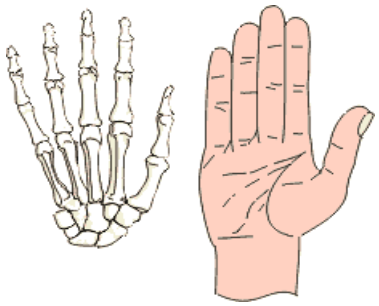
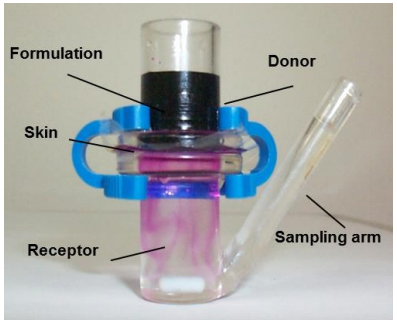
# Topical management of inflammation & pain with diclofenac






**Michael Roberts**

The Institute
basil hetzel institute for medical research

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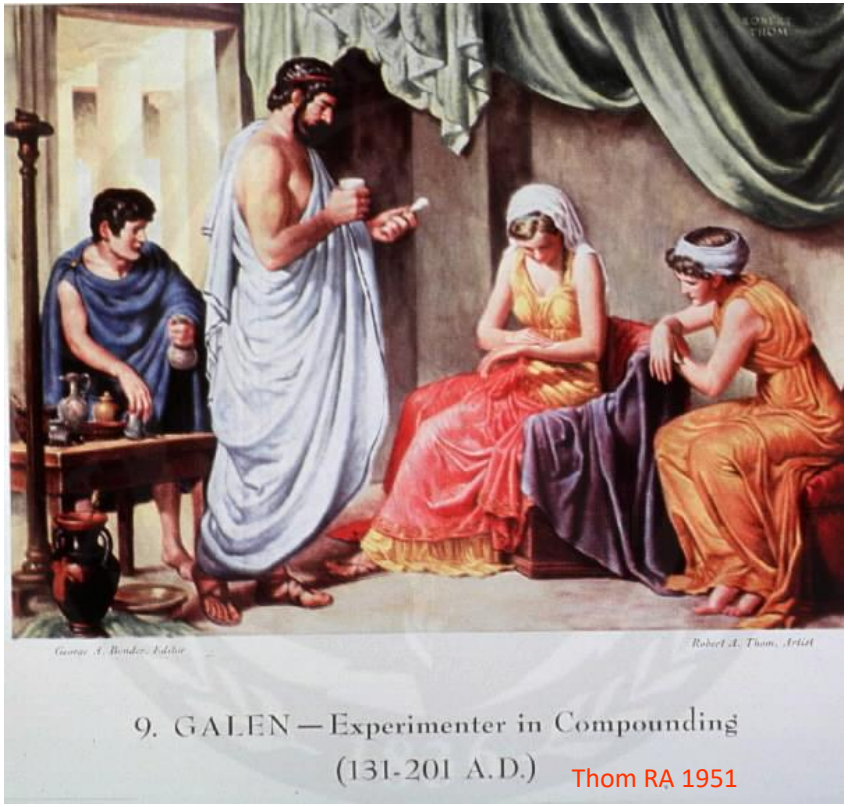
**University of Queensland**
**&**
**University of South Australia**

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

DIAMANTINA INSTITUTE

# Topical products - long history



Thom RA 1951

In *The Canon of Medicine,* **Ibn Sina** (Avicenne, 980-1037AD), a Persian physician:

- Topical drugs cross skin
- Have two spirits or states - Soft which penetrates skin and hard part which does not!



He also suggested topical products could have targeted delivery:

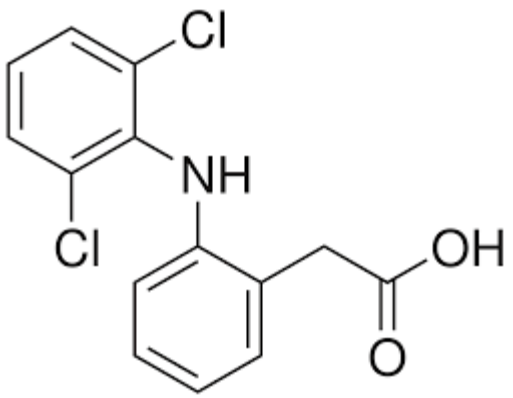
- act locally, immediately beneath the skin including joints (regional effects) & in remote areas (systemic effects).

# Overview – as put to me by Mila

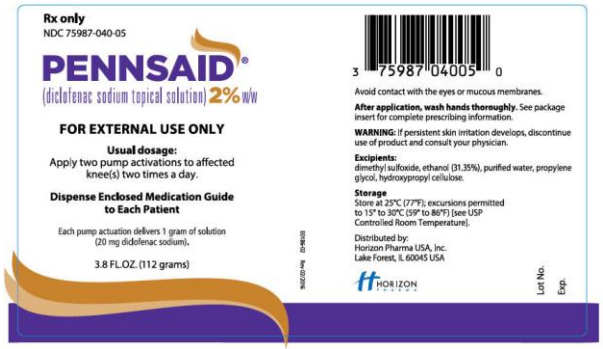
- Historical perspective on diclofenac
  - Knowns/unknowns
  - Our work
- IVIVC: what can a chemist/formulator do with Franz cell data
  - Knowns/unknowns in IVIVC for diclofenac
  - What else: potentially OFM?
  - Formulating for efficient diclofenac delivery to muscle, joint
- Our formulation work with FDA
  - Does it work? under which conditions? informs on what?
- Our PBPK modelling work with FDA

# Historical perspective on diclofenac

- Diclofenac *2-(2,6-**dich**lo**ro**anilino) **phen**yl**ac**etic acid*
  - Most widely prescribed NSAID worldwide
  - Synthesized by Alfred Sallmann and Rudolf Pfister
  - Introduced as **Voltaren** by Ciba-Geigy (now Novartis) in 1973
- Topical diclofenac sodium preparations were developed with the aim of treating local pain and inflammation while limiting diclofenac systemic exposure and potentially minimizing the risk of AEs associated with treatment with systemic NSAIDs.
- FDA approval of topicals
  - Diclofenac sodium; SOLARAZE® topical gel 3 % on16 Oct 2000 = 15 mg diclofenac bid (0.5 g gel per 5 cm2 skin) for actinic keratosis
  - Diclofenac epolamine; FLECTOR® topical patch 1.3 % on 31 Jan 2007 = 1 patch (180 mg) bid for acute pain due to minor strains, sprains, and contusions
  - Diclofenac sodium; Voltaren® Topical gel 1 % on 17 Oct 2007 = Maximum 32 g per day for OA pain of joints, such as the knees and hands
- Diclofenac sodium is the only NSAID approved by the FDA for topical use in the treatment of pain associated with osteoarthritis
  - Diclofenac sodium topical gel 1 % (Voltaren Gel, Novartis Consumer Health, Inc
  - Diclofenac sodium topical solution 1.5 and 2 % (PENNSAID Mallinckrodt Brand








Altman Drugs. 2015; 75(8): 859–877.

# Die perkutane Resorption von Diclofenac*)

Arzneim.-Forsch./ Drug Res. 36 (II), Nr. 7 (1986)
Riess et al. – Diclofenac

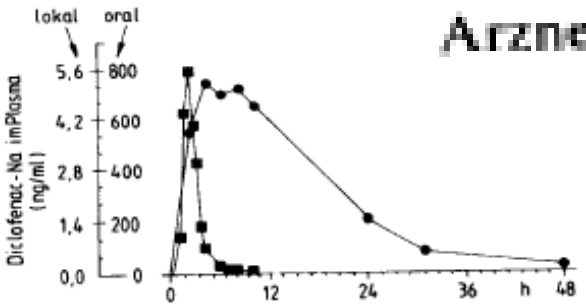



**Abb. 6:** Mittlere Konzentrationen von Diclofenac-Na im Plasma bei Versuchspersonen nach lokaler Applikation (●——●) von 7,5 g einer Cremezubereitung (entsprechend 75 mg Diclofenac-Na auf 750 cm² Rückenhaut ohne Okklusionsverband (n = 5) und nach einmaliger oraler Gabe (■——■) von magensaftresistenten Dragees in einer Dosis von 1 × 50 mg (n > 10).

**Tab. 1:** Konzentrationen von Diclofenac in Plasma, Synovialflüssigkeit und Synovialgewebe von 8 Patienten, bei denen Operationen an den Händen durchgeführt wurden. Den Operationen war eine lokale 3tägige Behandlung mit 2.5 g Emulgelzubereitung 4mal täglich sowie eine lokale Applikation von 2,5 g am Tag der Operation vorausgegangen. Durch Reiben der Hände wurde das Emulgel jeweils in beide Hände einmassiert.

| Zeitpunkt der Operation (h nach letzter Applikation) | Diclofenac-Konzentration ($\mu$mol/l oder $\mu$mol/kg) | | |
|---|---|---|---|
| | Plasma | Synovial-flüssigkeit | Synovial-gewebe |
| 2,17 | 0,16 | > 0,7 | 5,50 |
| 1,17 | – | > 2 | 1,01 |
| 3,17 | 0,07 | > 2 | 2,64 |
| 2,25 | 0,12 | > 10 | 8,62 |
| 1,25 | 2,20 | 0,4 | 5,15 |
| 2,17 | 0,02 | 0,37 | 0,41 |
| 3,00 | 0,13 | 1,18 | 2,34 |
| 3,34 | 0,06 | 4,21 | 3,13 |

0022-3565/94/2681-0144$03.00/0
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Vol. 268, No. 1
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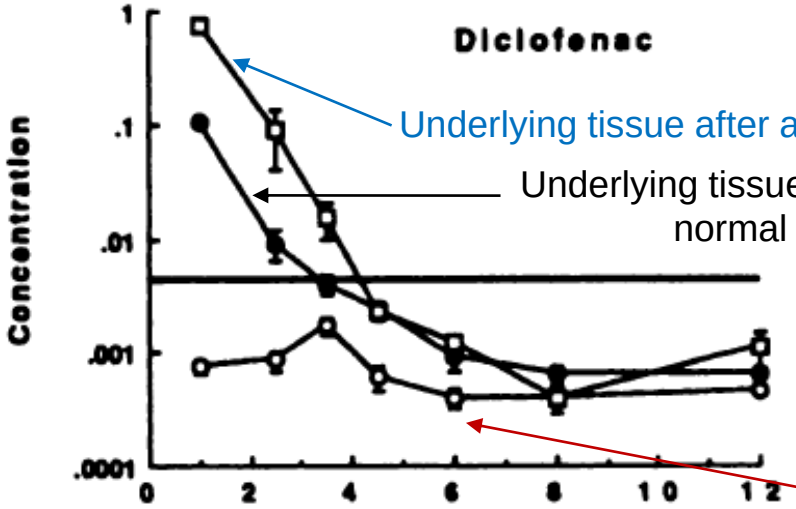
# Skin Permeability and Local Tissue Concentrations of Nonsteroidal Anti-Inflammatory Drugs after Topical Application[1]

P. SINGH[2] and M. S. ROBERTS
*Departments of Pharmacy (P.S.) and Medicine (M.S.R.), The University of Queensland, Queensland, Australia*
Accepted for publication August 23, 1993

- Two key models:
  - Dead versus alive rat for diffusion and blood clearance
  - Treated for contralateral tissue for direct penetration

**Clearance of NSAIDs applied to exposed rat dermis *in vivo***

| Compound | Dermal Clearance | | |
|---|---|---|---|
| | Anesthetized | Sacrificed | Blood Supply |
| | *ml/hr* | | |
| Salicyclic acid | 0.58 ± 0.08 | 0.10 ± 0.02 | 0.48 |
| Diethylamine salicylate | 0.62 ± 0.11 | 0.15 ± 0.04 | 0.37 |
| Indomethacin | 0.32 ± 0.08 | 0.13 ± 0.02 | 0.19 |
| Naproxen | 0.65 ± 0.09 | 0.20 ± 0.04 | 0.45 |
| Piroxicam | 0.48 ± 0.07 | 0.26 ± 0.04 | 0.22 |
| Diclofenac sodium | 0.66 ± 0.10 | 0.30 ± 0.04 | 0.36 |




Underlying tissue after applied to dead dermis

Underlying tissue after applied to normal dermis

Contralateral tissue after applied to normal dermis

We suggested that

- Direct penetration of NSAIDs is evident to a depth of 3 to 4 mm,
- With the systemic blood supply being the main means for compounds reaching deeper underlying tissues.

0022-3565/94/2681-0144$03.00/0
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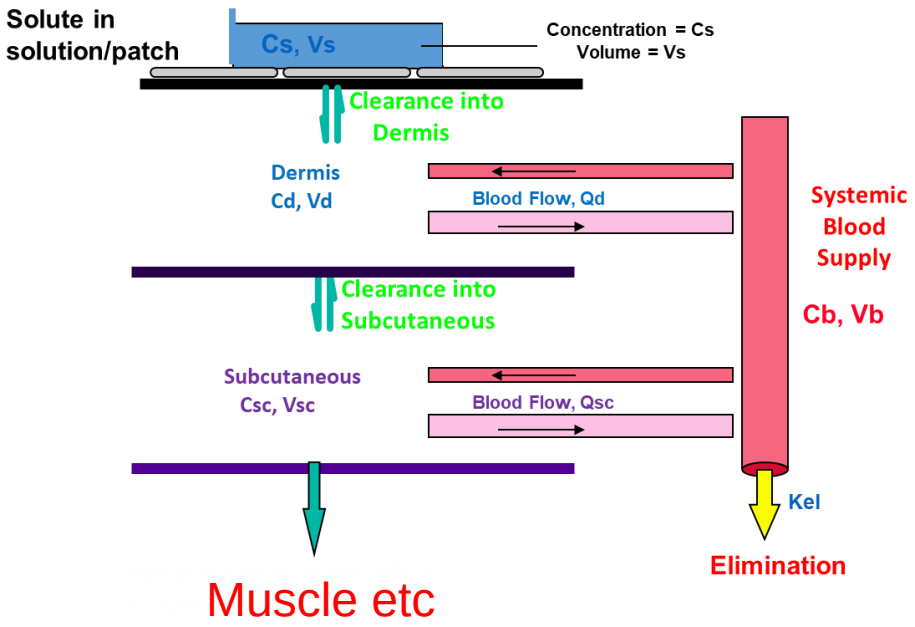
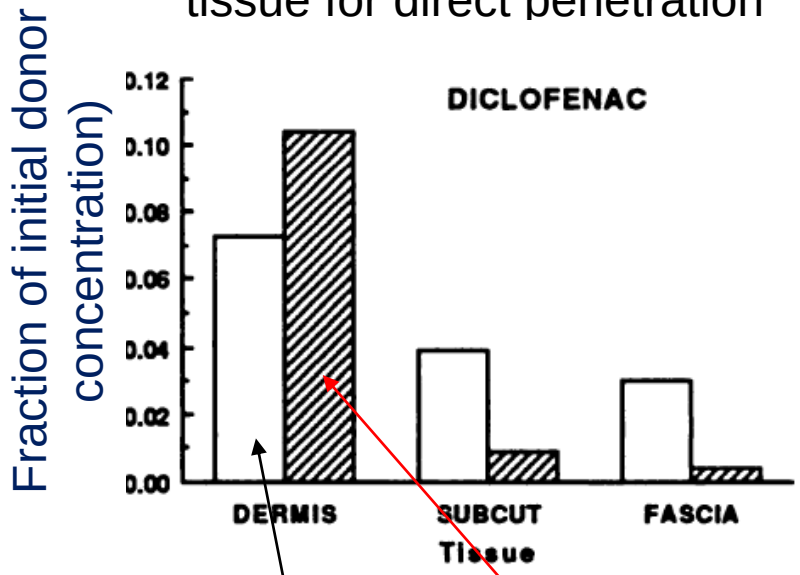
Pharmacokinetic modelling




Observed and Predicted from PBPK model

For the underlying (*i*th) tissue:

**Change in tissue concentration**

$$Vu_{T,i}\frac{dC_{uT,i}}{dt} = V_{T,i}\frac{dC_{T,i}}{dt}$$
$$= CL_{T,i+1\leftrightarrow i}(f_{uT,i+1}C_{T,i+1} - f_{uT,i}C_{T,i})$$
$$+ Q_{T,i}\,(C_b\,RM_{T,i} - f_{uT,i}C_{T,i})$$
$$+ CL_{T,i\leftrightarrow i-1}\,(f_{uT,i-1}\,C_{T,i-1} - f_{uT,i}C_{T,i})$$

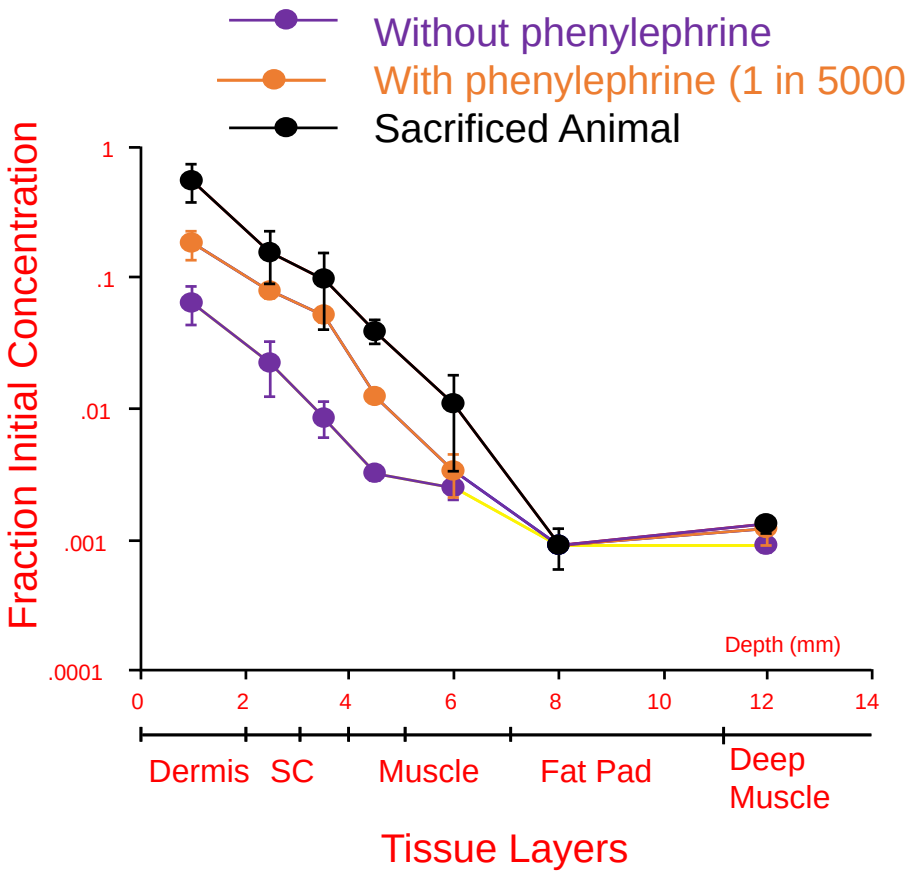
Input from tissue above

Removal by blood to systemic circulation

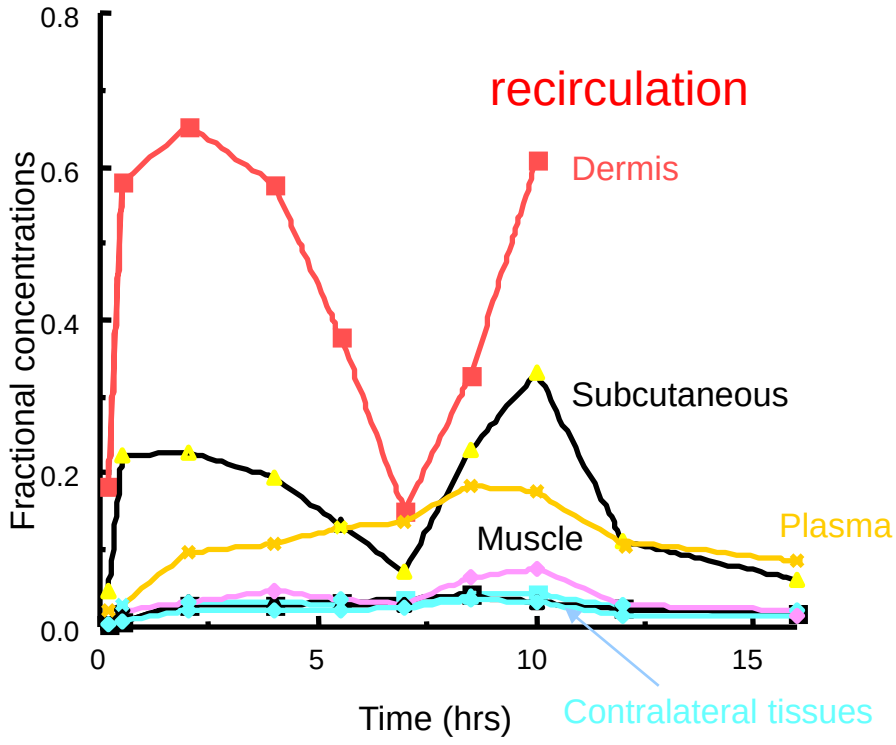
Clearance to tissue below

# Vasoconstriction and recirculation also can affect dermal and deeper tissue levels

## Salicylic acid 2 hr after dermal application



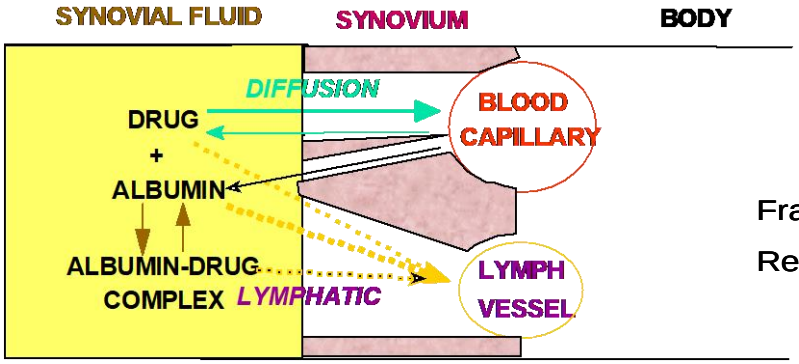

## Salicylic acid at various times after dermal application

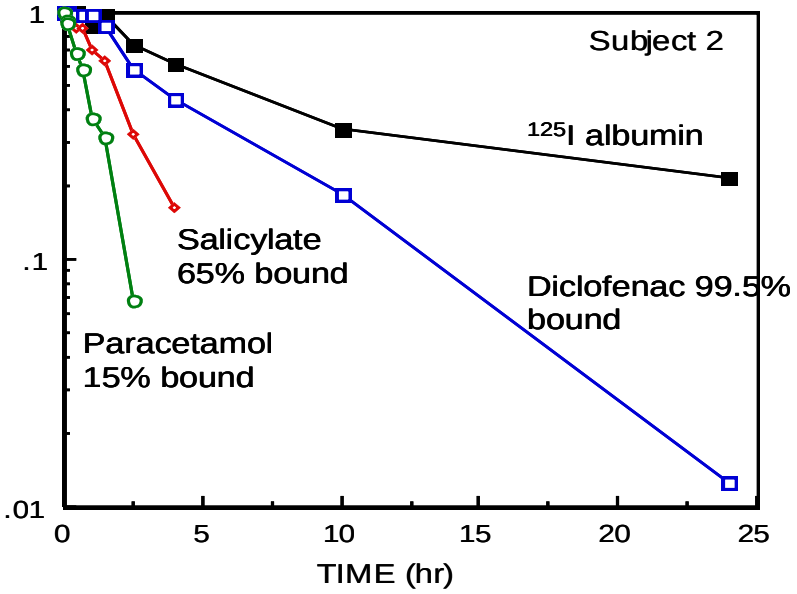



Singh & Roberts

Singh et al, 1998

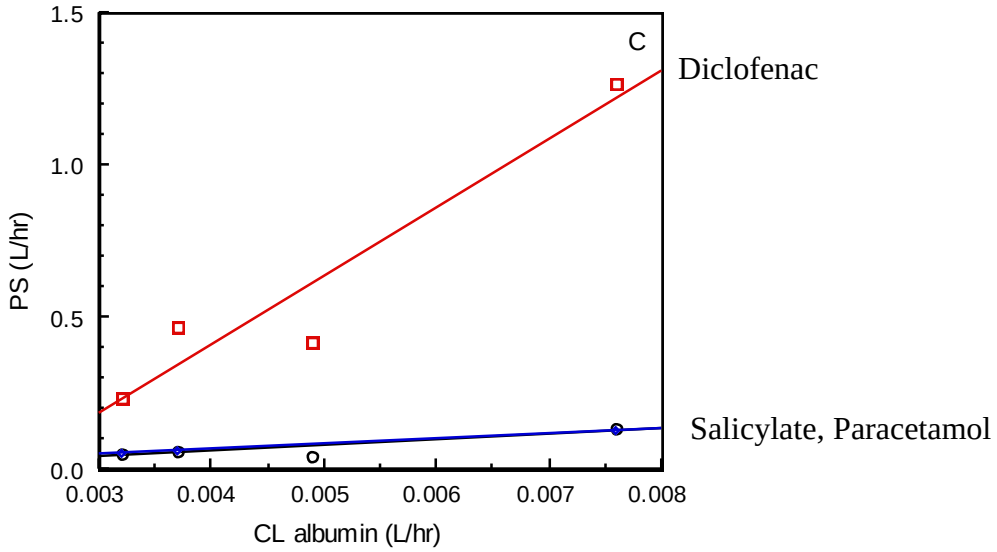
# Synovial fluid kinetics - role of albumin efflux on kinetics - studies in osteoarthritic effusions




Brit J Clin Pharmacol 38: 349 (1994)

# Synovial fluid kinetics -role of albumin efflux on kinetics

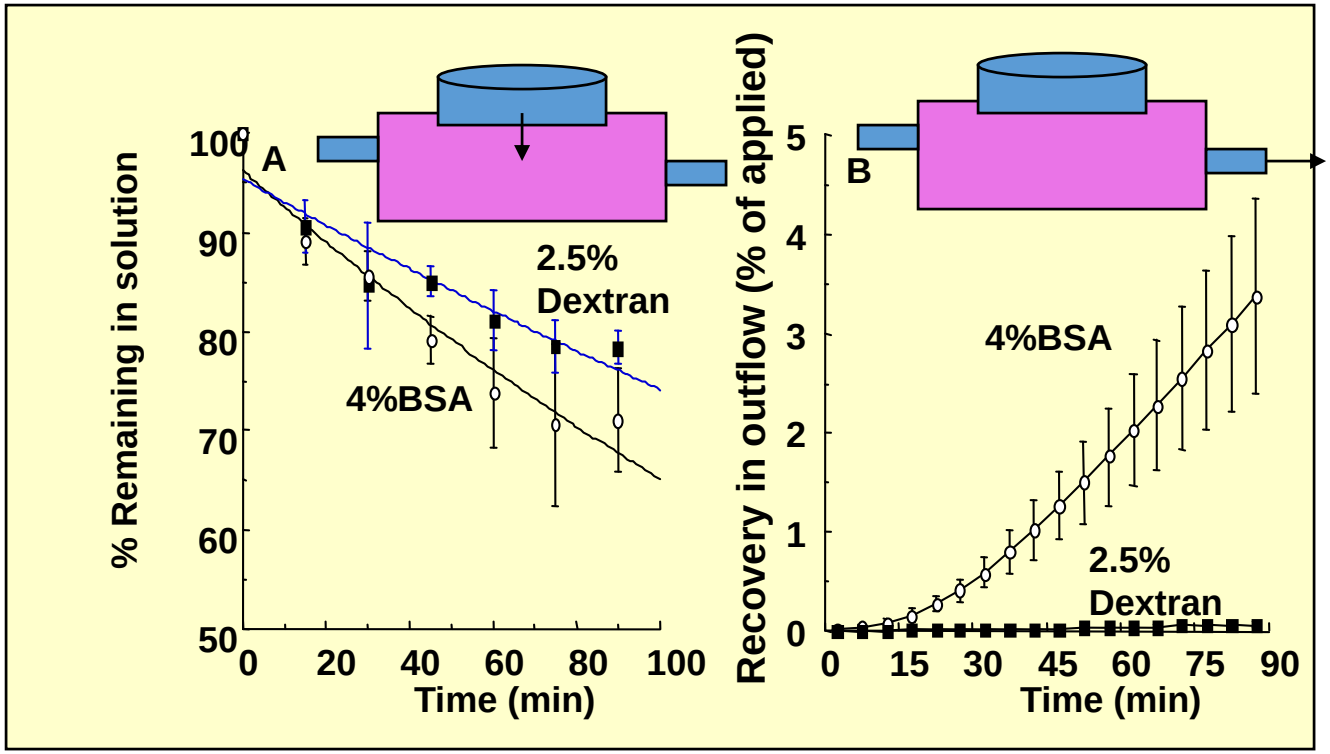



- Conclude albumin efflux involved in drug clearance from synovial joint
  - 50% of diclofenac (99.5% bound),
  - 10% of salicylate (65% bound) and
  - 1% of paracetamol (15% bound)

Brit J Clin Pharmacol 38: 349 (1994)

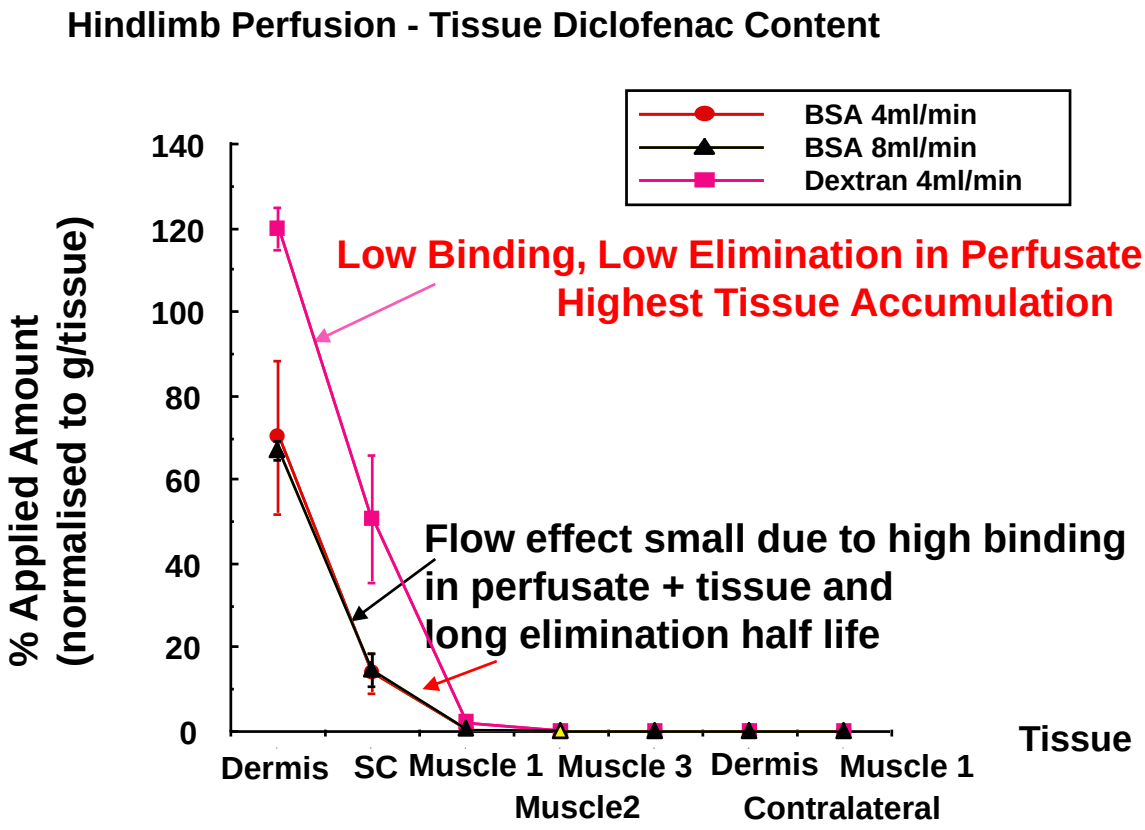
# Diclofenac kinetics after dermal application

## in a single pass perfused limb



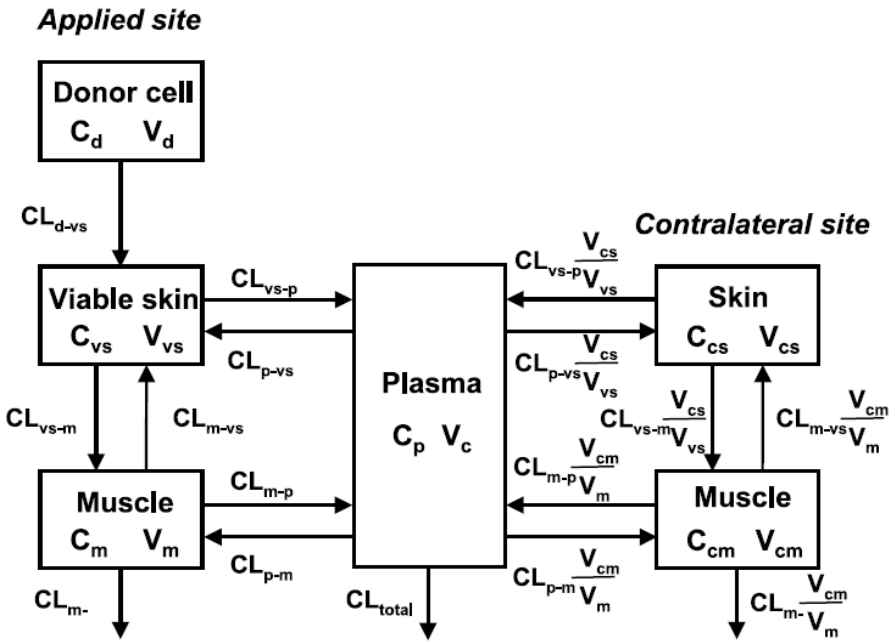

Pharm Res 16: 1394 (1999)

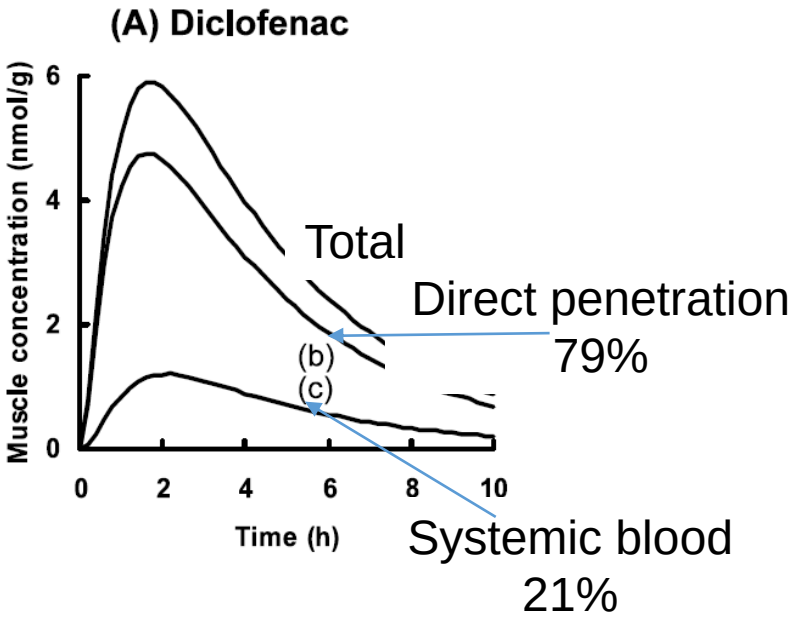
# Effect of Flow and Protein Binding on Topical Diclofenac Tissue Concentrations



# Validation of factors determining penetration of drugs from viable skin to muscle

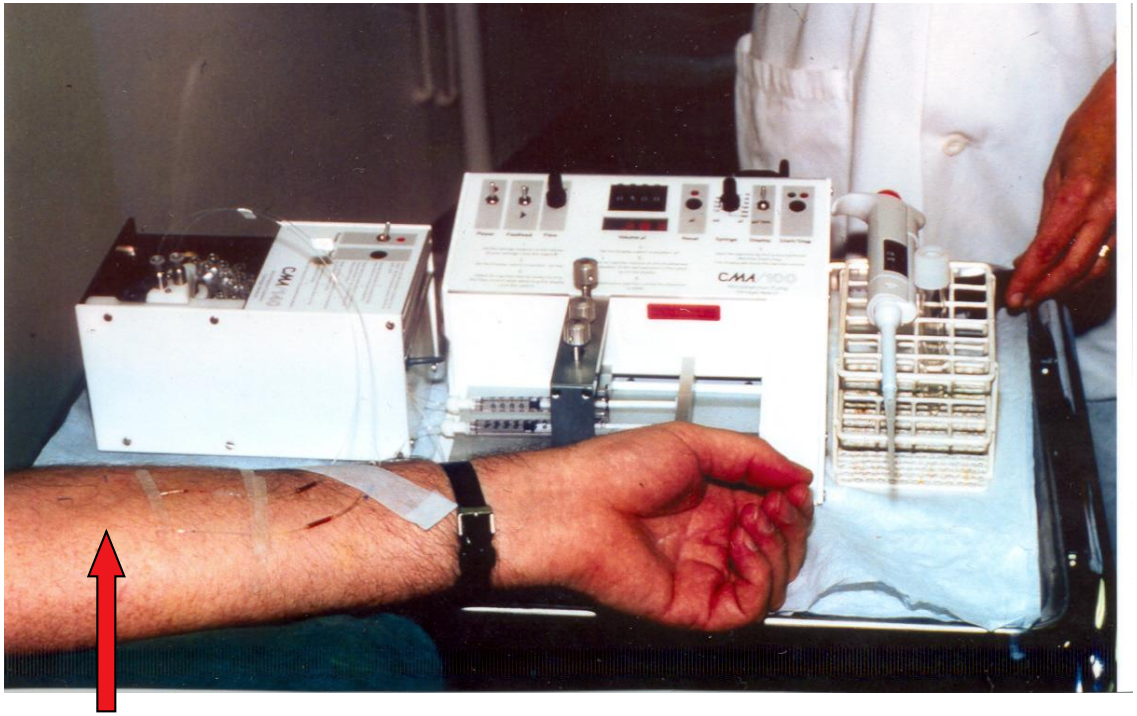
Higaki International Journal of Pharmaceutics 239 (2002) 129–141



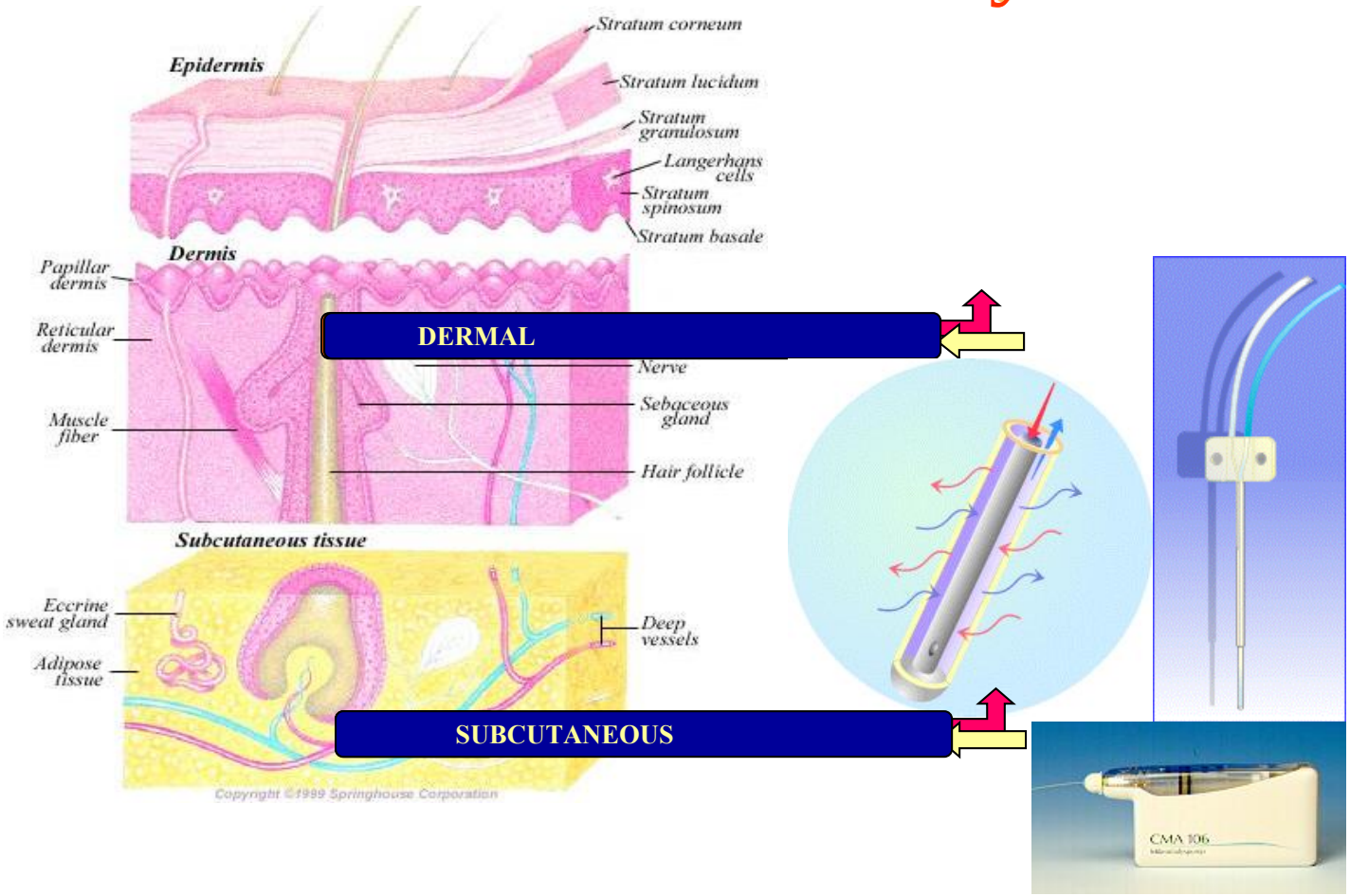
# Introduction to human microdialysis

Chris Anderson, Linkoping, Sweden - An expat Australian

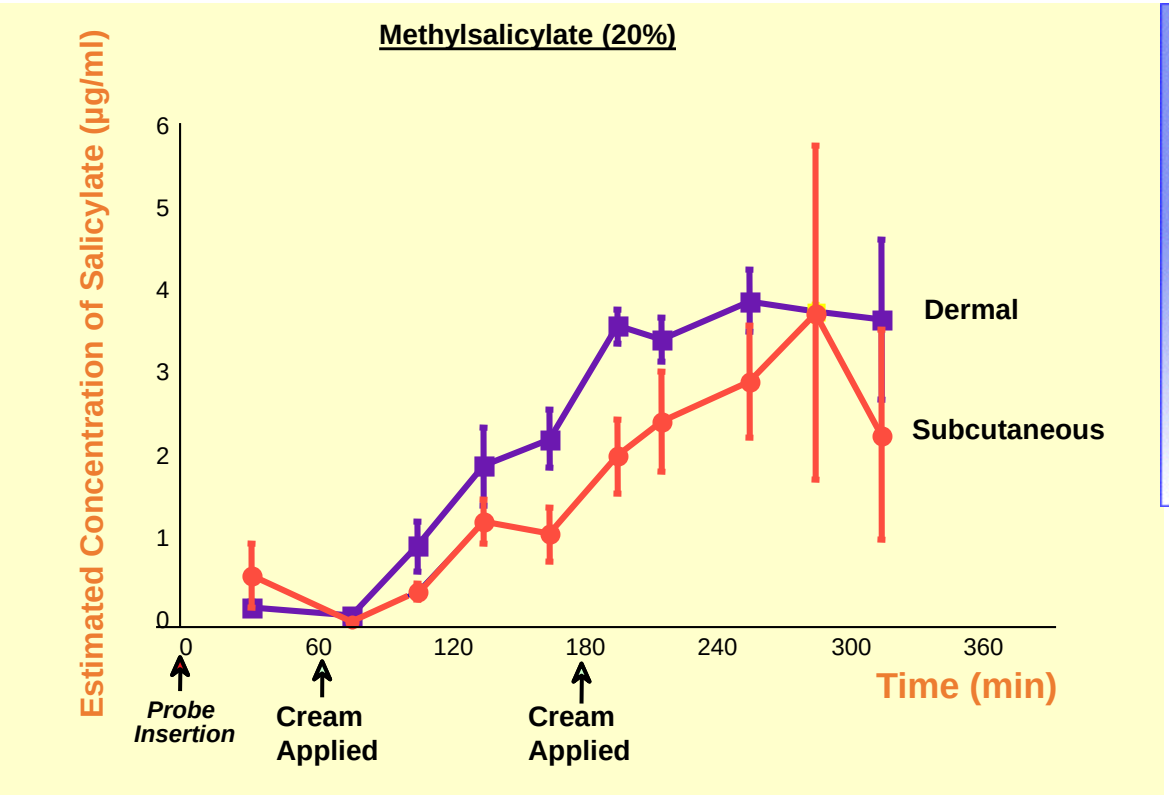


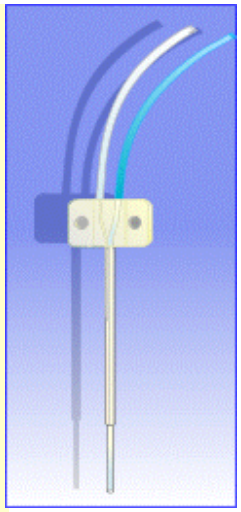
**Microdialysis probes in skin**

# Cutaneous Microdialysis



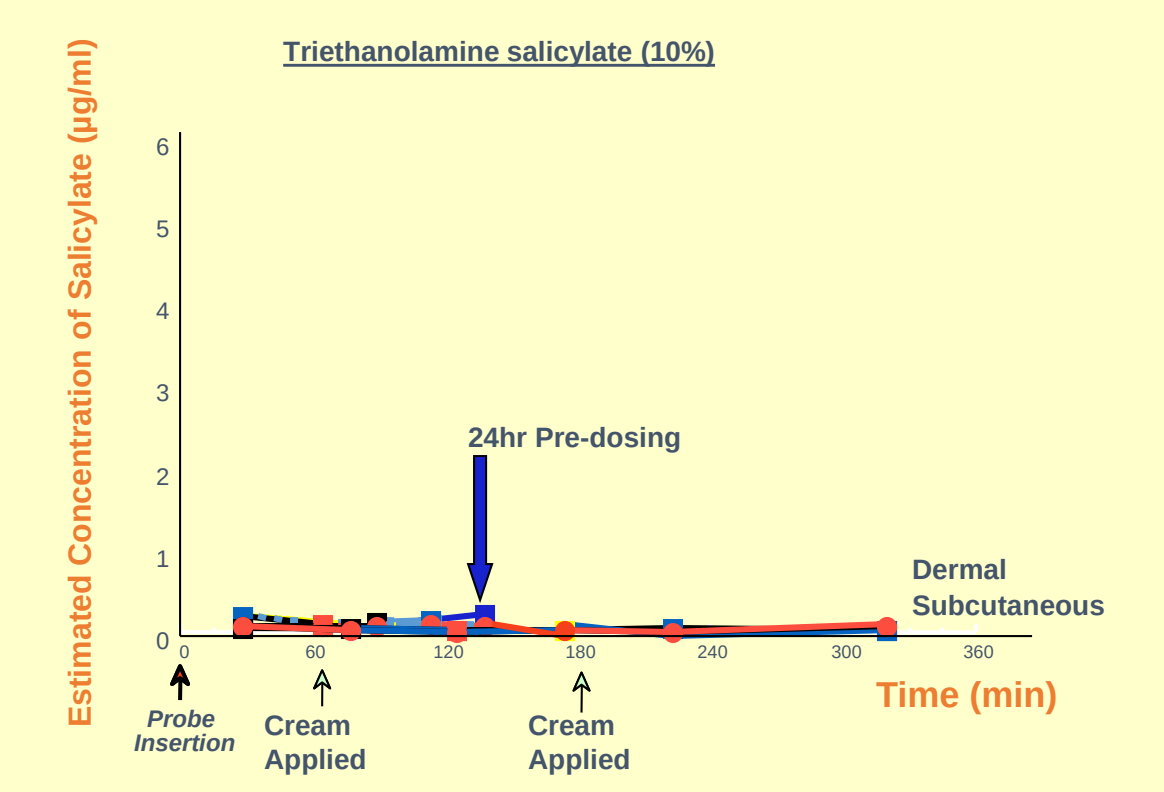
# Proving tissue penetration after topical application of Dencorub ?

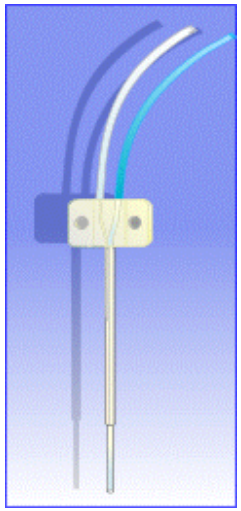


Cross et al, Lancet 1997

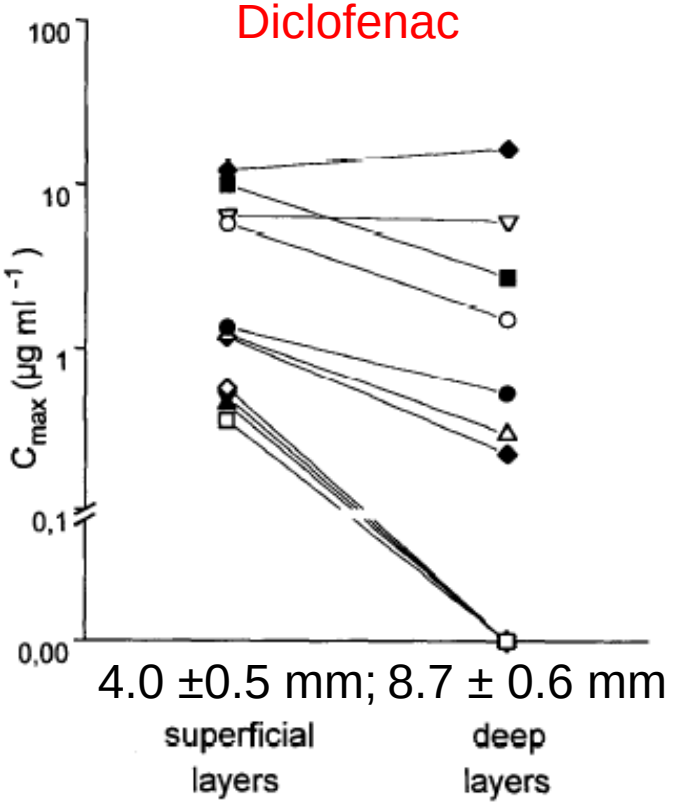
# How effective is the non-irritating product?

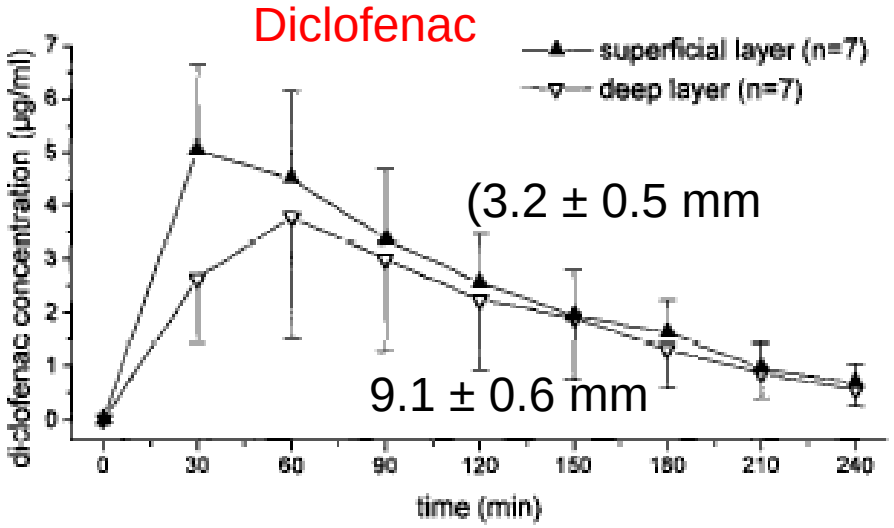


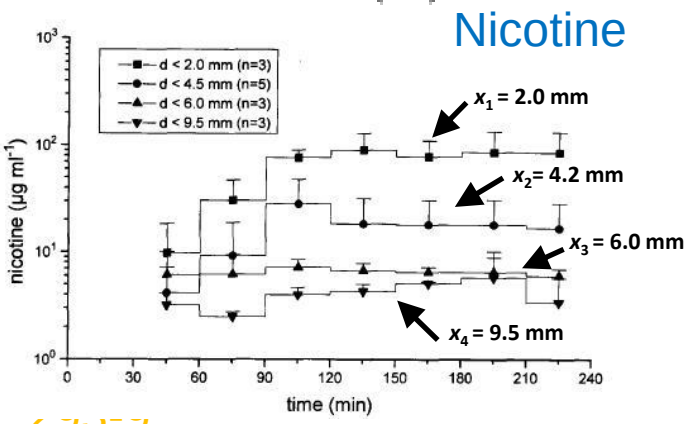



Cross et al, Lancet 1997

# Concentrations in defined human tissue layers after topical administration with microdialysis



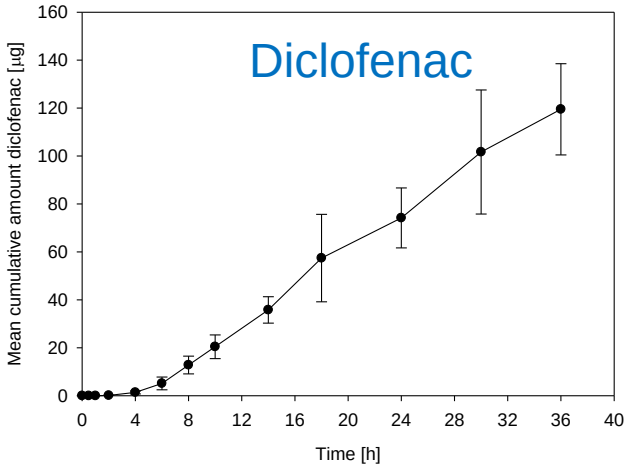



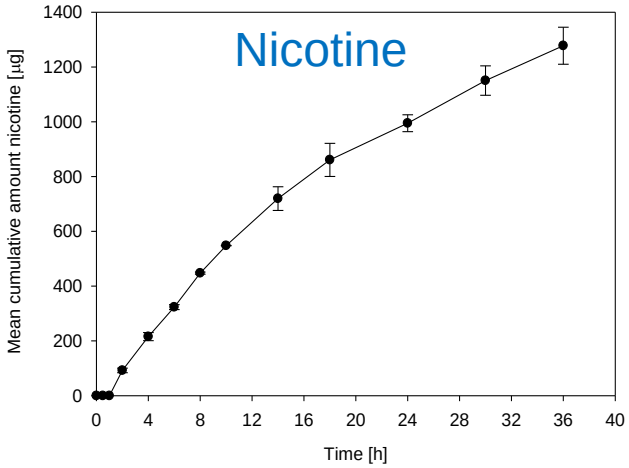




M. Muller et al. Clin Pharmacol Ther 1997;62. 293-9.

Müller *et al.*, J Control Rel, **37**(1-2) 1995

# Diclofenac and nicotine *in vitro* human epidermal skin penetration (IVPT) experiments



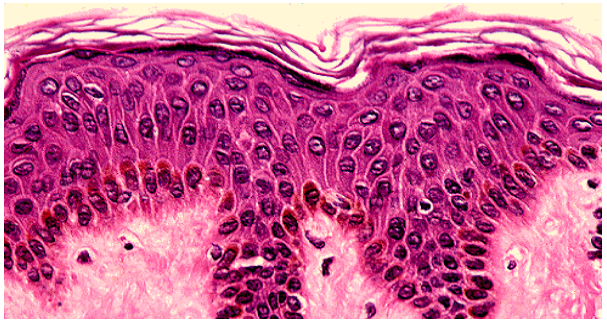

| | $fu_{de}$ | $t_{lag}$ [h] | $D_{diff}$ [$cm^2/s$] |
|---|---|---|---|
| Diclofenac | 0.01 | 4.20 | $5.9 \cdot 10^{-7}$ |
| Nicotine | 0.95 | 0.06 | $3.2 \cdot 10^{-6}$ |

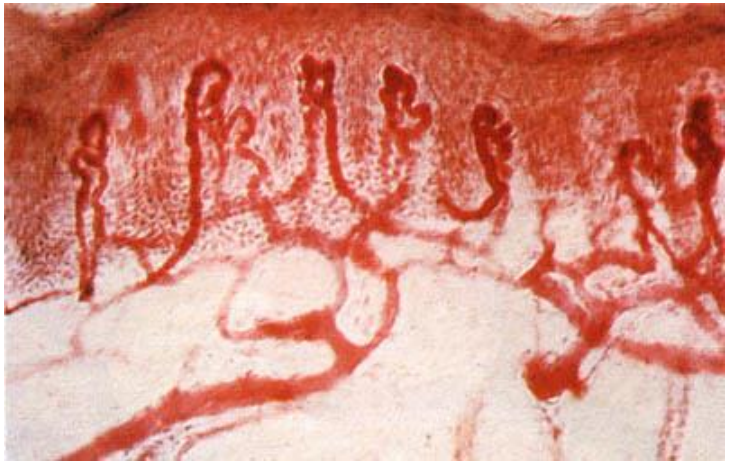
Note with dermis, may have longer lag time!

# How do we explain different deep tissue lag times for *in vitro* and *in vivo*?

| Chemical | $fu_{BSA}$ | *In vitro* $t_{lag}$ [min] Dermis | *In vivo* $t_{lag}$ [min] Microdialysis |
|---|---|---|---|
| Diclofenac | 0.05 | 537 | < 30; < 60 |
| Ibuprofen | 0.11 | 216 | 41 (subcutis)<br>104 (muscle) |
| Propranolol | 0.57 | 56 | 9.6-10.5 |
| Fluconazole | 0.85 | 26 | 30 |
| Lidocaine | 0.90 | 44 | 110 |
| Nicotine | 0.91 | 44 | 35; 180 |

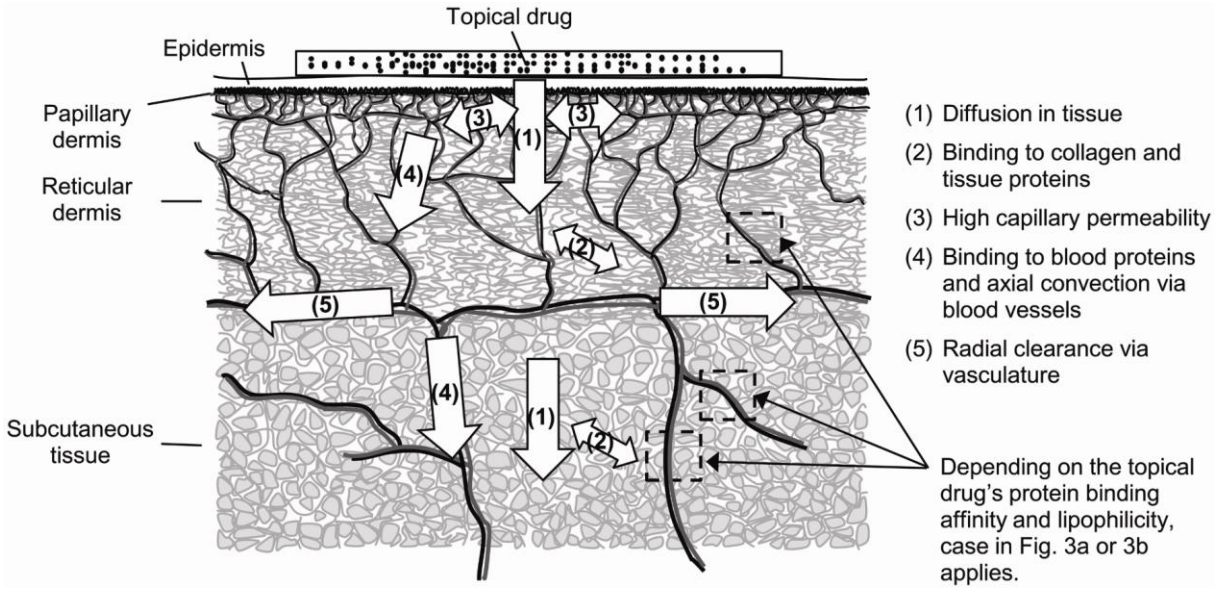
# Another consideration – deep location. How do we get there and do show we have?





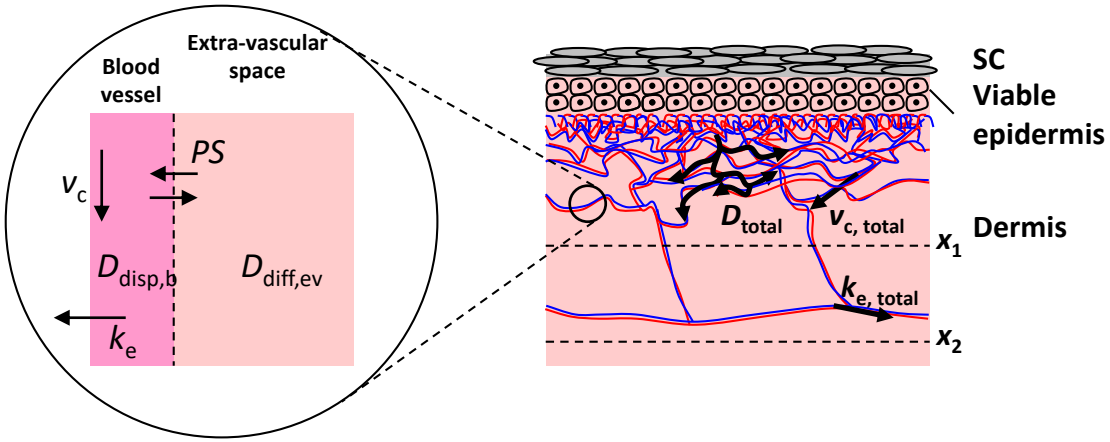
# Physiological pharmacokinetic model of drug transport in deep skin tissue

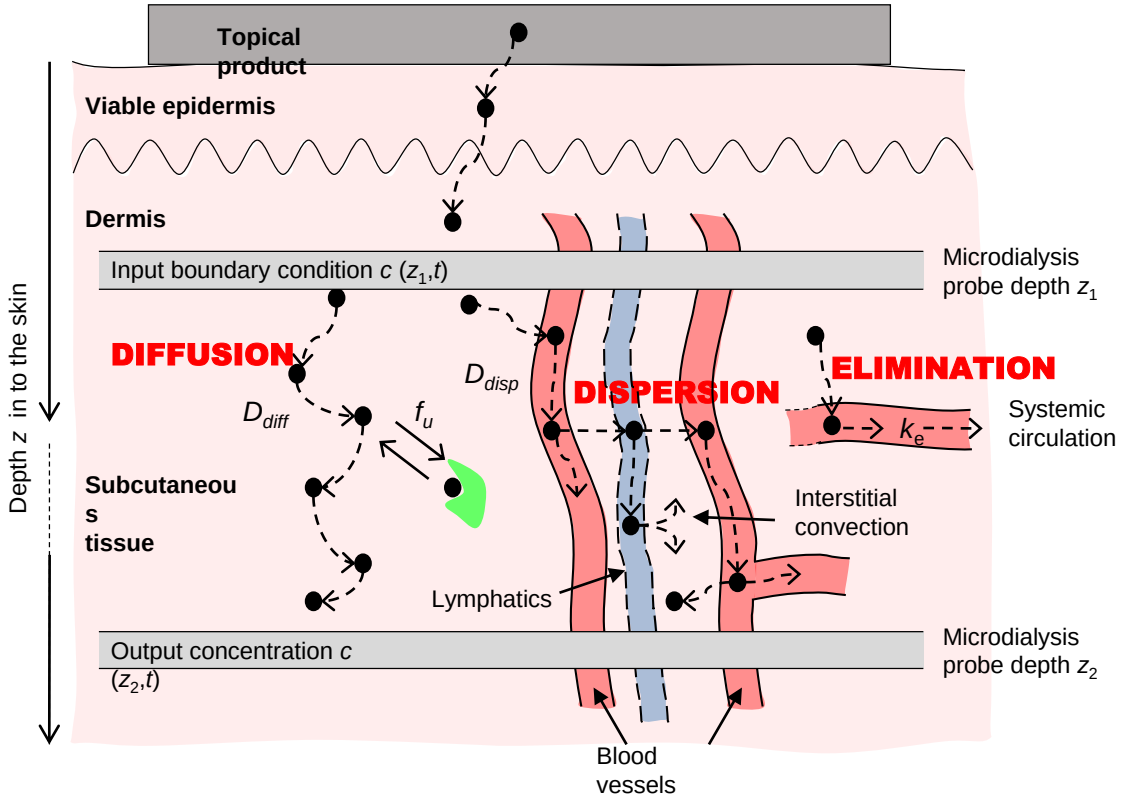
Yuri Dancik, Yuri G. Anissimov, Owen G. Jepps, Michael S. Roberts
Therapeutics Research Centre, University of Queensland School of Medicine
Brisbane, Australia




BJCP 2012

# PBPK model



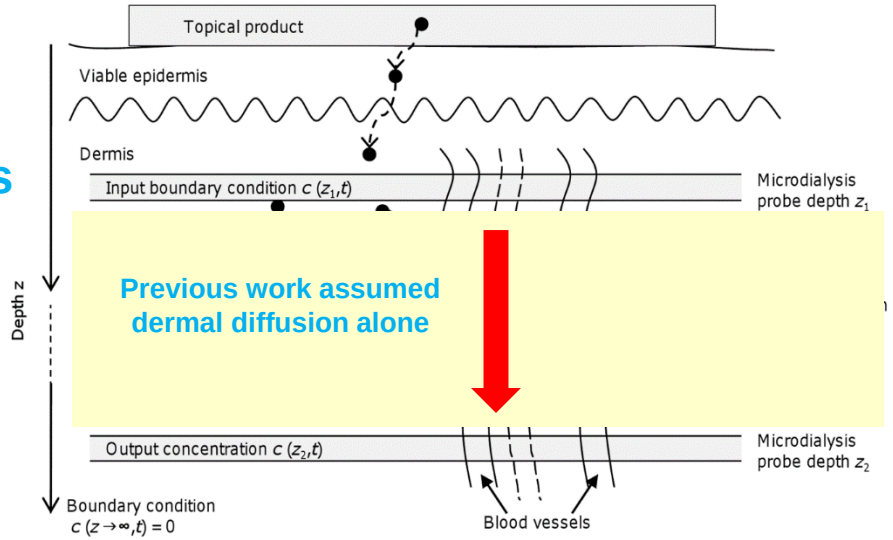




Dancik *et al*, Brit J Clin Pharm 2011

# Mechanism of dermal transport in man *in vivo*

**Found much shorter lag times & higher dermal levels than predicted**

**– especially if drug highly plasma protein bound**




Apply convection – dispersion – elimination model (as described earlier for liver)

$$\partial c(z,t)/\partial t = \left(D_{\text{disp}} + f_{\text{u}} D_{\text{diff}}\right)\left(\partial^2 c(z,t)/\partial z^2\right) - k_{\text{e}} c(z,t)$$

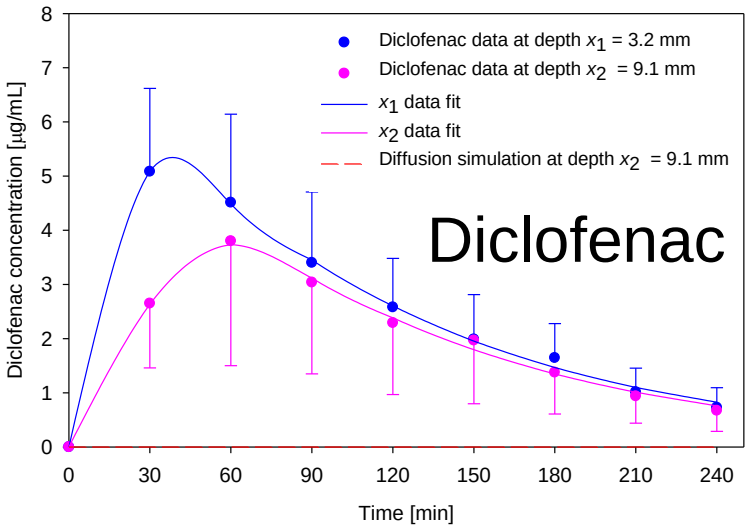
With input function $c(z_1,t) = c_1 = A\left(e^{-b_1 t} - e^{-b_2 t}\right)$

And numerical inversion and regression in the Laplace domain

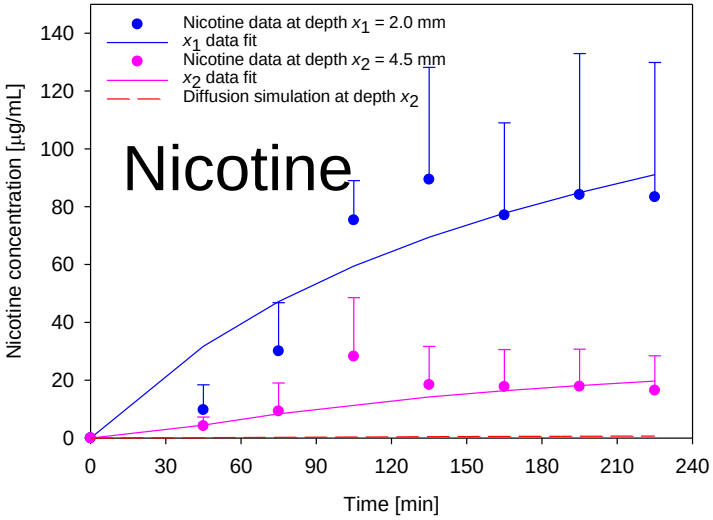
$$c_2(s) = \left[A/(s+b_1)(s+b_2)\right] \cdot \exp\left[\left(-\sqrt{(s+k_{\text{e}})/\left(D_{\text{disp}} + f_{\text{u}} D_{\text{diff}}\right)}\right)(z_2 - z_1)\right]$$

**Dancik BJCP 2011**

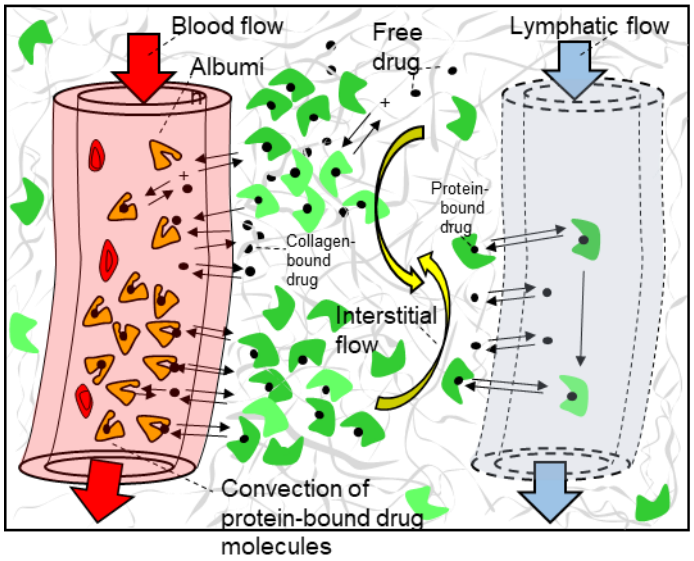
# Contrasting penetration mechanisms

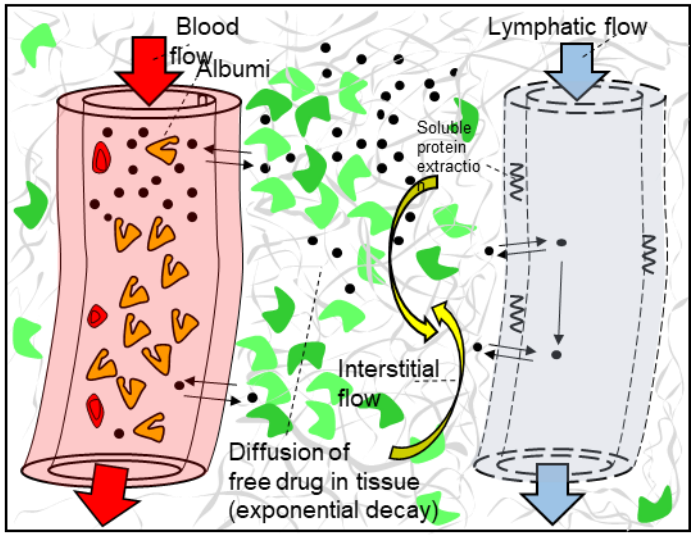



Moderate $K_{o/w}$, high protein binding

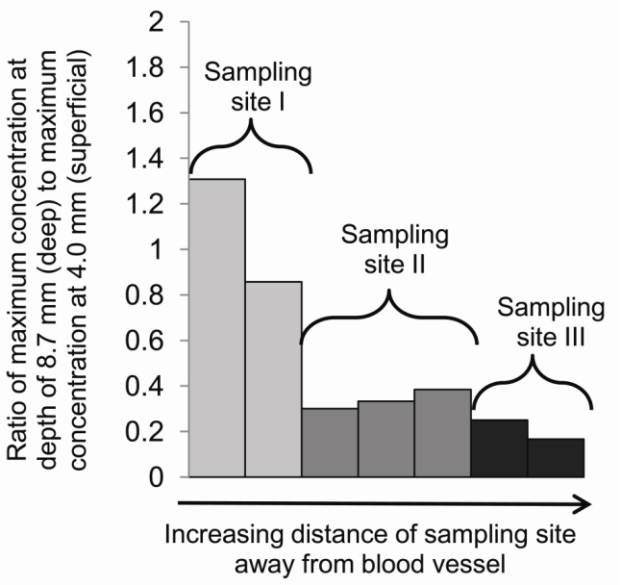


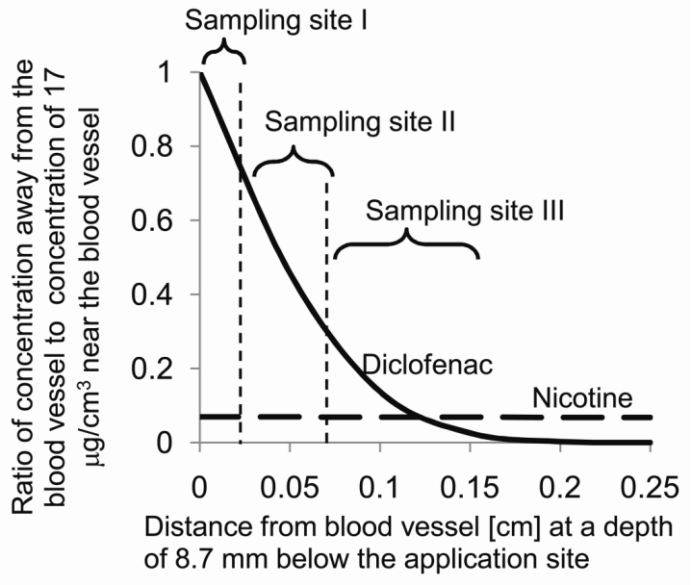

Moderate $K_{o/w}$, low protein binding



# Importance of blood vessel availability below site of topical application for diclofenac-like drugs



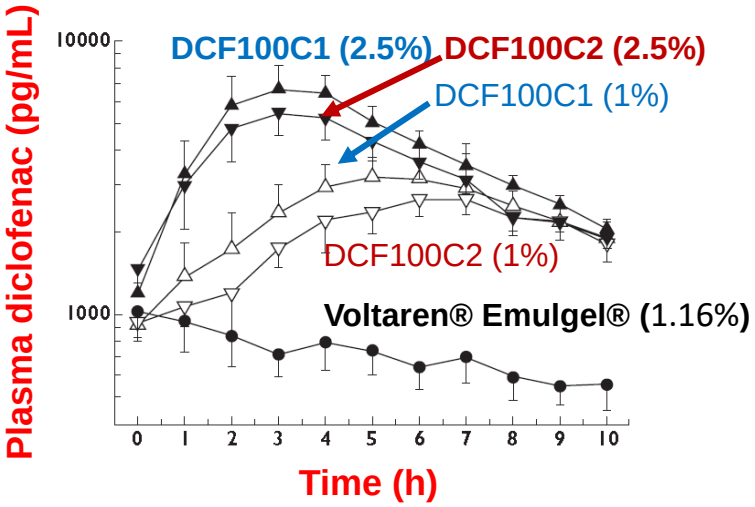



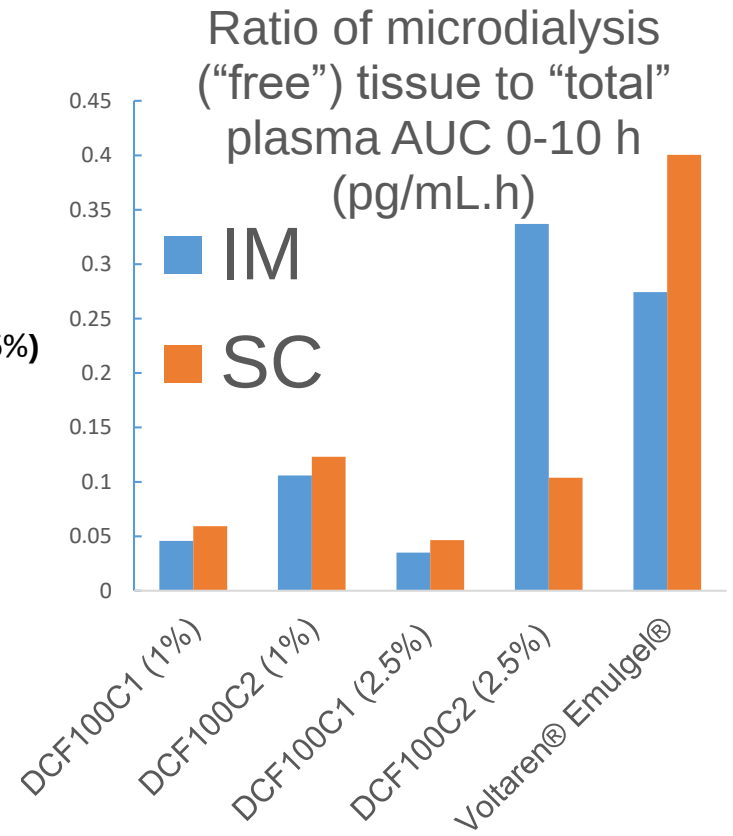

Max. diclofenac concentration from Müller *et al*., Clin Pharmacol Ther, 1997

# A new topical formulation enhances relative diclofenac bioavailability in healthy male subjects

➢ Single-centre, open-label, three-period, crossover clinical trial of five discrete diclofenac formulations.

- Two concentrations (1.0% and 2.5%) of DCF100C, with and without menthol and eucalyptus oil (total daily doses of 5mg and 12.5 mg).
- Voltaren® Emulgel® gel (1.0%) as reference (total daily dose of 40 mg).




Brunner et al Br J Clin Pharmacol / 71:6 / 852–859, 2011

# Diclofenac in soft tissues, plasma & synovium after topical and oral applications

- Diclofenac sodium applied to 14 subjects (four male and 10 female prior to knee arthroplasty for osteoarthritis:
  - ✓ Oral capsule of 37.5 mg diclofenac sodium (Voltaren SR)
  - ✓ Topical - two 70-cm$^2$ Voltaren Tapes® (total 30 mg diclofenac sodium dissolved in 3 g of adhesive for 2)
- At 12 h diclofenac concentration in the fat, muscle and synovial tissues by LCMS.

Found diclofenac concentrations for topical versus oral

- **Muscle** - Higher 9.29 ng/ mL vs 0.66 ng/mL (p=0.02)
- **Plasma** - No significant difference 4.70 vs 6.63 ng/ mL
- **Synovial** - Lower 4.99 vs 15.07 ng/mL (p=0.02)

S.Miyatake et al. BJCP 2008

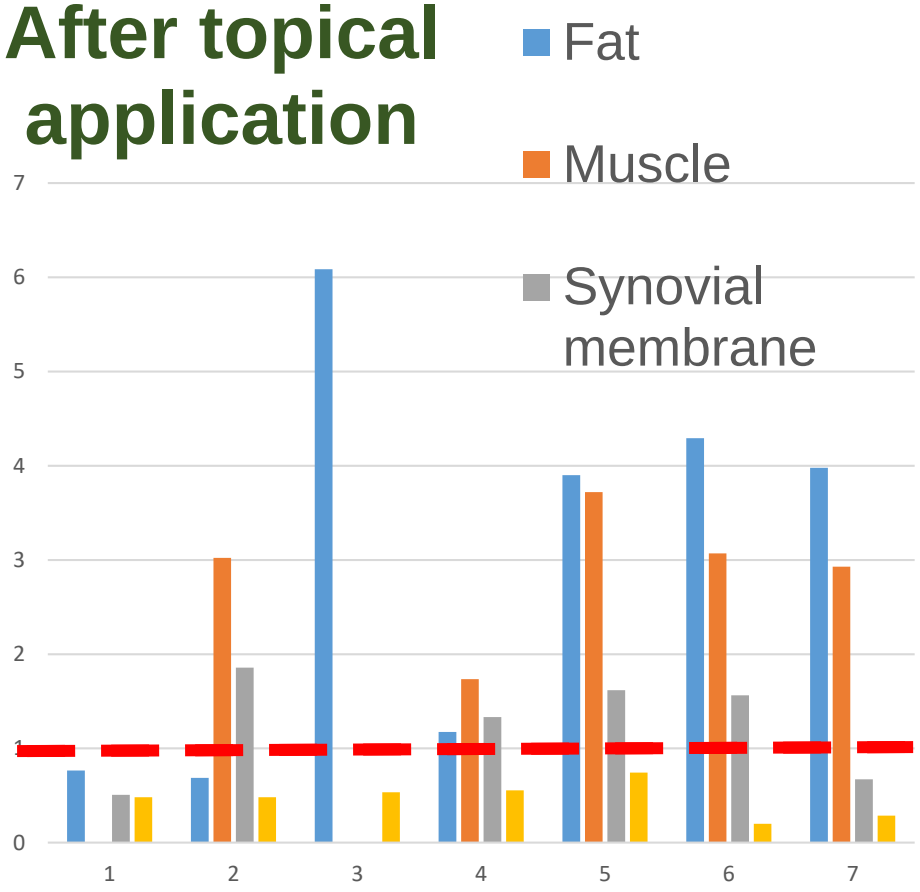
| Patient | Fat | Muscle | Synovial membrane | Plasma | Synovial fluid |
|---|---|---|---|---|---|
| 1 | 4.757 | <LOQ | 3.15 | 6.209 | 2.994 |
| 2 | 2.45 | 10.776 | 6.626 | 3.566 | 1.718 |
| 3 | 20.47 | <LOQ | <LOQ | 3.364 | 1.8 |
| 4 | 6.03 | 8.911 | 6.844 | 5.133 | 2.851 |
| 5 | 6.953 | 6.632 | 2.886 | 1.783 | 1.325 |
| 6 | 32.655 | 23.359 | 11.899 | 7.608 | 1.524 |
| 7 | 20.894 | 15.381 | 3.535 | 5.252 | 1.504 |
| Mean | 13.46 | 9.29 | 4.99 | 4.70 | 1.96 |
| SD | 9.81 | 8.24 | 3.84 | 1.95 | 0.68 |
| 5% CI | 3.35 | 1.84 | 1.55 | 2.96 | 1.35 |
| 95% CI | 16.81 | 11.14 | 6.55 | 7.66 | 3.31 |
| 8 | 4.236 | <LOQ | 6.695 | 4.242 | 8.301 |
| 9 | 2.946 | <LOQ | 11.242 | 5.069 | 15.747 |
| 10 | 6.494 | 3.167 | 16.166 | 5.255 | 7.858 |
| 11 | 1.857 | <LOQ | 12.413 | 3.415 | 17.233 |
| 12 | <LOQ | <LOQ | 4.787 | 2.37 | 2.655 |
| 13 | 5.907 | <LOQ | 24.232 | 11.728 | 32.485 |
| 14 | 5.276 | <LOQ | 29.965 | 14.335 | 33.064 |
| Mean | 3.85 | 0.66 | 15.07 | 6.63 | 16.76 |
| SD | 2.28 | 1.11 | 9.17 | 4.54 | 12 |
| 5% CI | 1.72 | −0.62 | 6.87 | 2.57 | 6.04 |
| 95% CI | 5.54 | −0.17 | 21.95 | 9.20 | 22.80 |
| *P*-value | 0.0476 | 0.0196 | 0.0181 | 0.6547 | 0.004 |

**Topical application**

**Oral dosing**

# Ratio of tissue to plasma diclofenac concentrations

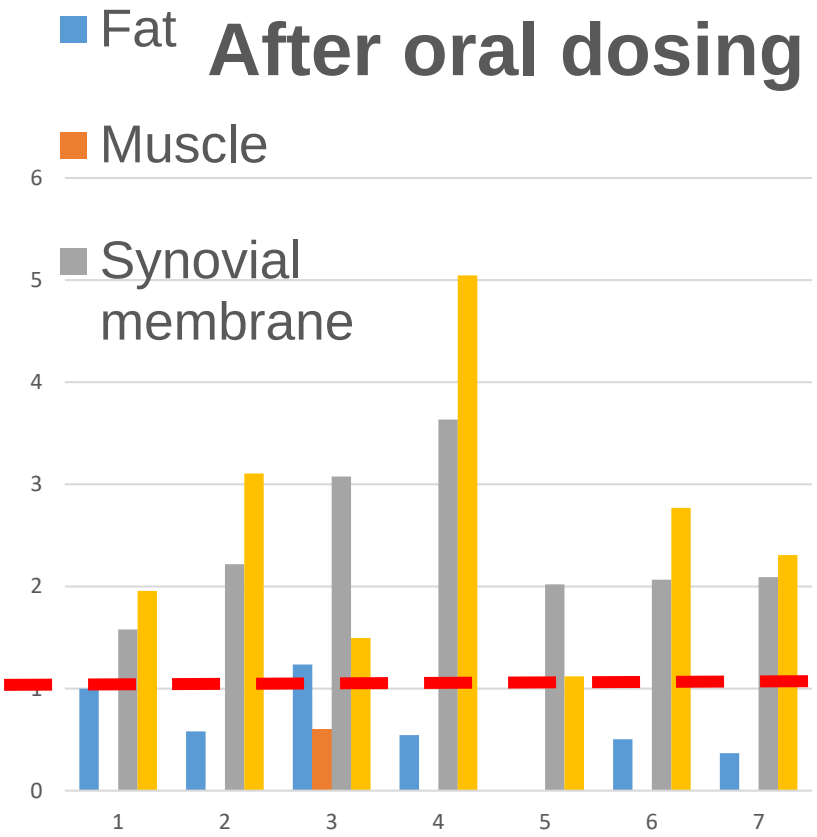
## After topical application




**Note Ratios:** Fat & Muscle ratio >1 for 5 subjects
Synovial membrane >1 for 4; Synovial fluid <1 for all

Adapted from S.Miyatake et al. BJCP 2008

## After oral dosing




**Note Ratios:** Fat & Muscle ratio <1 for all;
Synovial membrane & fluid ≥1 for all.

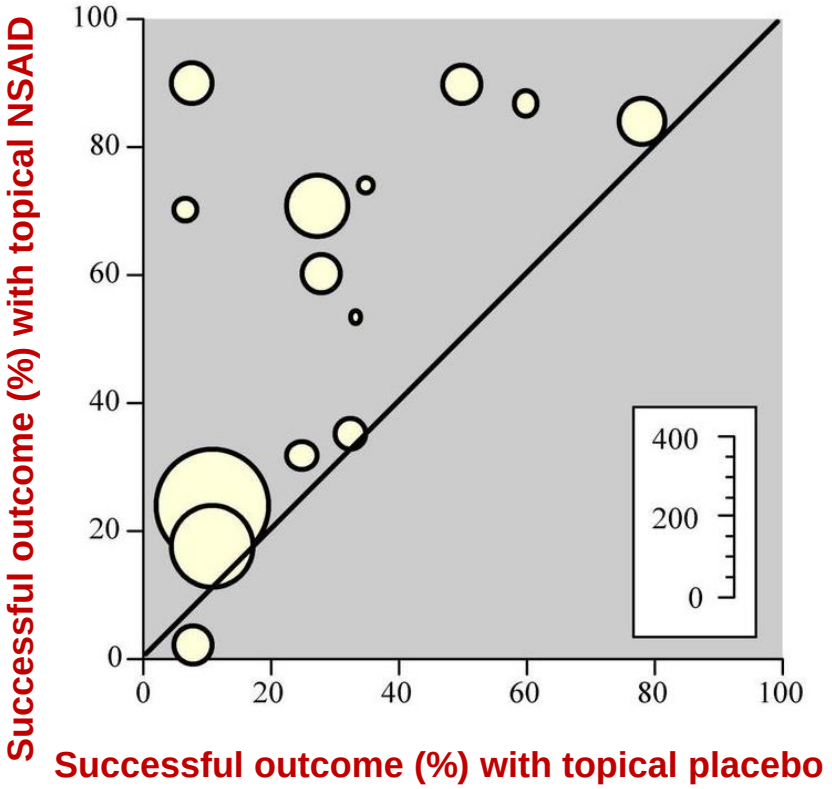
# Topical diclofenac – general principles

- Systemic exposure to diclofenac is limited after topical application.
- Diclofenac plasma concentrations were low or diclofenac was not detected irrespective the site of application of Emulgel on the body:
  - Back or forearm in healthy volunteers
  - Hand or kneel in patients
- Diclofenac has much higher concentrations in dermis and muscle than in plasma.
- Equivocal results for synovial fluid and tissue versus plasma

SIOUFI et al. Percutaneous absorption of diclofenac in healthy volunteers after single and repeated topical application of diclofenac emulgel. Biopharmaceutics & Drug Disposition, Vol. 15, 441-449 (1994)

# Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis

- Topical NSAIDs in chronic musculoskeletal pain Randomised double-blind studies of topical NSAID compared to topical placebo for two-week outcome of successful treatment. Inset scale shows size of individual trials.




*Mason et al BMC Musculoskeletal Disorders* 2004, 5:28

# Topical NSAIDs versus placebo for chronic pain

diclofenac hydroxyl-ethylpyrrolidine plasters

2% diclofenac in lecithin organogel

Piroxicam-gel **99% plasma bound**

Ibuprofen 5% cream **99% bound**.

Eltenac gel **97% plasma bound**

Felbinac-Gel **95% plasma bound**

Ffufenamic acid ointment 99% bound

diclofenac DHEP plasters

Indomethacin spray

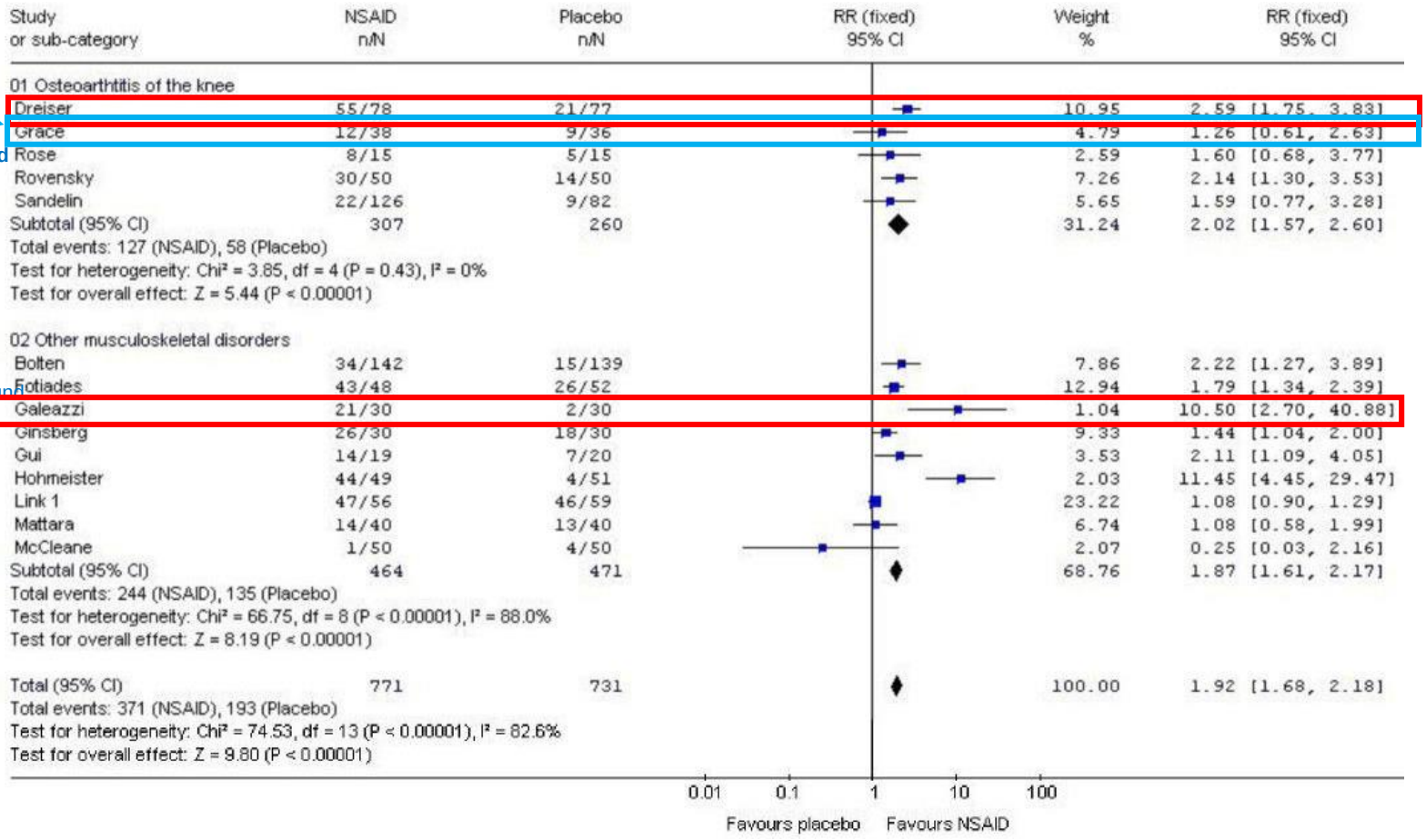
Ibuprofen 5gel **99% bound**.

Ffufenamic acid gel 99% bound

Ketoprofen gel 99% bound

Flurbipofen 99% bound

Flurbipofen 99% bound

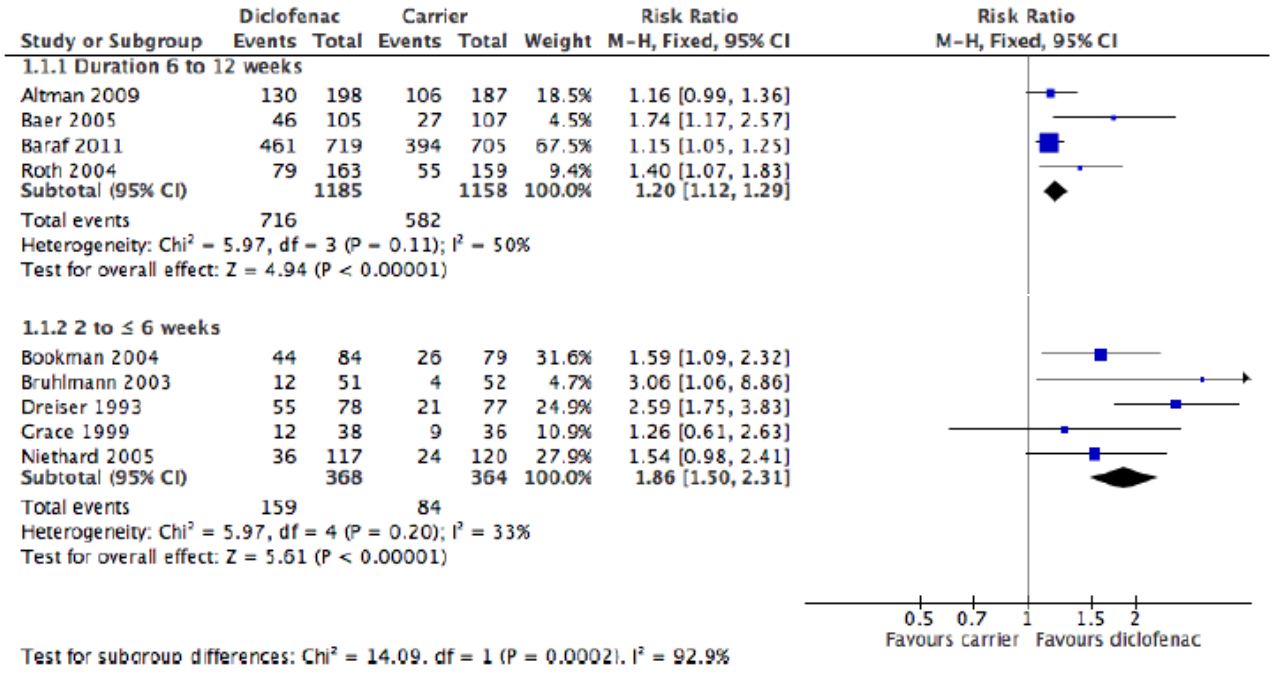



*Mason et al BMC Musculoskeletal Disorders* 2004, 5:28

# Forest plot: diclofenac vs carrier for chronic musculoskeletal pain

- Six studies (four publications; 2343 participants) of **6 to 12 weeks' duration**
  - 4 gel formulation
  - 2 solutions
  - knee arthritis in 5, hand arthritis in 1
- **Risk ratio (RR)** of treatment compared with carrier was **1.2** (95% confidence interval (CI) 1.1 to 1.3), and the NNT was 9.8 (7.1 to 16).
- Five studies (732 participants) of 2 to < 6 weeks' duration in knee arthritis
  - 2 plaster formulation
  - 2 gels
  - 1 solution
- The **RR** of treatment compared with carrier was **1.9** (1.5 to 2.3), and the NNT was 5.0 (3.7 to 7.4)
  - Plaster alone (258 participants) the RR was 2.7 (1.8 to 3.9) and the NNT was 3.1 (2.3 to 4.6).
  - Gel and solution (474 participants), the RR was 1.5 (1.2 to 2.0) and the NNT was 7.5 (4.6 to 20).

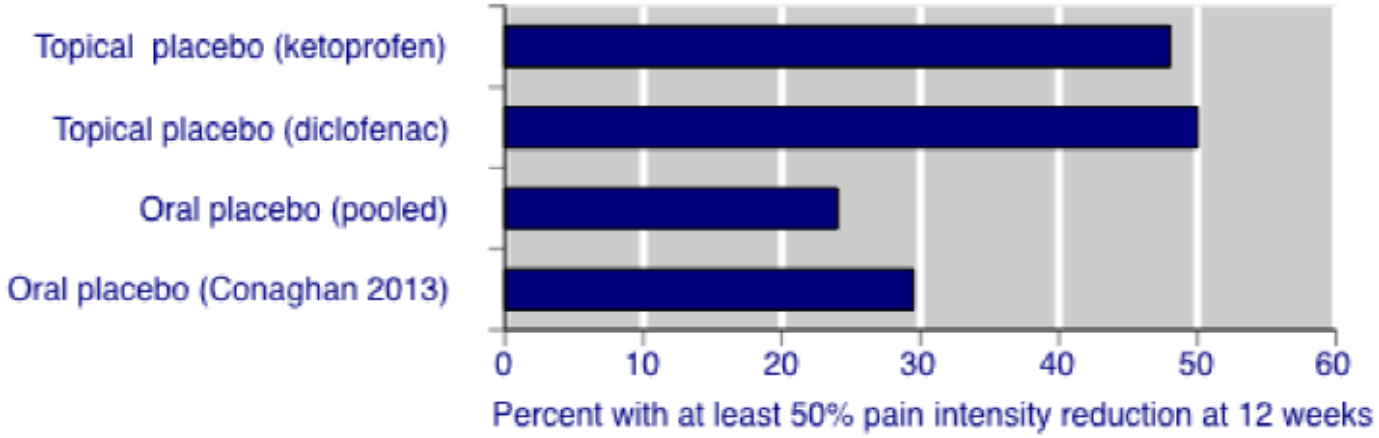
Clinical success' is either: A. >50% reduction in pain intensity or B. Osteoarthritis Research Society International Index (OARSI) response that includes response to pain, pain, function, and patient's global assessment




**Derry S, et al Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. Update April 2016**

# Topical placebo response can be quite profound

Figure 6. Placebo responses in topical NSAID studies for at least 50% pain intensity reduction after 12 weeks, compared with oral placebo from a pooled analysis and a single study with direct comparison with topical placebo.




**Implications for practice for people with chronic musculoskeletal pain**

Topical diclofenac and topical ketoprofen can provide good levels of pain relief in knee osteoarthritis in people aged over 40 years, but only in about 10% more people than with carrier. Adverse events are minimal with topical nonsteroidal anti-inflammatory drugs (NSAIDs).

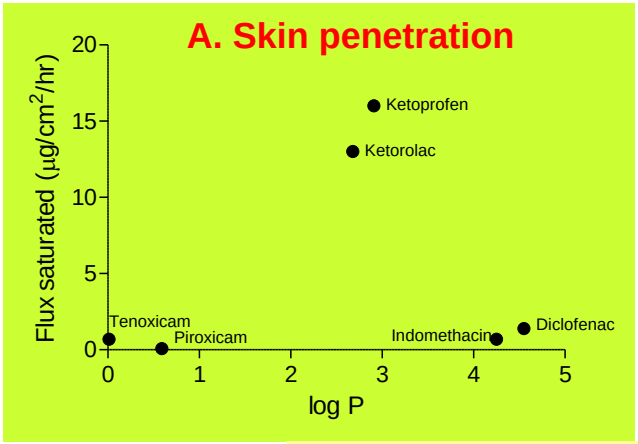
**Derry S, et al Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. Update April 2016**

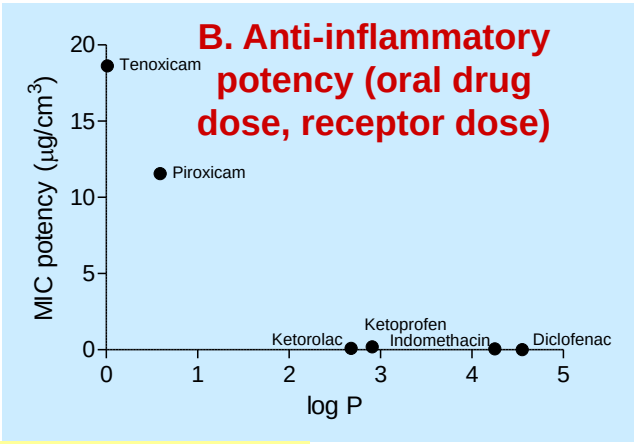
# Topical analgesics for acute and chronic pain in adults – an overview of Cochrane Reviews (Review)

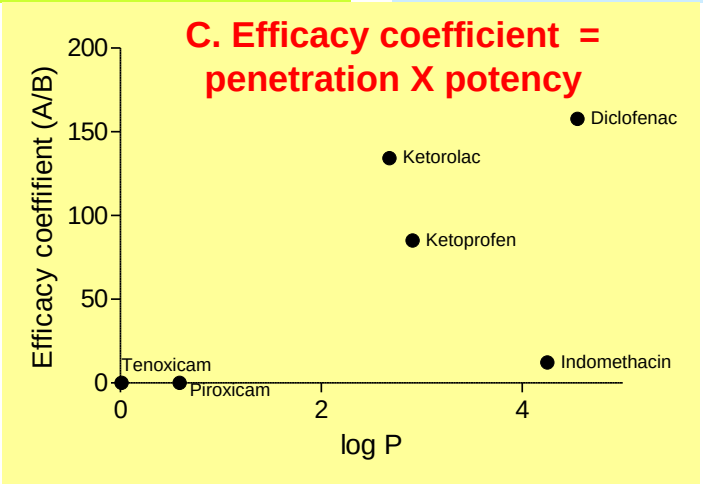
- The major implication for clinicians is the knowledge that there is a body of reliable evidence about a number of topical analgesics in acute and chronic pain. Drug and formulation matter, so choice of therapy should usually be driven by the evidence:
- Topical diclofenac and ketoprofen gel for strains and sprains, and to an extent in knee and hand osteoarthritis.
- Topical capsaicin high-concentration may be of limited use in some people with postherpetic neuralgia.
- Topical salicylate, low-concentration capsaicin, clonidine, and lidocaine are not well supported by evidence, or much evidence of effect.
- The issue is not which topical analgesic product works best, but achieving success for individual people with pain.

Derry S,Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, Gaskell H, Moore RA. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2017, Issue 5.

# Product Efficacy – Topical NSAIDs




Jepps et al
ADDR

# FDA Bioequivalence evaluation

- **A Modular Framework for In Vitro BE Evaluation Q1/Q2** sameness of inactive ingredient components and quantitative composition
- **Q3 (Physical & Structural Characterization)** as relevant to the nature of the product
- **IVRT** (In Vitro Release Test) for moderately complex products
- **IVPT** (In Vitro Permeation Test) or another bio-relevant assay for more complex drug products

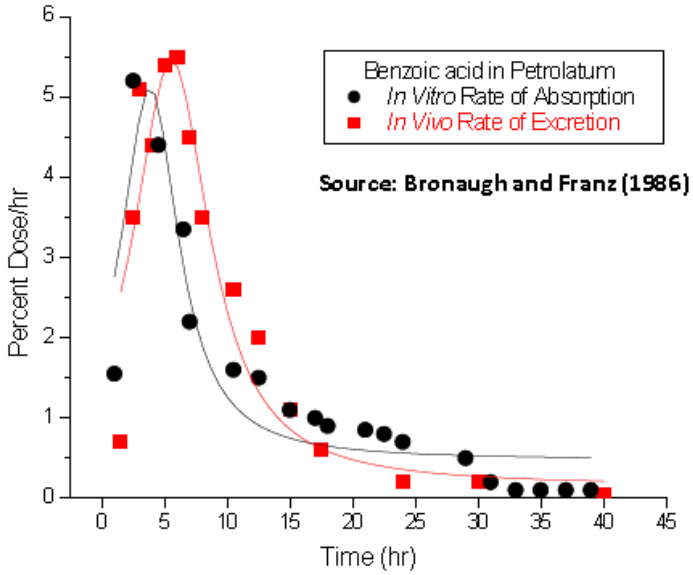
- **A Scalable Framework for BE Evaluation In Vivo** systemic PK studies may be appropriate
- **In Silico** computational modeling may be useful

From Sam Raney AAPS 2017

# FDA continued

- **Q1/Q2 Sameness** (components and composition of excipients)
- Mitigates the risk of known failure modes related to:
  - Irritation and sensitization
  - Formulation interaction with diseased skin
  - Stability, solubility, etc. of the drug
  - Vehicle contribution to efficacy

**IVIVR**

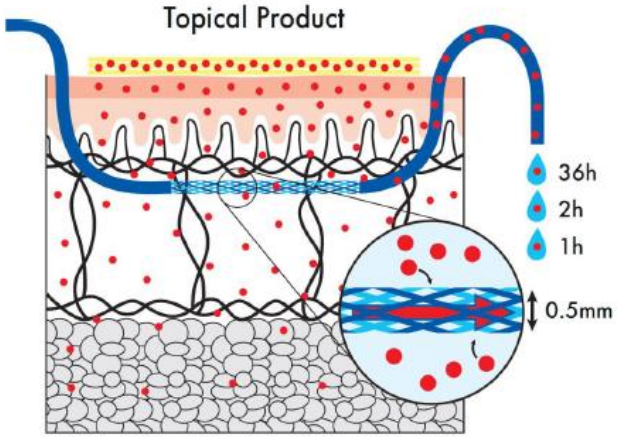


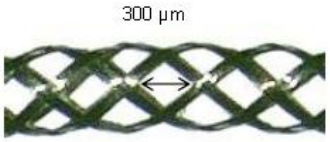

From Sam Raney AAPS 2017

# Frank Sinner's OFM work

*Open Flow Microperfusion*
*an introduction*

✓ **OFM samples represent diluted but unfiltered interstitial fluid**

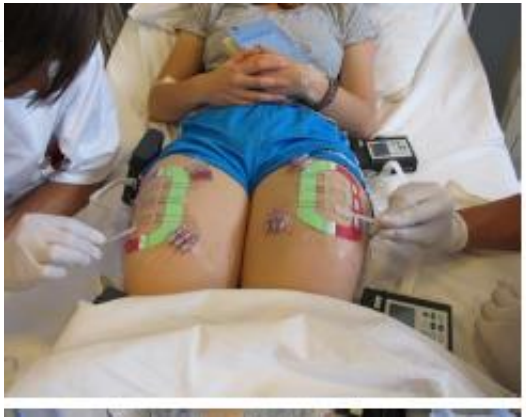


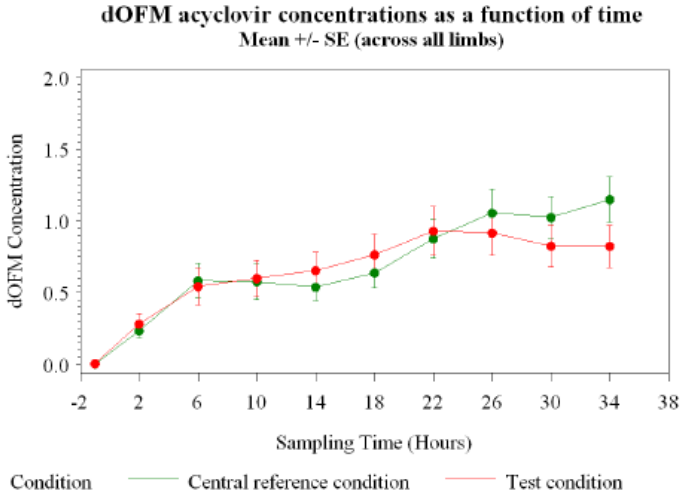




CE-certified for clinical use

**Variations may result from differences in**

**Trauma formation**
Application site
Dosage application
Probe depth
Flow rate
Local blood flow
Lateral diffusion and cross-talk
Systemic absorption and cross-talk

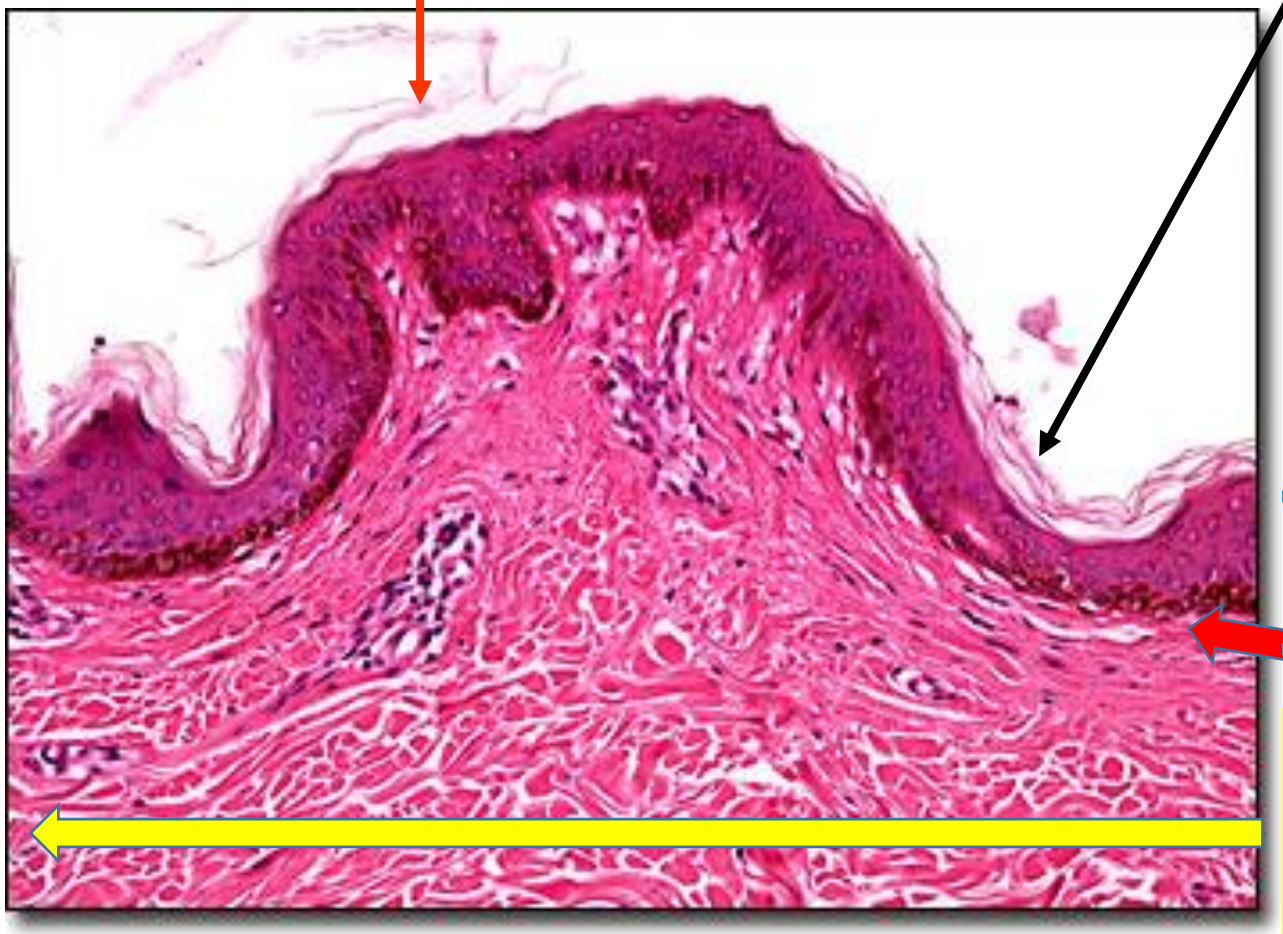





From Frank Sinner AAPS 2017

# FDA - Let us look at formulation testing in terms of the skin morphology & sites of action

Sampling - stratum corneum stripping is potential method to assess skin permeation



Stratum corneum – main barrier – also potential target site

**Various regions in viable epidermis & upper dermis = key target site**

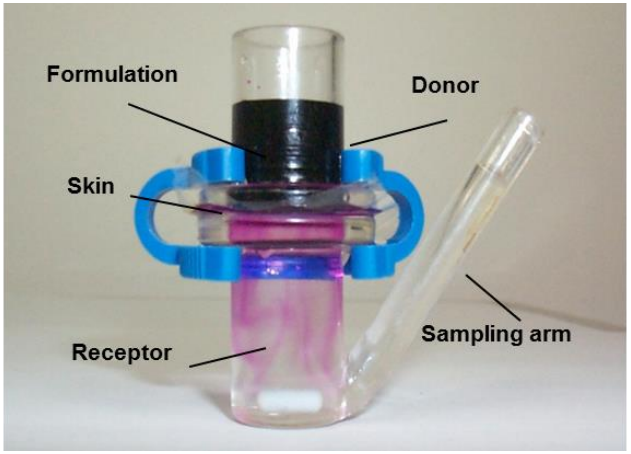
Epidermal membrane sampling site

Dermal sampling site for microdialysis and dermal microperfusion (*in vivo*) & *in vitro* dermatomed skin

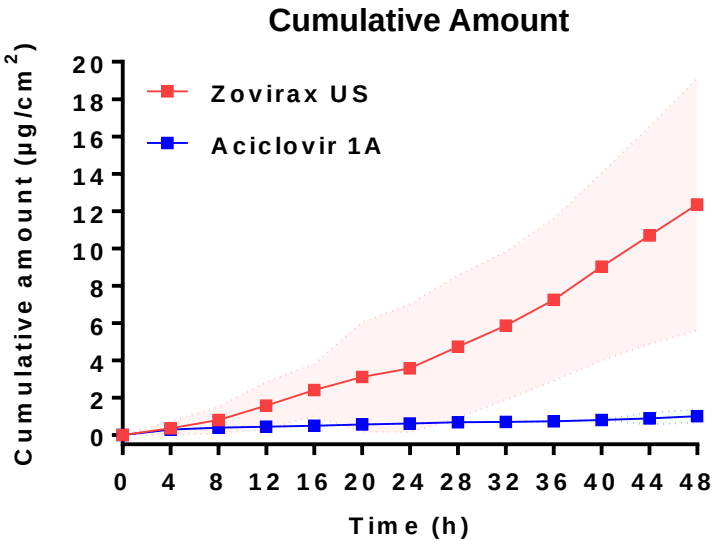
# One focus is *In Vitro* Permeation Test (IVPT)

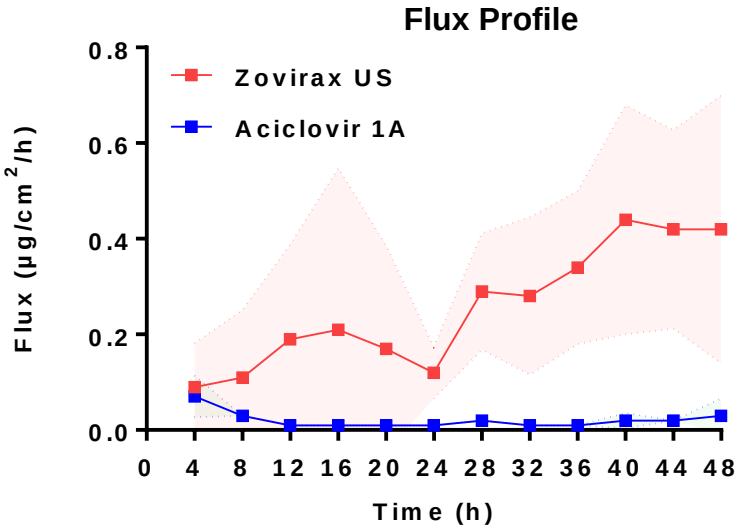
## Sandwich stratum corneum, epidermis, dermatomed skin & full thickness skin in a static or flow through Franz diffusion cell

- Long history
- Robust
- Simple
- Precise
- Reproducible




Here, epidermal membranes used for 2 acyclovir products

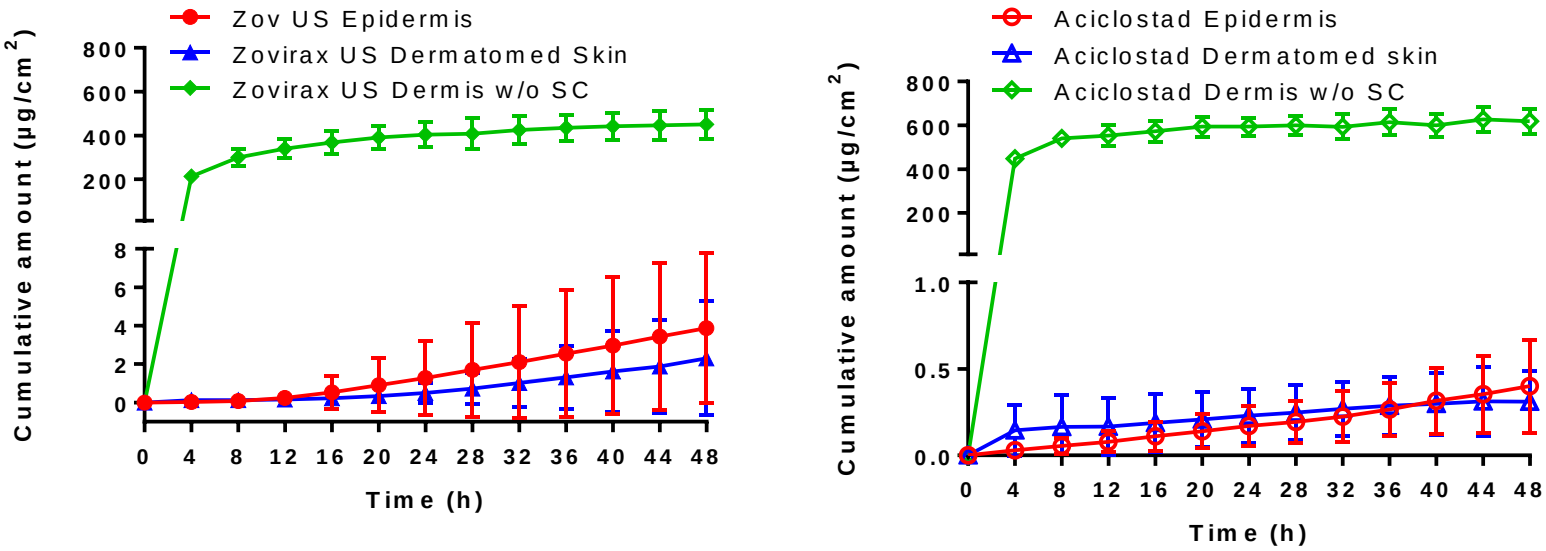



**Data shown as mean ± 95% Confidence Interval (CI)**
**Each point is the mean of 9* (3 donors & 3 replicates per skin)**

# *In Vitro* Permeation Test (IVPT) Studies

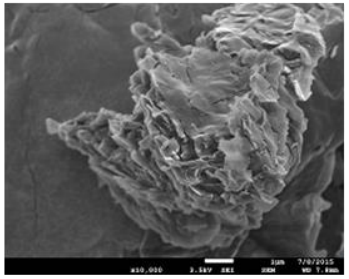
## We found similar permeation profiles for 2 acyclovir products using human epidermal membranes & dermatomed skin; dermal membranes are very permeable!

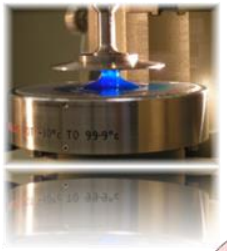


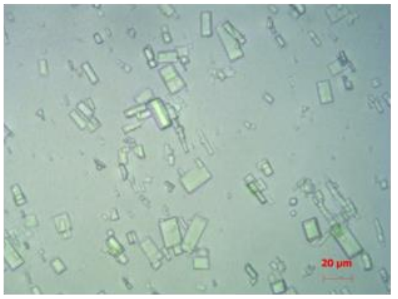

**Data shown as mean ± 95% Confidence Interval (CI)**
**Each point is the mean of 9* (3 donors & 3 replicates per skin)**

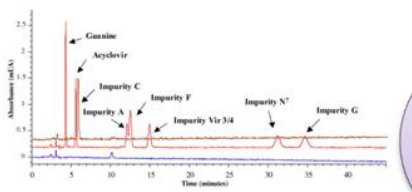
- Supports SC being main underlying barrier
- Suggests that either epidermal membranes or dermatomed skin could be used in acyclovir IVPT studies
- Skin barrier integrity is an important control component to get right.

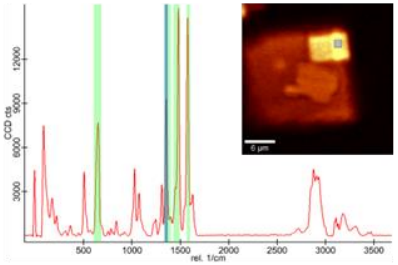
# ***In vitro* testing for product quality** by an articulated battery of physicochemical tests - potential critical quality attributes, i.e. Q3



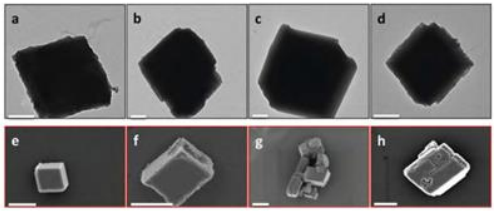


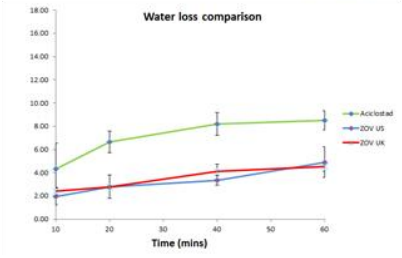




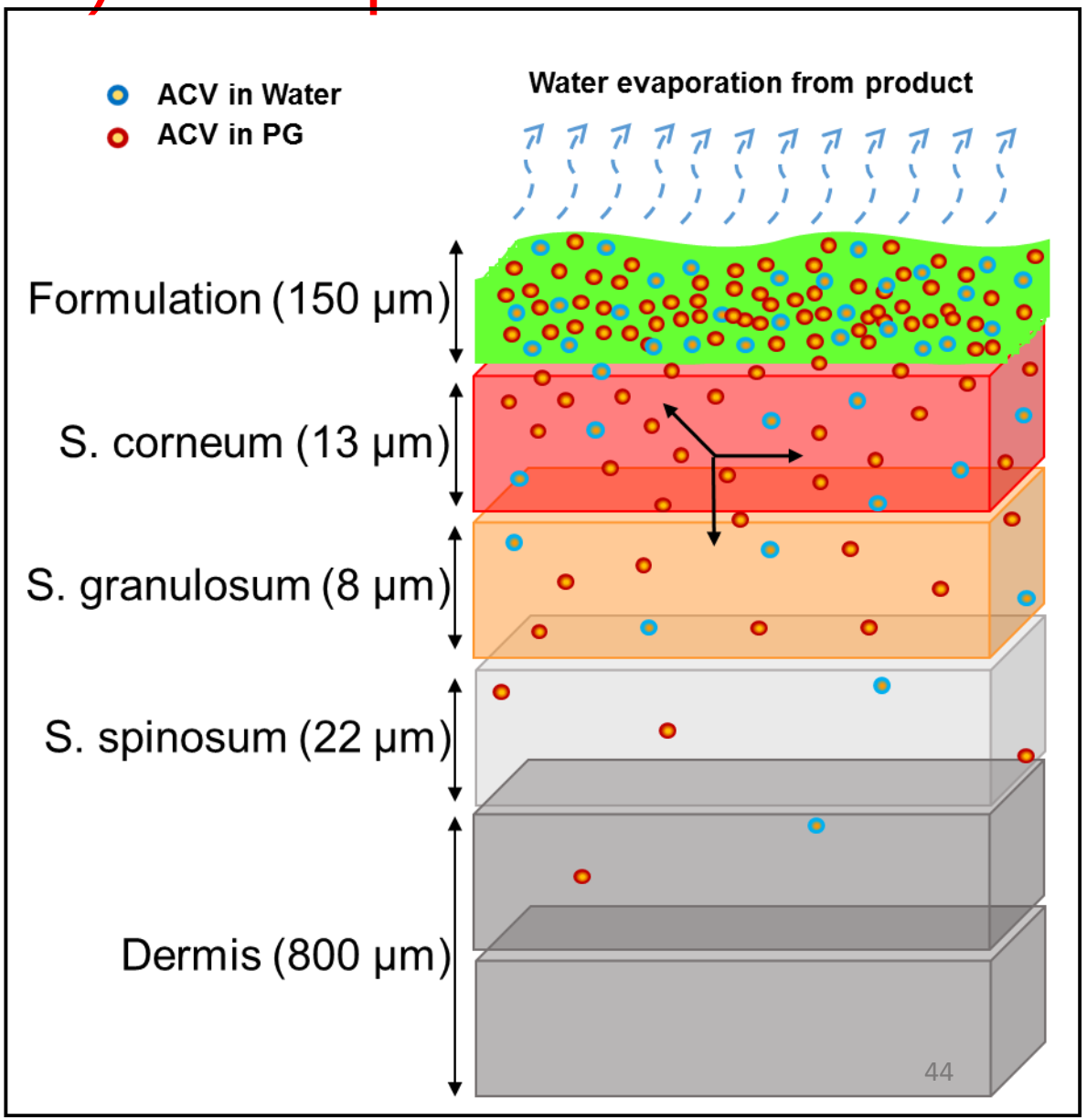







# Excipients interact directly with the stratum corneum (SC) can impact on IVPT

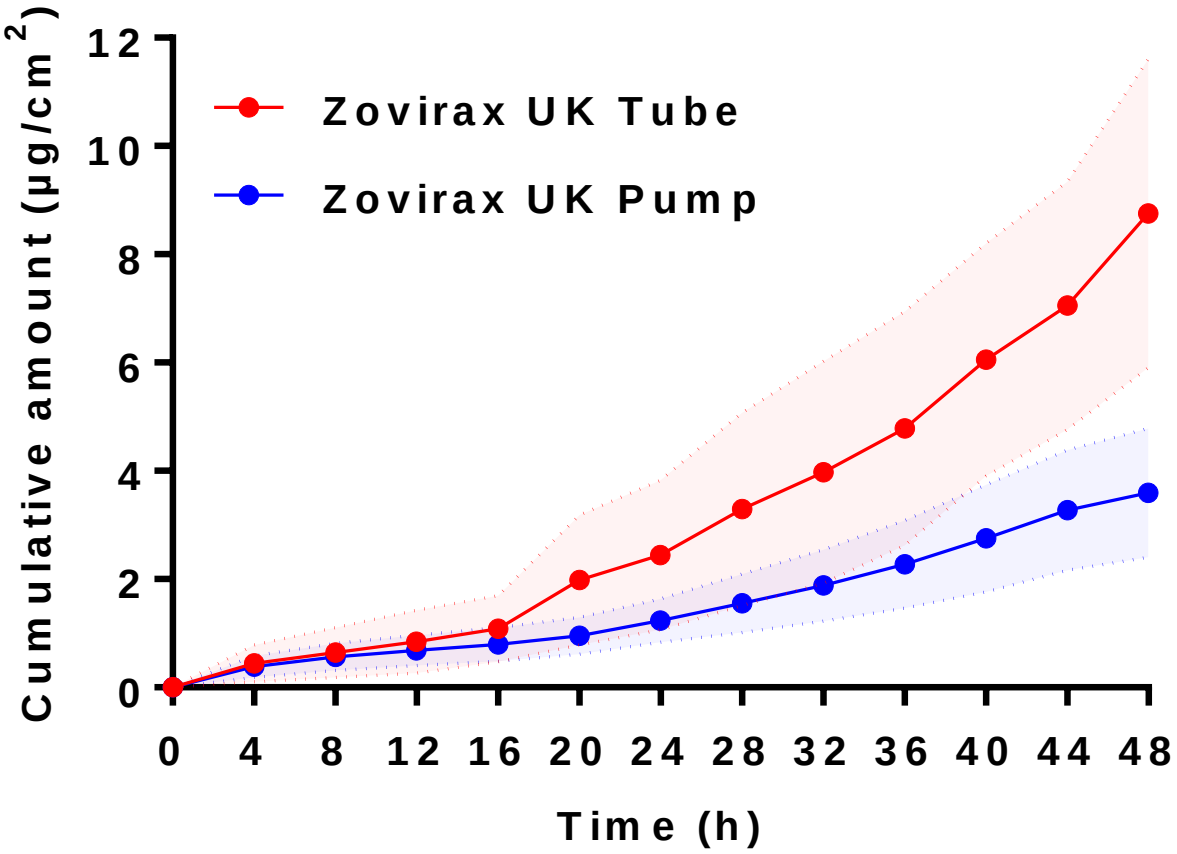
- Propylene glycol (PG) and water, known penetration enhancers, are two excipients present in all products
- Our work has also shown that PG and water can carry solutes into the SC & promote their permeation
- Both are likely to promote direct acyclovir uptake into the stratum corneum
- Potentially, product microstructure (Q3) can impact on acyclovir & enhancer bioavailability to the stratum corneum



# Q1, Q2 is important. What about Q3?

## Need to consider specific case when Q1 and Q2 are the same

- The Q1 and Q2 of acyclovir packaged in a tube and a pump dispenser are the same;
- But their IVPT profiles differ – Why?



# Using confocal Raman & rheology to assess impact of dispensing on Q3 metamorphosis & IVPT

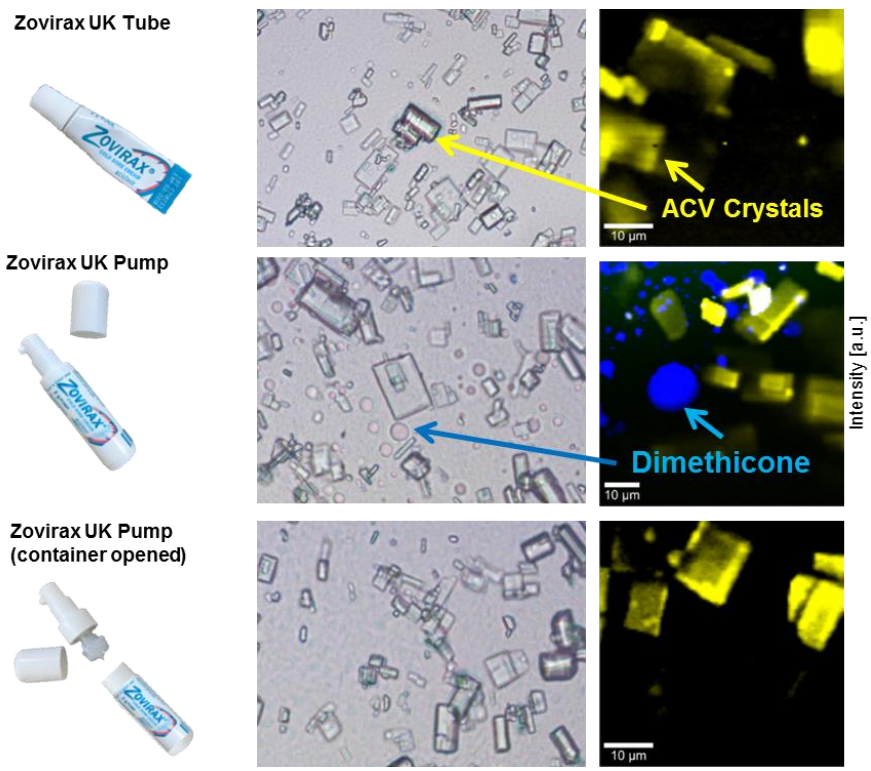
- Confocal Raman suggests that pumping affects the crystal habit for acyclovir and leads to the formation of dimethicone globules
- Rheology suggests that the packaged tube and pump have a similar yield stress but that the product after pumping is higher – due to dimethicone agglomeration?

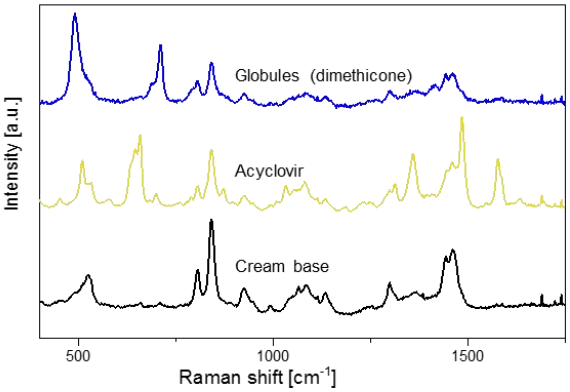
Yield stress from strain sweep (Pa)

78 ± 1.3

**182 ± 0.6**

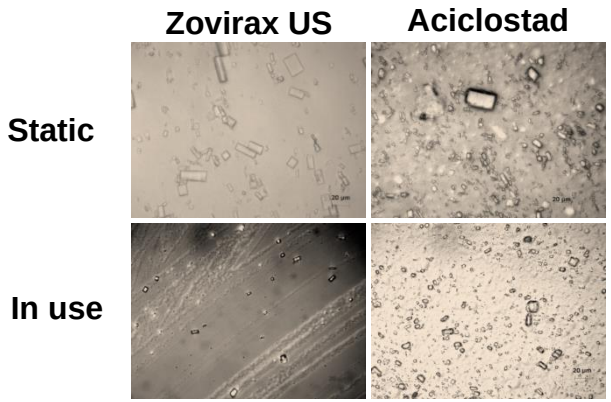
70 ± 10



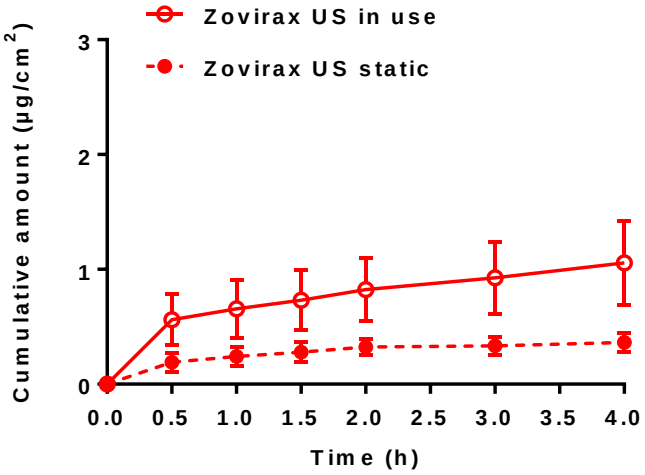



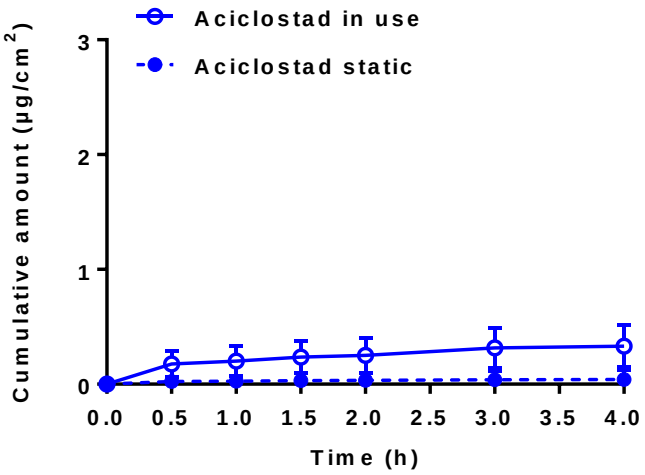
# Does how a product is applied to the skin also change the product microstructure (Q3) and resulting IVPT?

- In use (rubbing onto the skin for 30sec) led to a reduction in acyclovir particle size and redistribution of acyclovir in the various phases



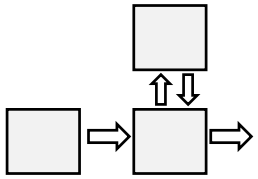

The IVPT for both Zovirax and Aciclostad suggests that rubbing enhances permeation and that this effect is more pronounced for the Zovirax product – indeed the ratio for rubbing/static amount permeated for Zovirax is 8-10 times higher than Aciclostad.



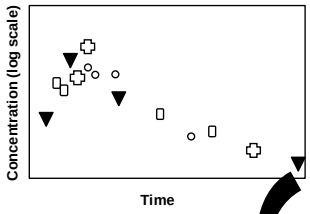



# Pharmacometric approach

Often need to assume or use a simple model

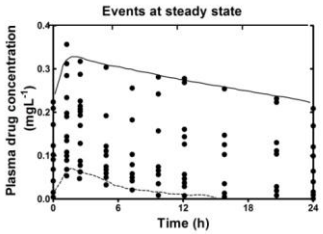


**Phase 1,2 studies**



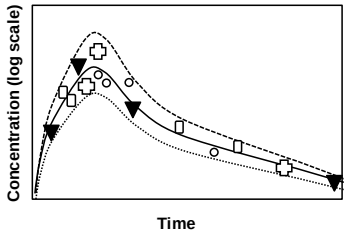

**Top down population pharmacokinetic approach**

**Phase 3 studies**



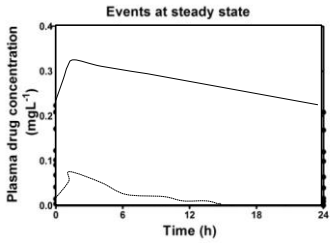

**Co-variates**

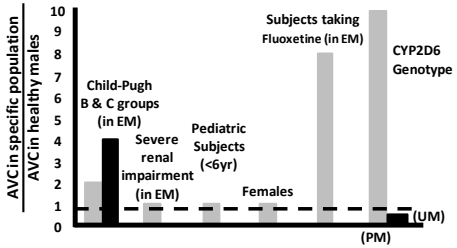
Age, Disease, Drugs, Genetics, Gender, Food, Formulation, Environment

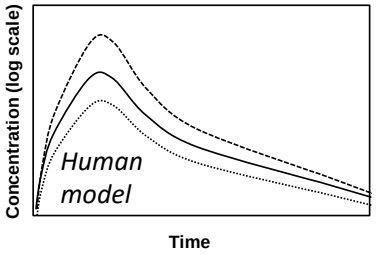



Roberts 2010

# Physiological pharmacokinetics




**Phase 3 studies in broader population 1000 - 3000**

**Phase 2 studies targeted condition (100 – 300)**

**Phase I volunteer pk studies (20 – 100)**

*Microdosing in man*

*Human* data

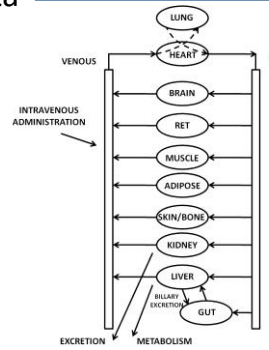
**Plan**

**Simulate, verify**

**Verify**

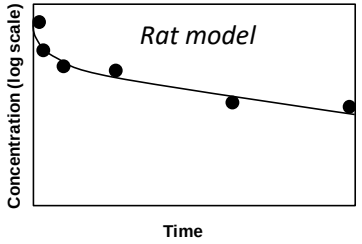
**Simulate**

**Compound properties**




**Verify**

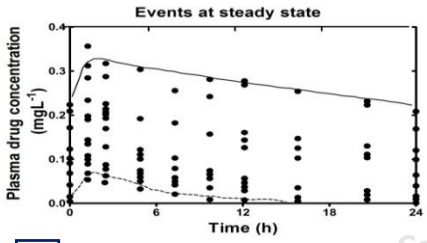
**Simulate**




*In silico, In vitro* animal data

**Preclinical**

**Bottom up physiological pharmacokinetic approach**



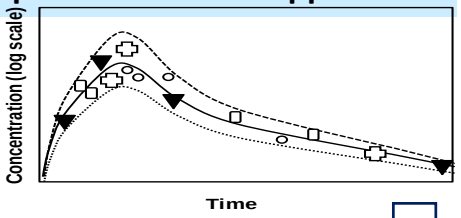

Phase 3 studies

Phase 1,2 studies

Co-variates

Age, Disease, Drugs, Genetics, Gender, Food, Formulation, Environment

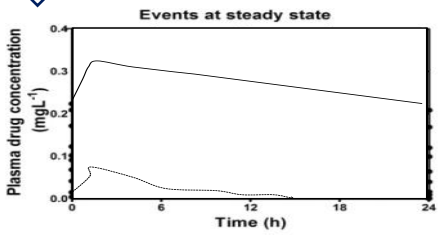
**Top down population pharmacokinetic approach**



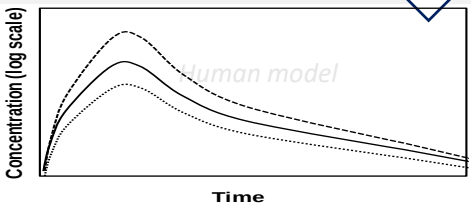

**Confirm Phase 3 data within expectations**

**Middle out pharmacokinetic approach**

**Refine preclinical PK with early experimental human (Phase 0, I & II) data.**




**Future is combination of approaches**




Human model

Phase 3 studies in broader population 1000 - 3000

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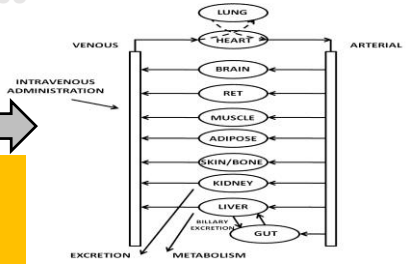



Verify

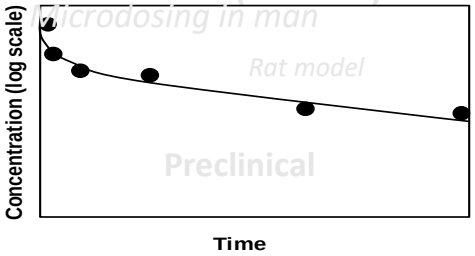
Rat model

Simulate

Preclinical

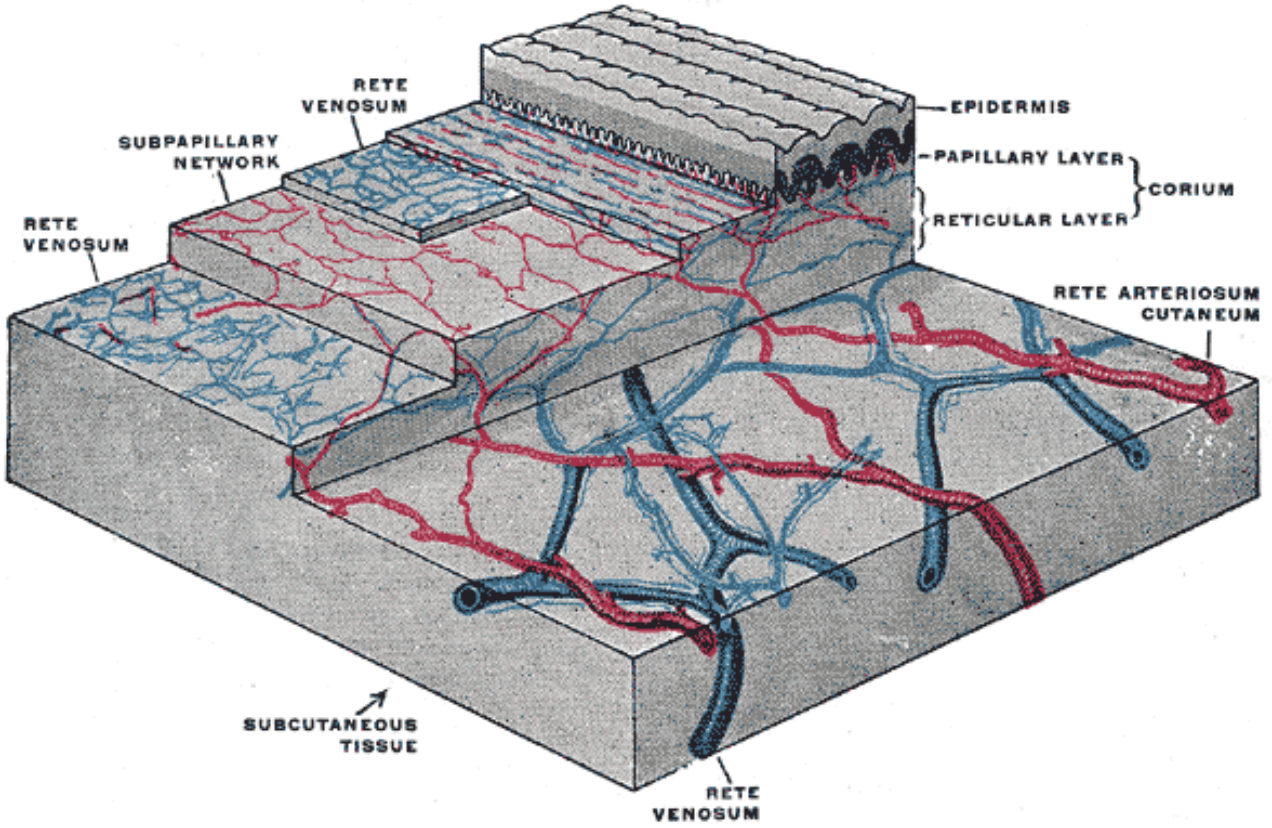
**Bottom up physiological pharmacokinetic approach**

*In silico, In vitro* animal data



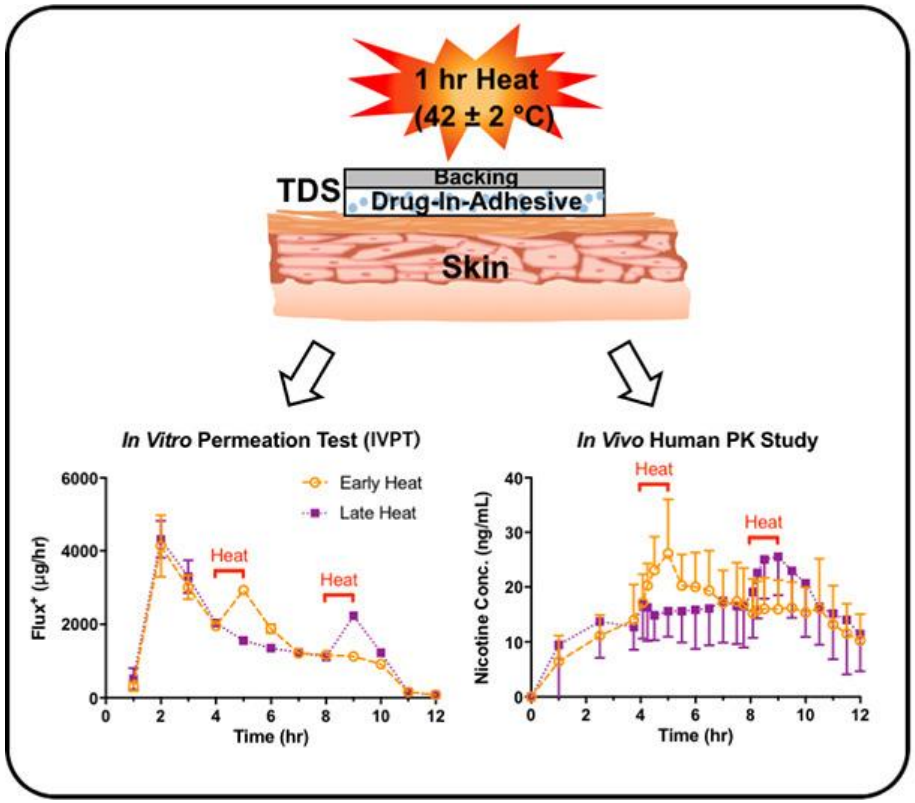
# Work with FDA involves 4 D modelling (space and time)

## Blood vessels in skin (foot)



# *In vitro–in vivo* correlations for nicotine transdermal delivery systems for transient heat application

*Shin et al Journal of Controlled Release 270 (2018) 76–88*




IVIVC