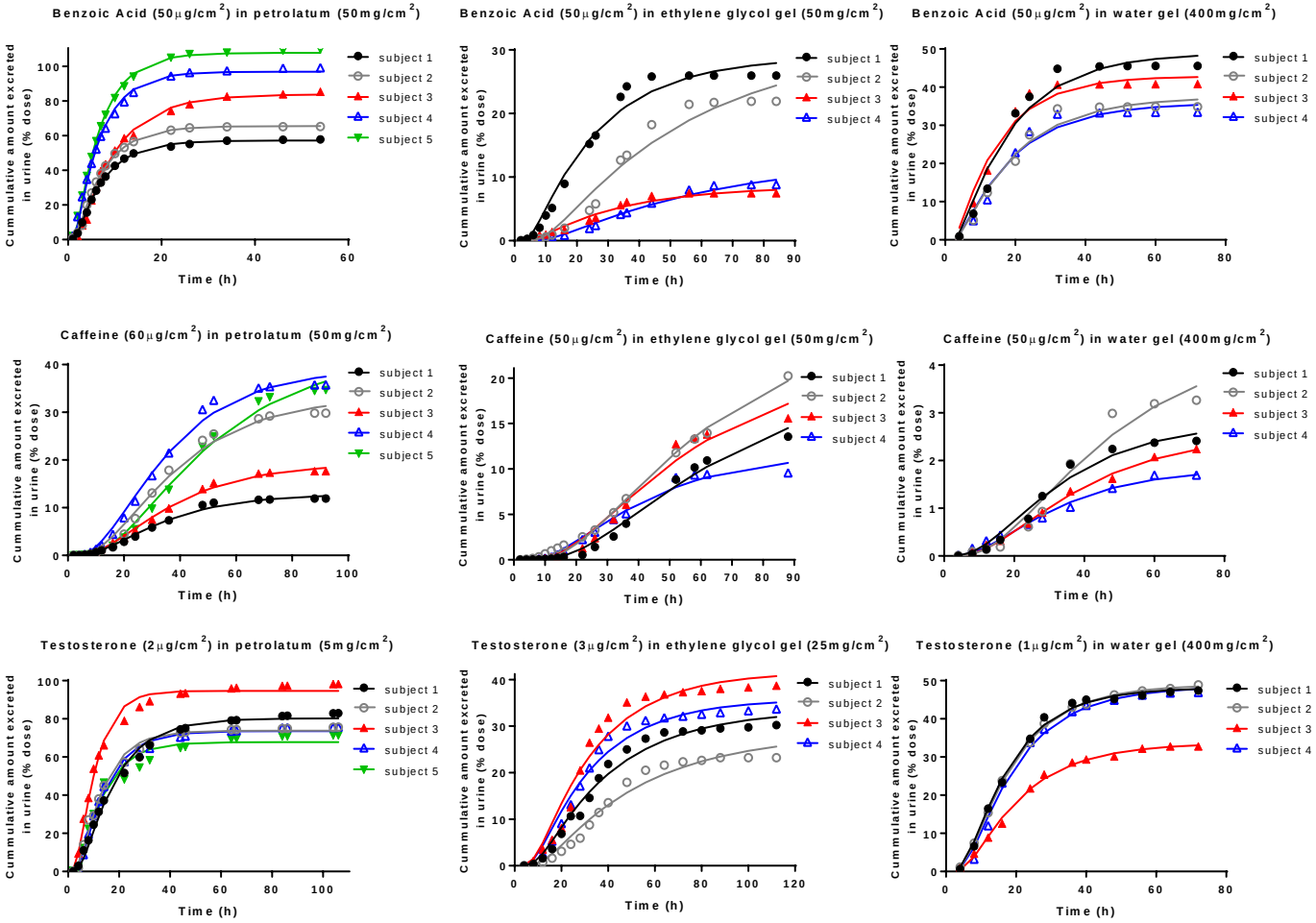
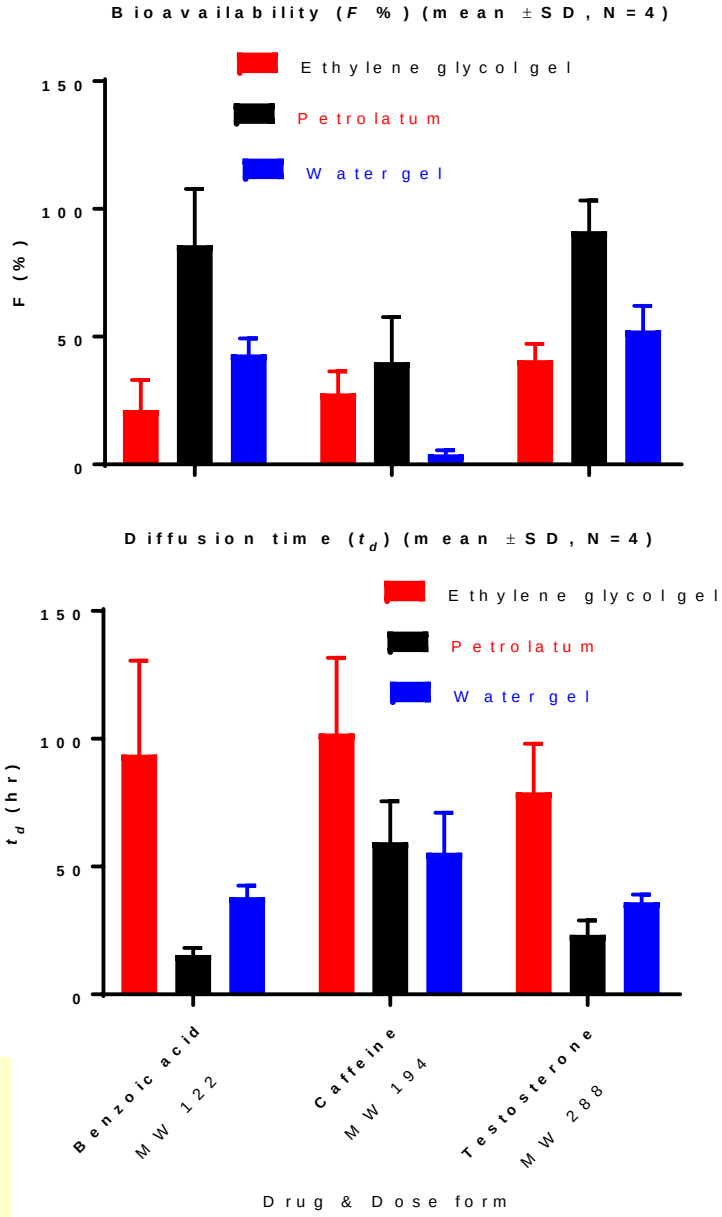
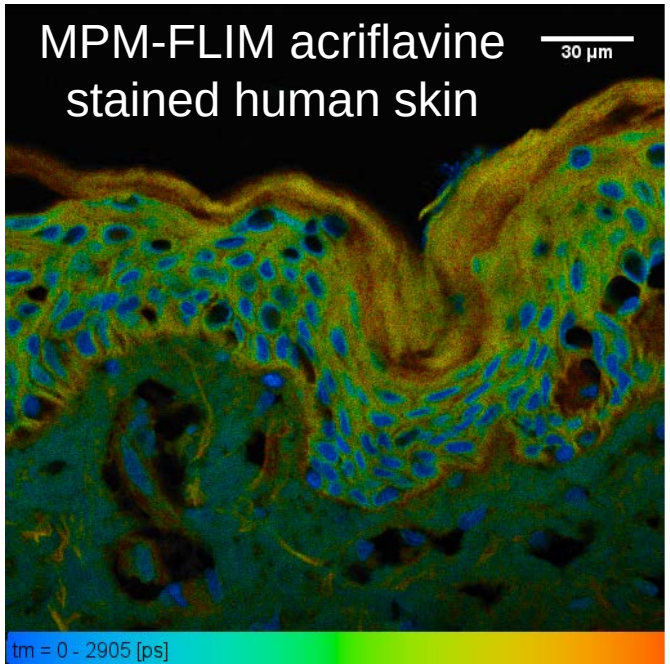



Fig 1. Individual fitting curves of cumulative amount excreted into urine versus time profiles. Symbols represent experimental data and lines represent fitting curves.



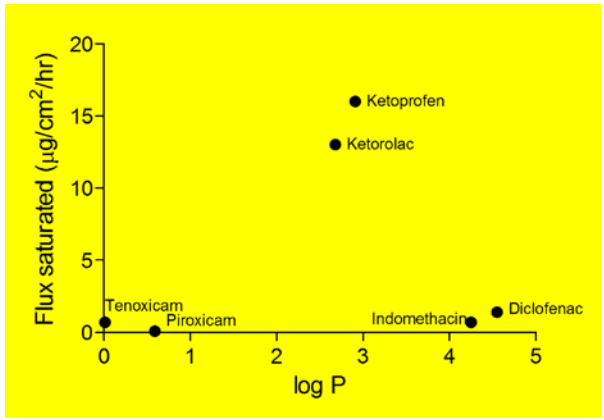

**Take home message:** Petrolatum yields higher bioavailability, F, than other products but with slow diffusion time, i.e. long lag. Ethylene glycol increases diffusion time with poor *F* %. Suspect *F* % results reflect "like-dissolves-like"

# I now want to turn to the mathematical modelling of topical products

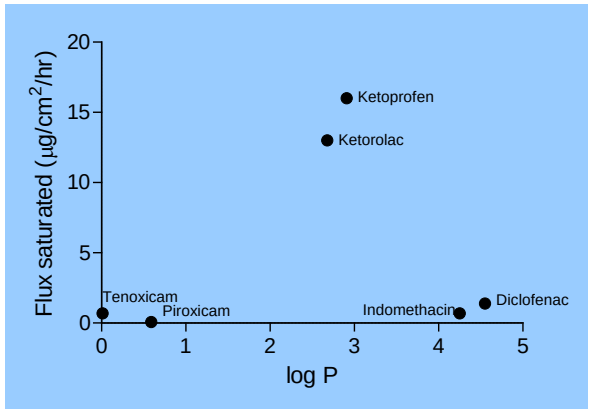



- General principles – we need to aim for a target site of action concentration $C_{ss,L}$ at a local site, e.g. in melanosomes, Langerhan cells, basal keratinocytes, stem cells, sebaceous glands, papillae etc
- If efficacy is not known, it has to be defined by an *in vitro* response – concentration relationships & known absorption rates

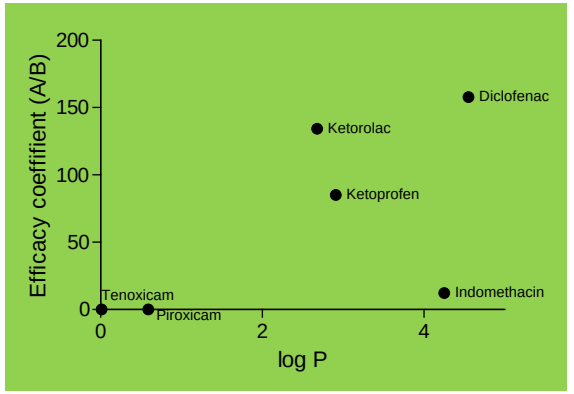
***In vitro* anti-inflammatory minimum inhibitory concentrations for NSAIDs**




**Observed skin penetration rates**




**Efficacy coefficient = penetration X potency**




Jepps et al ADDR 65 (2013) 152–168

# But, model is limited in that it ignores clearance from the putative target site

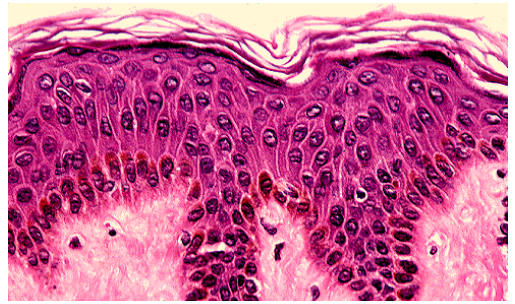
## The concentration at this local site $C_{ss,L}$ is dependent on both rate of delivery to the site & $CL_L$

$$C_{ss,L} \sim \frac{Rate\ in.A}{CL_L}$$

For completeness, this is an approximation and only applies when the clearance is much greater than any back diffusion from the site. The full equation

- $C_{ss,\mathrm{L}} = \frac{Rate\ in}{\frac{CL_L}{A} + \frac{K_{SC} D_{SC}}{K_{ve} h_{SC}}}$ reduces to this simple equation when the clearance term >>diffusion term.
- At the other extreme of minimal clearance, $C_{ss,L}$ approximate the donor concentration $C_d.K_{ve}$.

Where Rate in= steady state flux per unit area
$CL_L$ is clearance from skin site of action/unit area
$\frac{K_{SC}}{K_{ve}} \frac{D_{SC}}{h_{SC}}$ allows for back partitioning at site when there is poor clearance as would occur with steroid vasoconstriction



In contrast, a similar looking equation applied to systemic blood levels

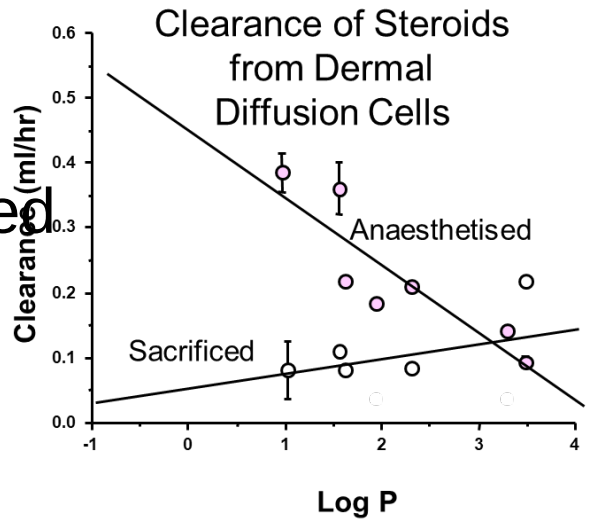
$$C_{ss} \sim \frac{Rate\ in.A}{CL}$$

The difference here is that clearance is mainly due to liver metabolism and renal excretion and the rate in is defined by the slowest process – diffusion across the epidermis (including the SC), which is usually much slower than removal by the dermis

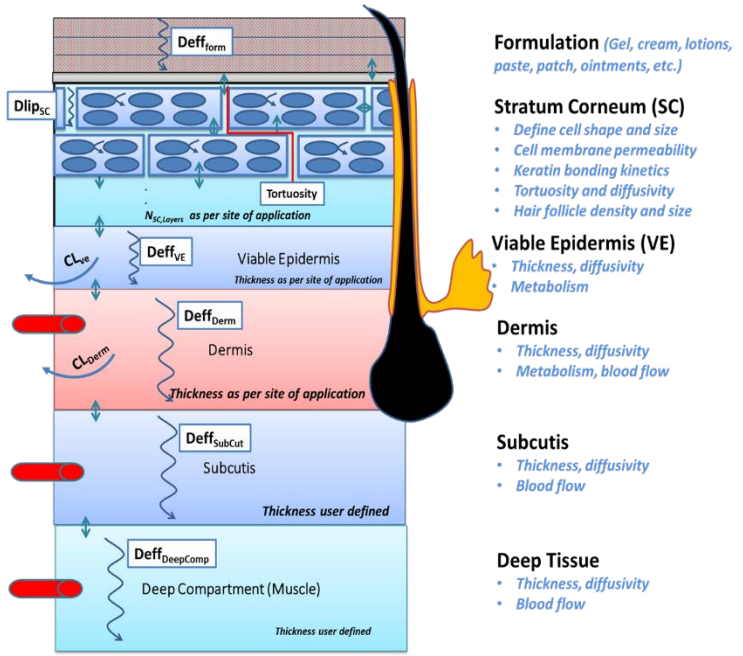
# Generally, we do not have this clearance & we have to estimate it

## Three approaches.

- **Experimentally** measure the loss of a solute injected at the target site or it appearance in the blood over time, e.g. dermal clearance of cortisol Or, use a dermal cell applied to skin where the epidermis has been removed
- **Model the clearance** by combining the transfer across the epidermal-dermal junction, diffusion in the dermis above the papillae, transport across the papillae wall & removal by the blood supply to the systemic circulation based on the physicochemical properties of the solute & related physiology
- **Estimate it** from a knowledge of absorption rate & observed concentrations




*Note that blood flow (probably due to protein binding is a major determinant of steroid clearance)*




**CERTARA Simcyp** MPML MechDermA Model

# We can also estimate $C_{ss,L}$ as an effect response

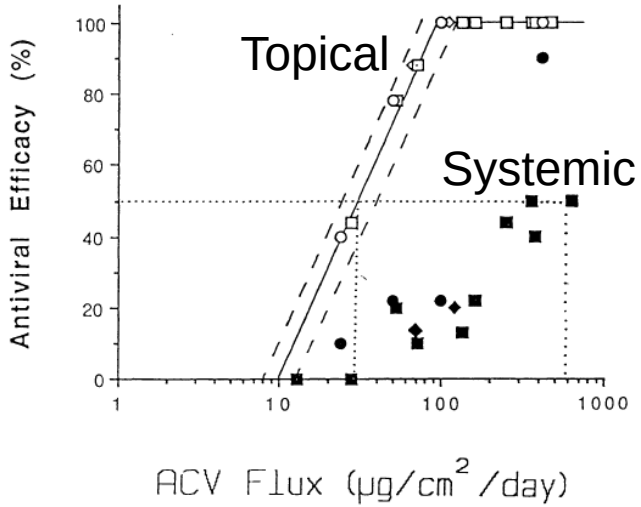
One elegant example on $C_{ss,L}$ is the work of WI Higuchi's group on the use of acyclovir to treat herpes virus 1 infections in an *in vivo* animal model

$$C_{ss,L} \sim \frac{Rate\ in.\ A}{CL_L}$$

They then deduced

$$\text{Topical}_{EC50} \sim \frac{\text{Topical Rate giving 50\% kill}}{in\ vivo \text{ permeability coefficient for sub papillary de}}$$

$$= \frac{30\ \frac{\mu g}{cm^2}/day}{1.4\ x\ 10^{-3} cm/sec} = 0.25 \mu g/mL$$

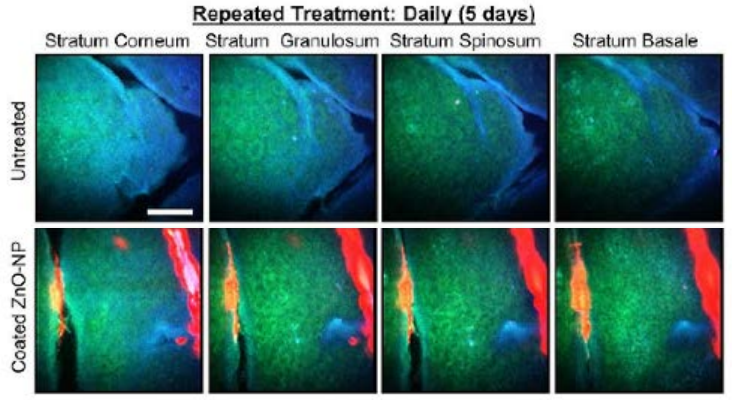



Similar to *in vivo* blood & *in vitro* cell culture efficacies

Imanindis et al Pharm Res 11(7): 1034-41 (1994)

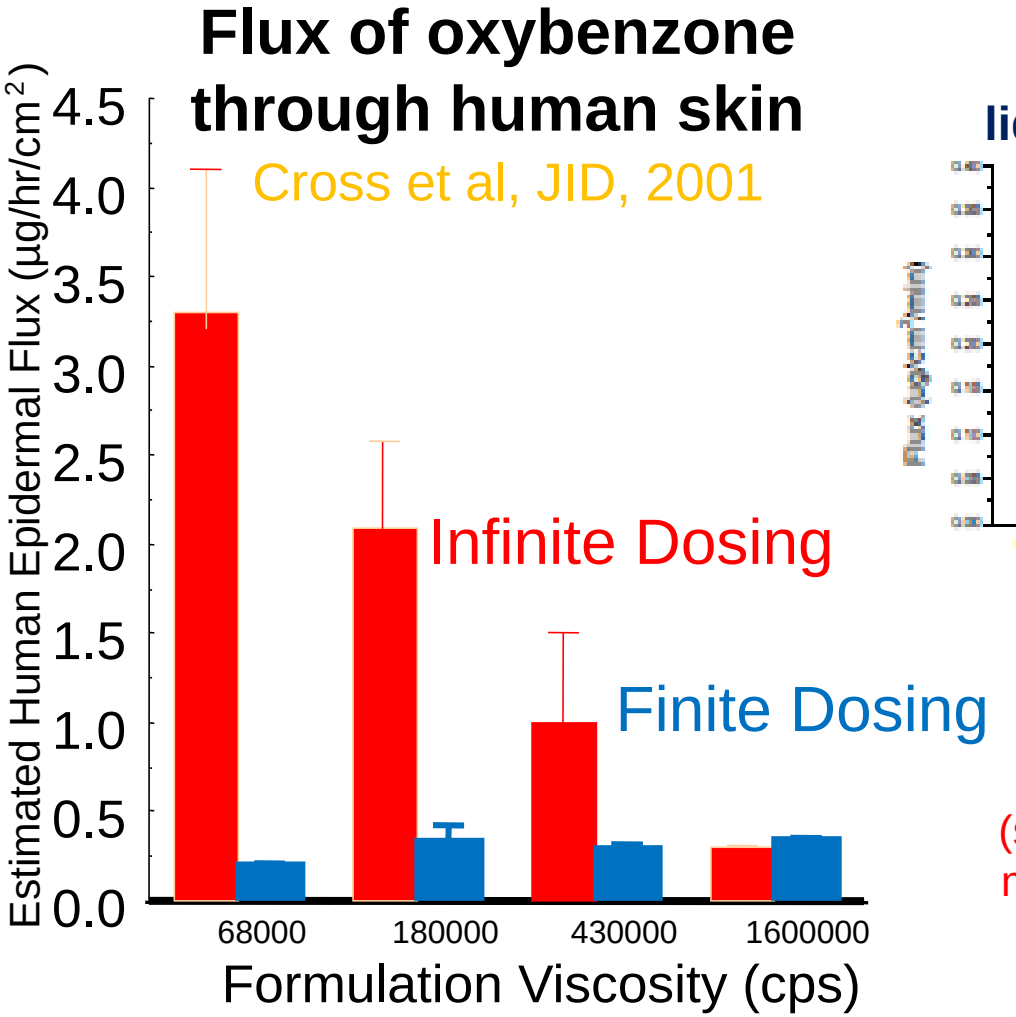
In principle, can then evaluate efficacy of other creams & ointments with this delivery rate

Today, we & others are using changes in individual skin cells' autofluorescence to quantify their response to applied exogenous solutes as we can be imaged *in vivo* non invasively down to about 200 µm below the surface with high resolution. NAD(P)H fluorescence lifetime imaging changes, for instance, define the keratinocyte redox state.

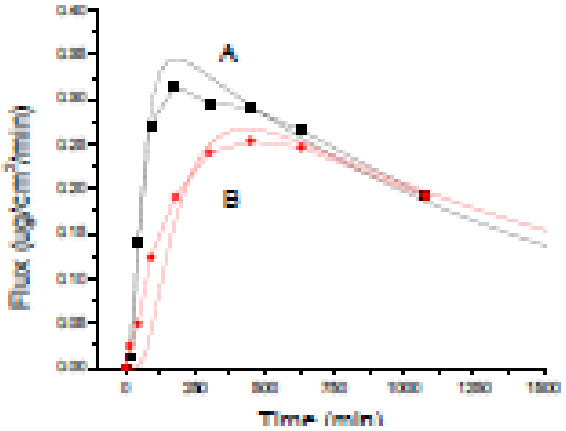


# Let us now return to modelling of the absorption of topical products

- Most of the literature has been concerned with infinite dosing.
- There are major dangers in extrapolating to finite dosing, which is how products are applied.
- Lehman (2014) points out that infinite dose study design has proven problematic as the *stratum corneum* is often damaged, saturated, or modified by the continuous exposure to the dosing vehicle.
- He has also shown that when the vehicle is relatively inert, IVPT finite dose modelling is relatively straightforward.




**Finite dosing of lidocaine products**




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

# Modelling the complexities of formulation changes after application of finite doses

## Consider what happens with Zovirax cream

**Complex vehicle**

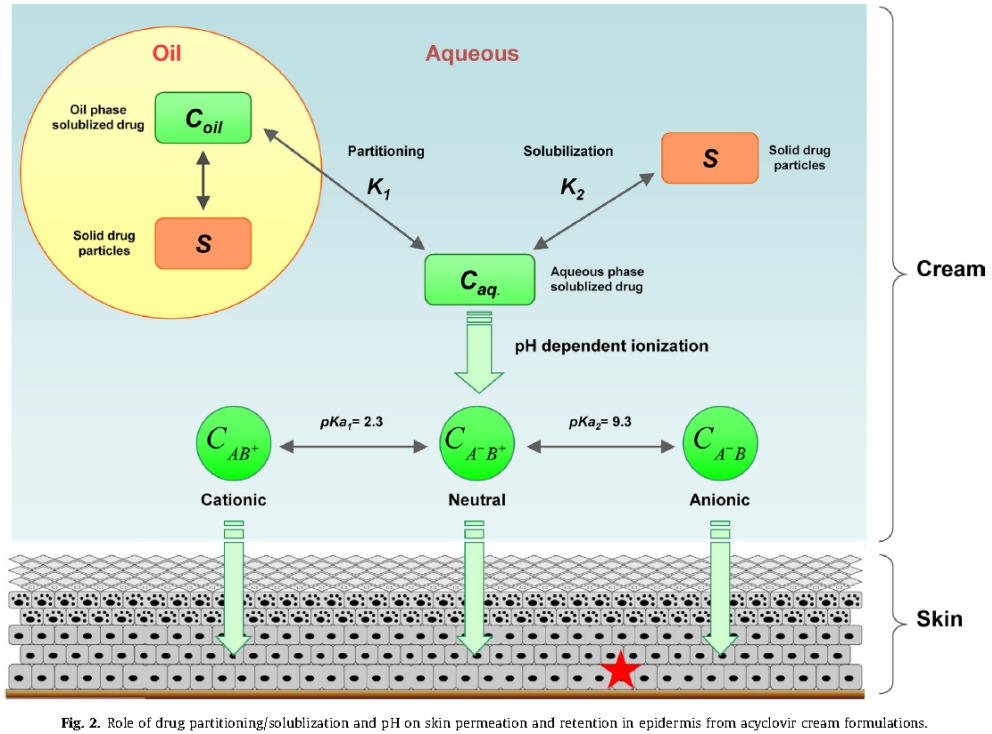
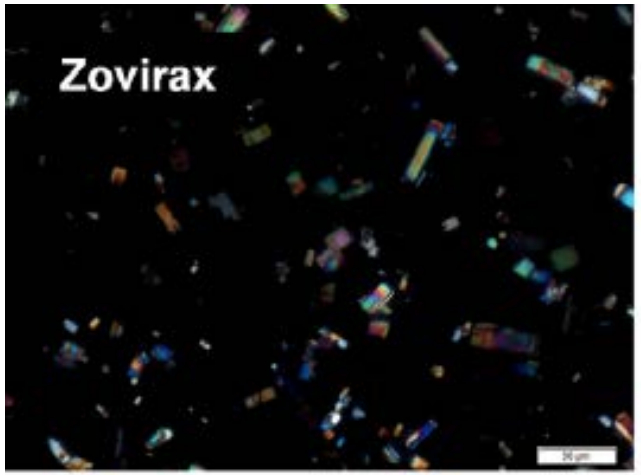
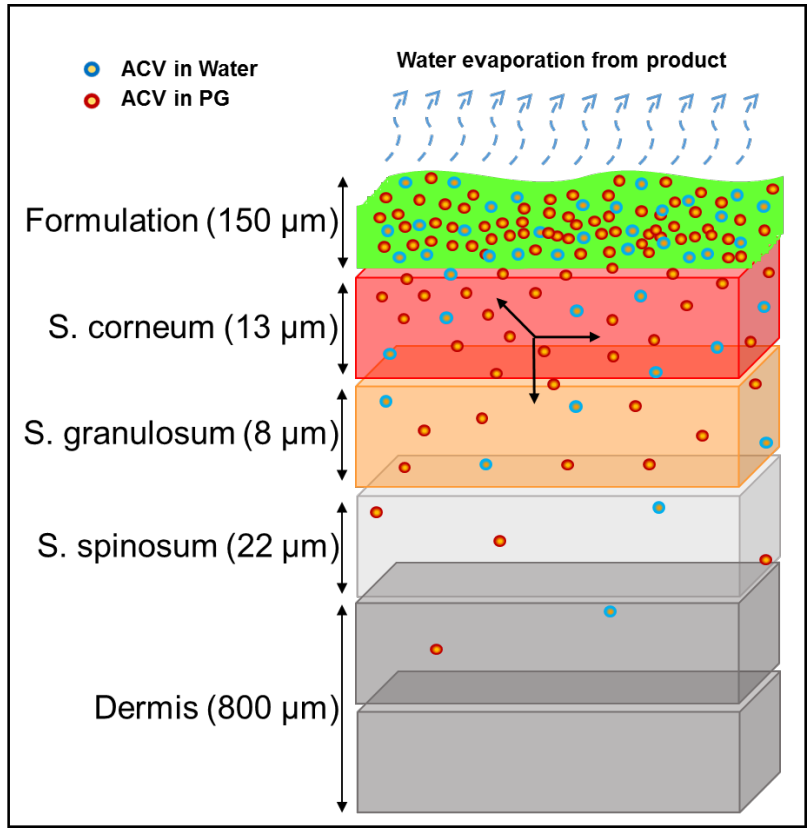



Fig. 2. Role of drug partitioning/solublization and pH on skin permeation and retention in epidermis from acyclovir cream formulations.



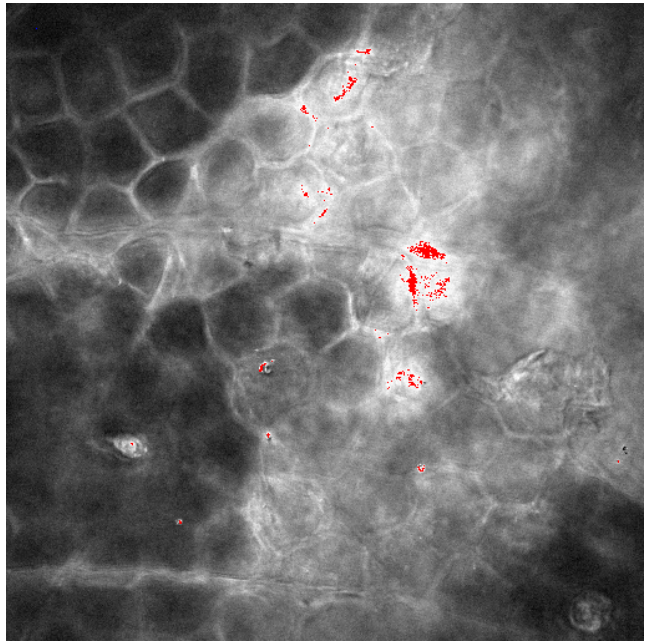

Polarized light microscopy images of various acyclovir cream formulations (200 magnification, bar= 50 mm).

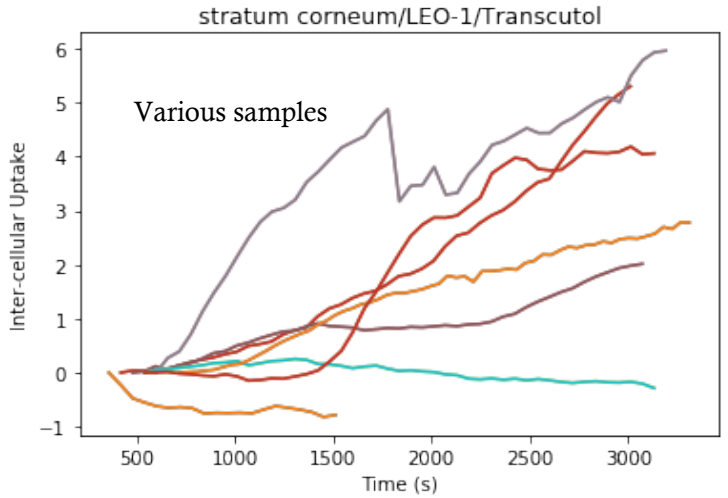


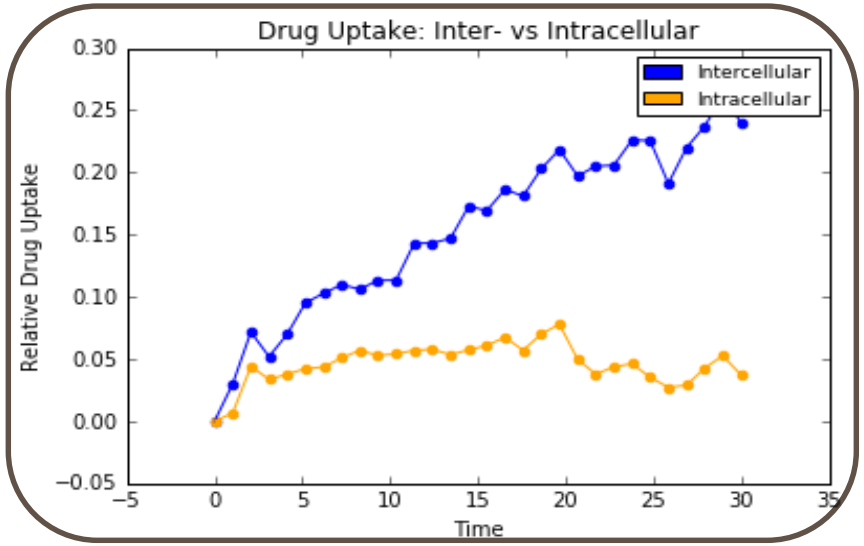

Krishnaiah et al IJP 475 (2014) 110–122

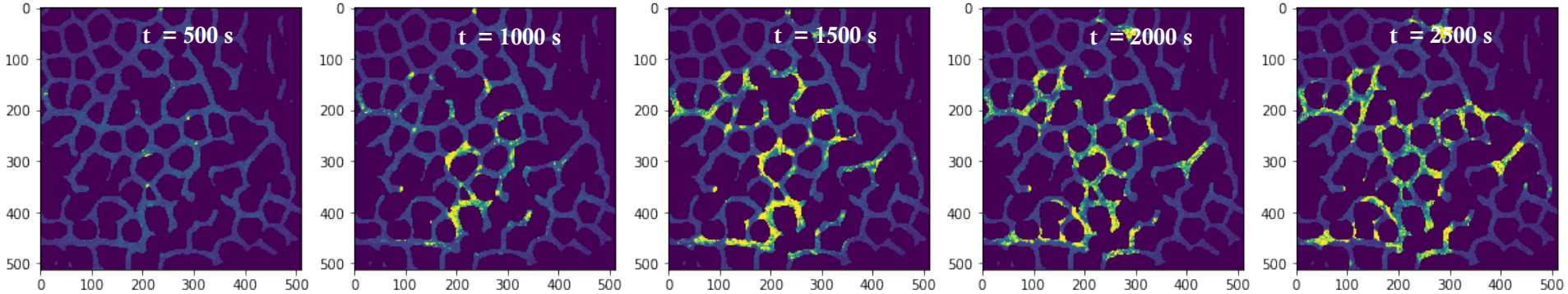
# And also depends on mechanisms of skin transport

## possibly mainly via SC lipids as per Connor Evan's Raman imaging transport of ruxolitinib in Transcutol





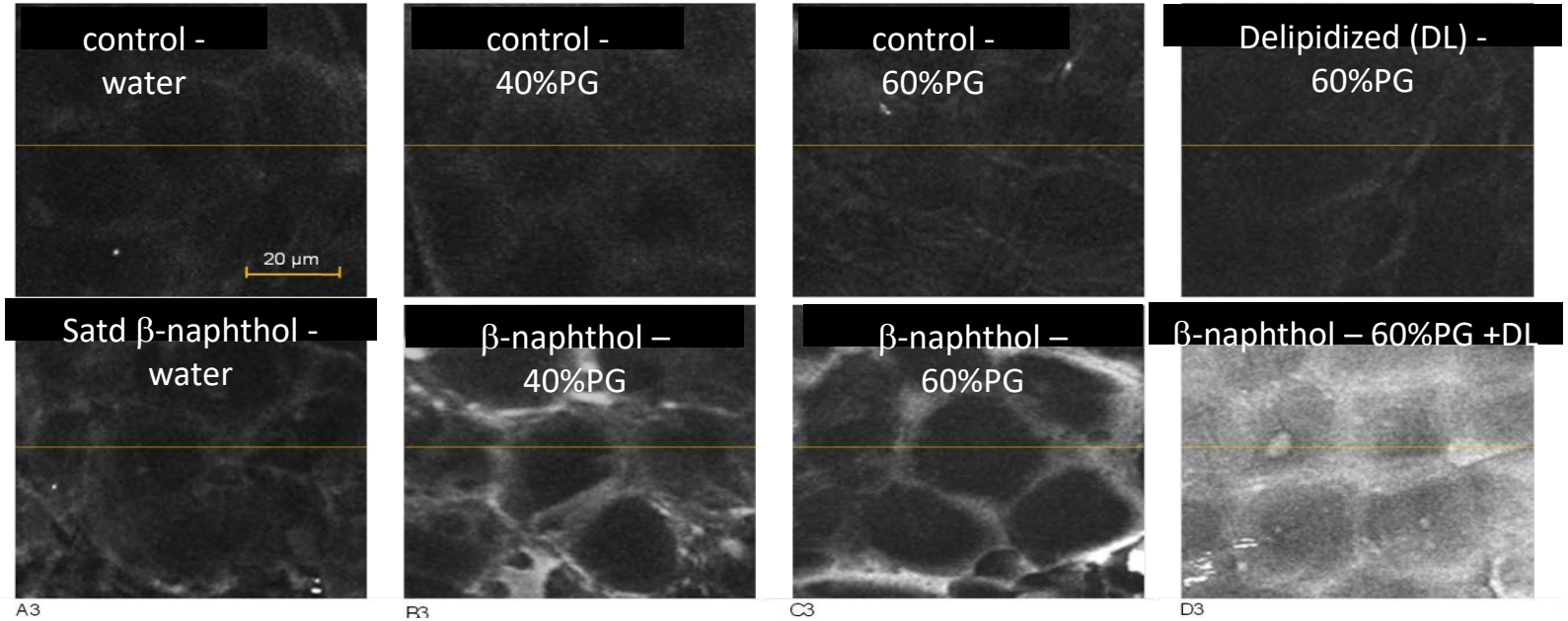




Evans Group, Wellman-MGH-Harvard (Submitted)

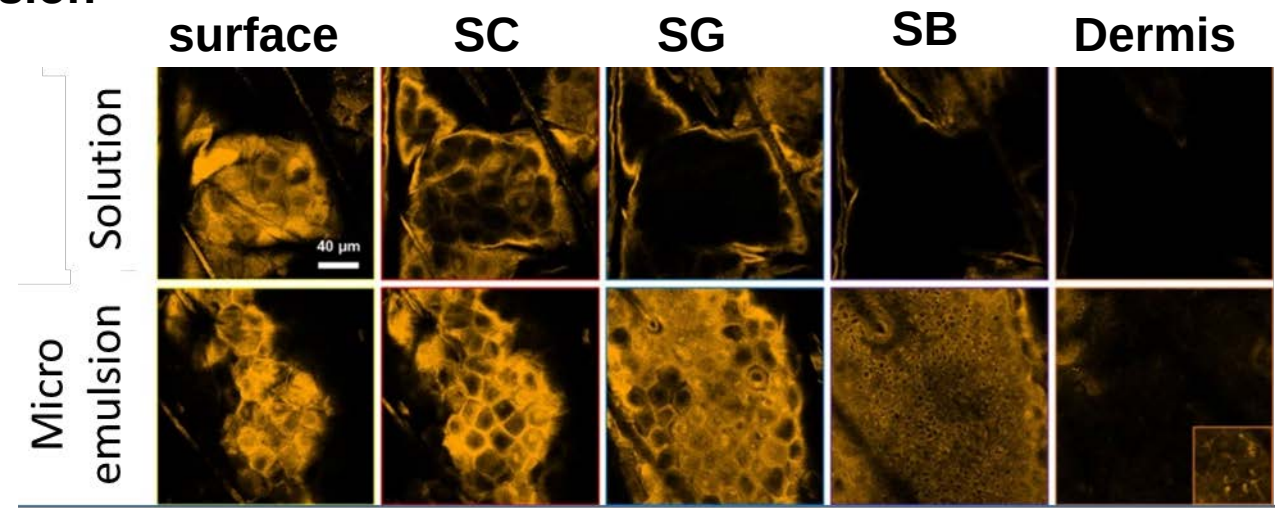
# Whilst our MPM data supports Connor's conclusions, there are provisos – the formulation & nature of skin may matter!

**Human stratum corneum (SC)**

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




**Rose Bengal products applied to ~ 2.5 mm melanoma lesion**

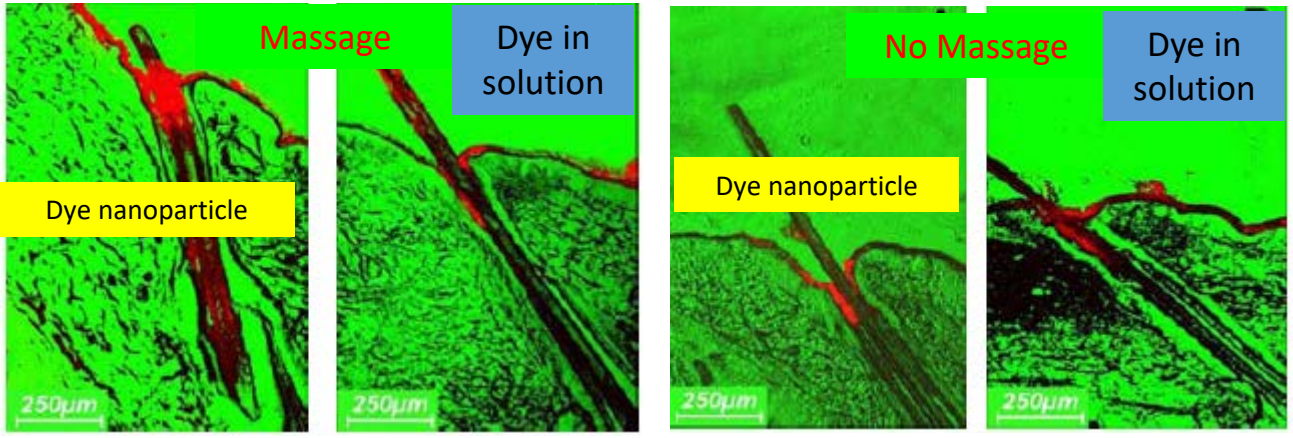



- We have a lot to learn about how formulations affect SC permeability & underlying skin
- A key part of future physiologically based PKPB modelling must be the impact of the various types of skin – site, disease, climate, age etc

# Lastly, there may be other pathways that matter

## Appendageal & polar pathway a long history of rapid effects

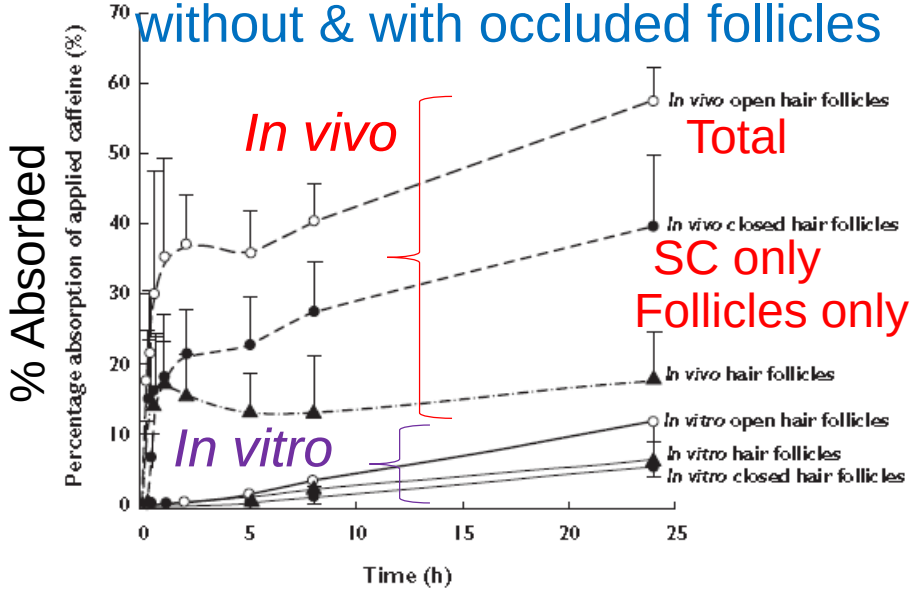
- **Shelley and Melton (1949)** observed perifollicular wheals 5 min after the application of 10 % histamine free base in water.
- Histologic studies by **Mackee et al. (1945)** have also demonstrated follicular diffusion occurring within 5 min.
- Formulation will really matter in depth of follicular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

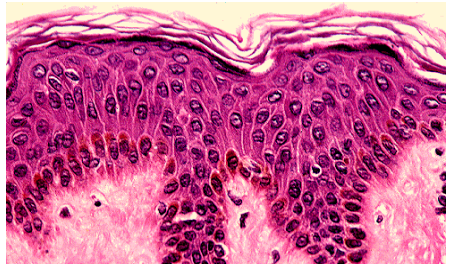
Human *in vivo* and *in vitro* after solvent deposited solid of caffeine without & with occluded follicles

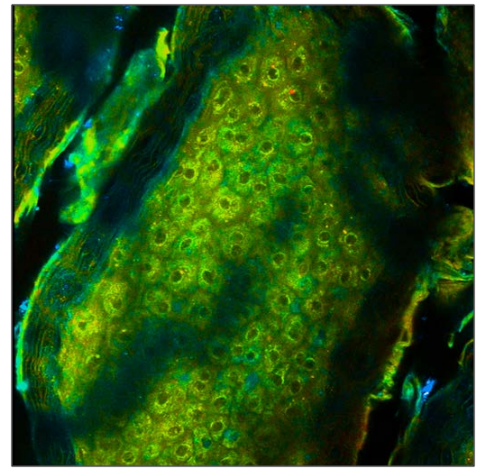



Liu et al *Br J Clin Pharmacol* 2011: **72**: 768–774

# Conclusion

- The mathematical modelling of skin transport  is relatively straightforward in assessing transdermal delivery
- However, it is not so straightforward for topical delivery where it is difficult to measure both the target site concentrations of actives & local clearance from the site
- Our future will very much depend on us using a combination of mechanistic predictions and observation – the middle out approach.
- Thank you for listening





*The views expressed in this presentation are mine alone and do not reflect the official policies of the Food and Drug Administration, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.*

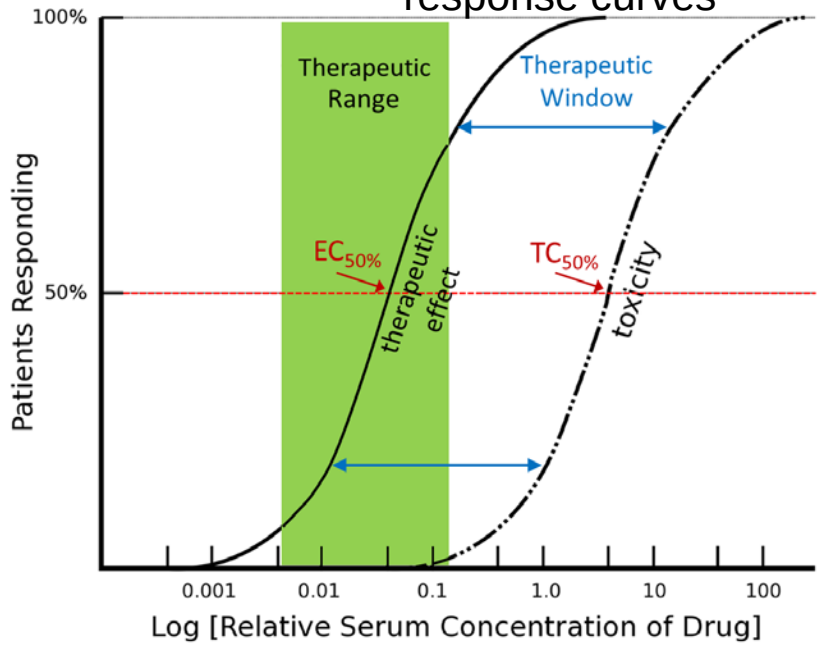
# Efficacy & safety of transdermal & topical products

Mathematical models can define $C_{ss}$ from desired therapeutic effect, maximum response, $EC_{50}$ & time to effect. Individual PBPK defining dosing regimen is then used to achieve $C_{ss}$

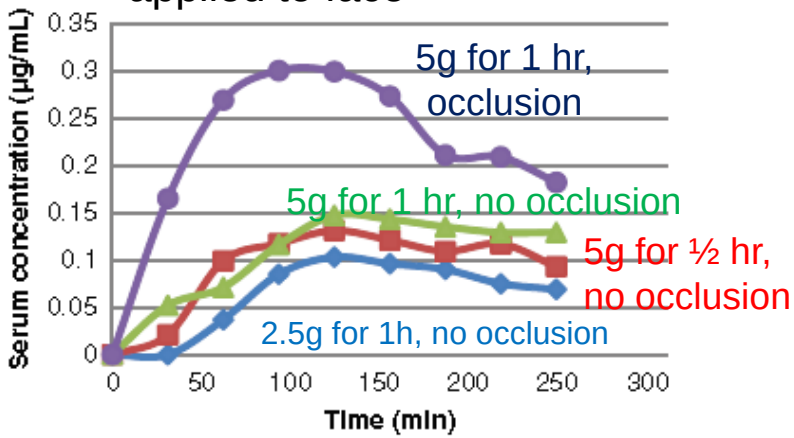
http://holford.fmhs.auckland.ac.nz/docs/immediate-time-course-of-drug-effect.pdf 2019

- **Transdermal products** $C_{ss}$ must be **within** the **Therapeutic Range**
- **Topical products systemic plasma concentrations** should be **less** than the **Therapeutic Range to** not cause any unwanted systemic effects

Blood/plasma/serum toxic & therapeutic response curves




Lidocaine 4% topical anesthetic cream (LMX 4, Ferndale Laboratories, MI) applied to face




< Lower lidocaine therapeutic concentration of 1µg/mL for symptomatic dysrhythmias.

Oni Aesthetic Surg J 30(6) 853–858, 2010

"Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment."

https://www.galderma.com/sites/g/files/jcdfhc196/files/inline-files/Clobex%20Shampoo%20PM_E_Jan.%2006%2C%202020.pdf