Prediction and optimisation of drug delivery into and through the skin

Richard H. Guy

University of Bath

XIII[th] Spanish-Portuguese Conference on Controlled Drug Delivery

Santiago de Compostela, Spain, January-2020

"I've got you under my skin", written by Cole Porter in 1936, and a Frank Sinatra classic.

Acknowledgements: Begoña Delgado-Charro, Annette Bunge, Jane White, Sarah Cordery, Alice Maciel Tabosa, Natalie Belsey, Andrea Pensado-López, Wing Sin Chiu, Hazel Garvie-Cook, The Leo Foundation, U.S. Department of Health & Human Services, Food & Drug Administration (award numbers: D3921303, 1-U01-FD004947 and 1-U01-FD006533). *The views expressed in this presentation do not reflect the official policies of the U.S. Food & Drug Administration or the U.S. Department of Health & Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.*

1

Skin (or dermal) pharmacokinetics

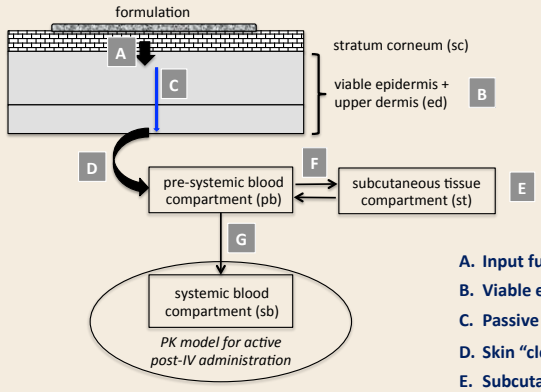
Objectives for a practical PK description of skin absorption:

1. Incorporates a 'sensible' and relevant description of the "input" kinetics of the active from the applied formulation.
2. Realistically describes the 'clearance' of active from viable skin.
3. Permits estimation of the concentration of active in 'compartments of interest' in the skin (basal epidermis, appendages, etc.).
4. Enables systemic exposure to active (i.e., safety) to be assessed.
5. Is testable and validated.

William of Ockham (1287-1347): Occam's Razor - among competing hypotheses, the one with the fewest assumptions should be selected.

2

Pharmacokinetic model for skin absorption



A. Input function of active from SC into viable skin.
B. Viable epidermis and upper dermis combined.
C. Passive diffusion from SC to dermal microcirculation… and more.
D. Skin "clearance" (diffusion, blood flow, 'extraction coefficient').
E. Subcutaneous tissue compartment.
F. Extent of distribution into subcutaneous tissue.
G. 'Elimination' of active from skin into blood.

3

Predicting the skin permeability and input flux of an active

Algorithm derived by Potts & Guy* from extensive database of ~100 k_p values across human skin *in vitro* following application of the chemicals in water:

$$\log k_p = -2.7 + 0.71 * \log P - 0.0061 * MW$$

$$J_{max} = k_p \times C_{w,sat}$$

P = octanol-water partition coefficient of active
MW = molecular weight
$C_{w,sat}$ = aqueous solubility
Equation has reasonable predictive power
Units of k_p are cm/hr

Cleek & Bunge correction for highly lipophilic compounds:

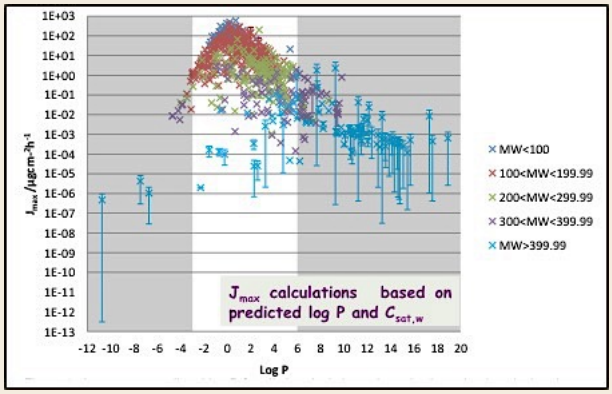
$$k_p^{corr} = \frac{k_p}{1 + \frac{k_p \bullet \sqrt{MW}}{2.6}}$$

*R.O. Potts and R.H. Guy. Predicting skin permeability. *Pharm. Res.* 9, 663-669 (1992).

4

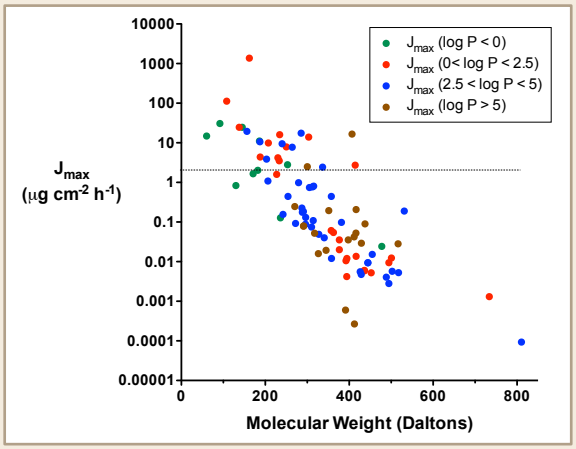
Predicting the skin permeability of an active

Algorithm derived by Potts & Guy* from extensive database of ~100 k_p values across human skin in vitro following their application in water:



5

Topical and transdermal drugs (n=92)

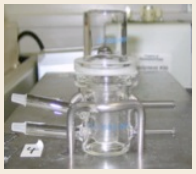


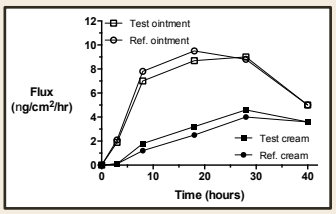
R.H. Guy. Pharmacology of the Skin: Principles of Topical Drug Delivery. Chapter 13 in Rook's Textbook of Dermatology, 9th Edition. ISBN: 978-1-118-44119-0. Edited by C.E.M. Griffiths, J. Barker, R.J.G. Chalmers, T.O. Bleiker and D. Creamer, Wiley-Blackwell, Ltd., Chichester, U.K., 2016.

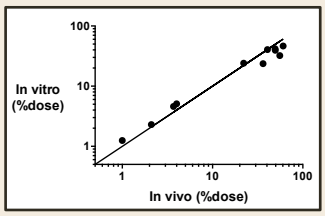
6

Measuring and validating drug "input kinetics" *in vitro*

- In vitro skin penetration experiments
  - long history, substantial data resource, but…
  - no dermal microcirculation… clearance?
  - usually, not 'alive'… metabolism?
  - relevance of epidermal/dermal levels?
  - application technique(s) relevant to real-world use of products?



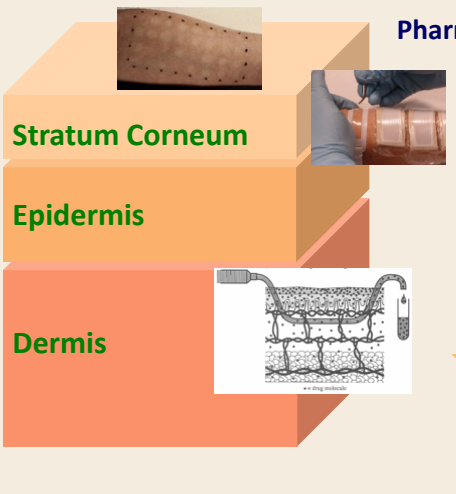




Franz, Lehmann, Raney, *Skin Pharmacol. Physiol.*, 2009, 2011

7

Assessing skin bioavailability *in vivo* in man



Pharmacodynamic assay

SC sampling, IR/Raman spectroscopy/imaging

Suction blister x

Microdialysis/oFM

Biopsy x

Blood levels

8

Measuring and validating drug "input kinetics"

How can drug "input kinetics" into skin *in vivo* be measured, and the method validated?

A. Hypothesize that drug quantification in stratum corneum provides useful information.

B. Test using transdermal drug delivery systems of well-characterised 'input'.

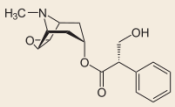
C. Additional opportunity to establish in vitro – in vivo correlations.

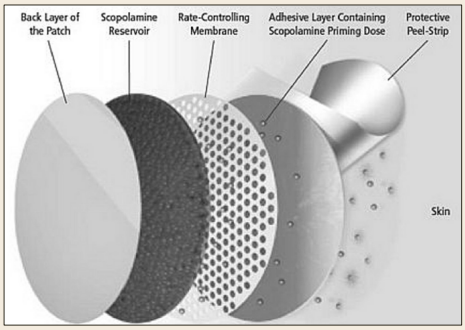
D. Proof-of-concept permits unknown "input kinetics" to be determined.

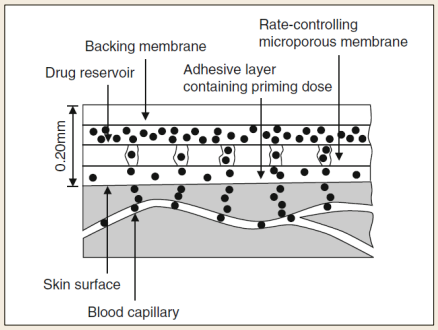
E. Example: scopolamine (buprenorphine, nicotine, lidocaine have also been studied).

9

Transdermal scopolamine





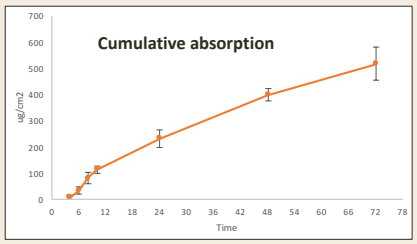


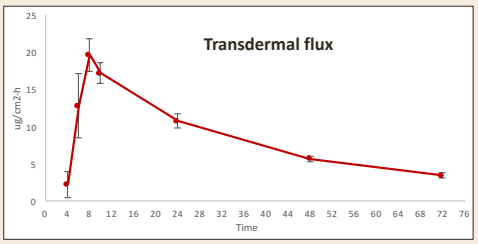
Drug loading distributed between adhesive layer (~140 µg) and reservoir.

Delivery from a 2.5 cm^2 patch (across post-auricular skin) is about 1 mg over 3 days.

10

Transdermal scopolamine – in vitro skin penetration





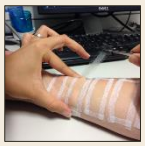
High initial flux observed as 'priming' dose in adhesive is rapidly released.

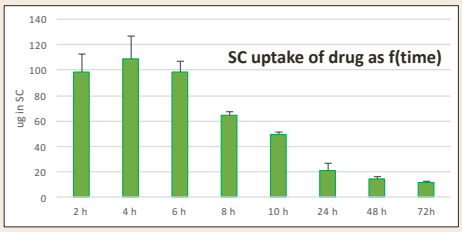
Subsequently, slower, controlled delivery from the drug reservoir.

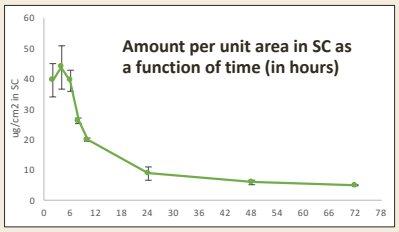
Pensado A et al. (2017) unpublished data.

11

Transdermal scopolamine – SC sampling *in vitro*





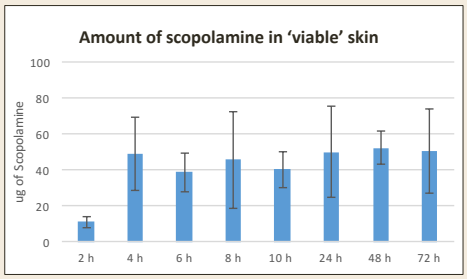


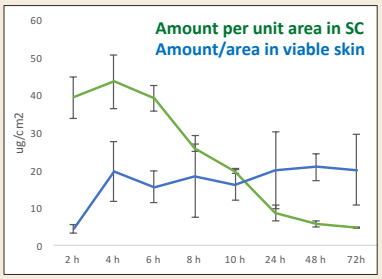
SC uptake is initially substantial, reflecting flux measurements, then achieves a lower 'steady-state level at longer times.

Pensado A et al. (2017) unpublished data.

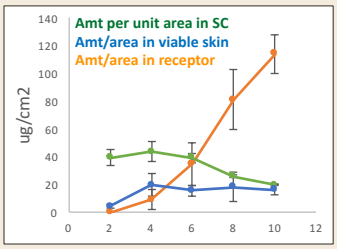
12

Transdermal scopolamine – skin PK *in vitro*





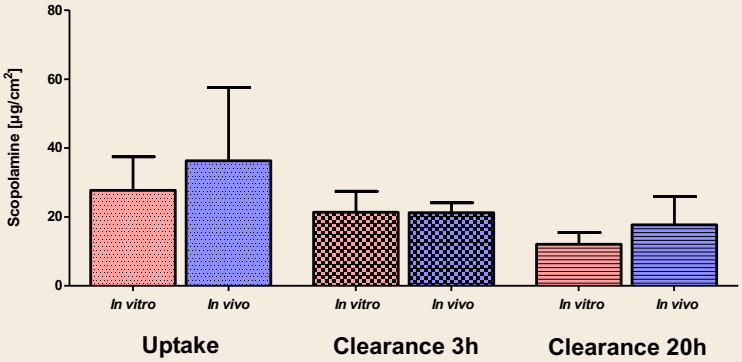
Amount in 'viable' skin reaches steady-state levels quickly and these are then sustained over duration of patch use.



Pensado A et al. (2017) unpublished data.

13

Transdermal scopolamine – *in vivo* skin PK



Reasonable correlation observed between *in vitro* and *in vivo* measurements.

Pensado A et al. (2017) unpublished data.

14

Stratum corneum (SC) sampling *in vivo*

what if stratum corneum is not the target?

Translational *in vivo* methodology for *in vitro* correlation

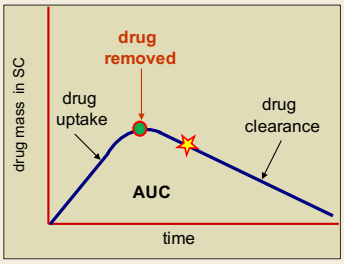
- drug/formulation specific for IVIVC
- simpler than PK; feasible when plasma levels too low
- simpler than open flow microperfusion/microdialysis

Measures drug delivery rate from SC

- measure mass of drug in SC after period of clearance (★)
- compare to mass of drug in SC at end of uptake (●)

Calculate the average flux from the SC to deeper tissues:

$$\text{Average Flux} = \frac{(M_{Up} - M_{Clear})/A}{t_{Clear} - t_{Up}}$$

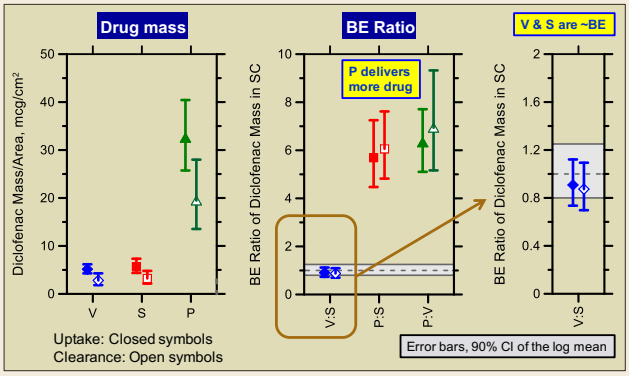


15

Stratum corneum (SC) sampling *in vivo*

Diclofenac: target = subcutaneous tissue

- **Protocol identical to that used for econazole (n = 14 healthy subjects)**
- **3 formulations: Solaraze, Penssaid, Voltaren**
- **One uptake time – 6 hours. One clearance time – 17 hours**

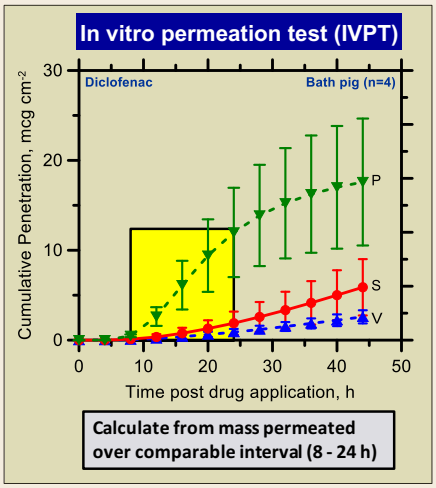


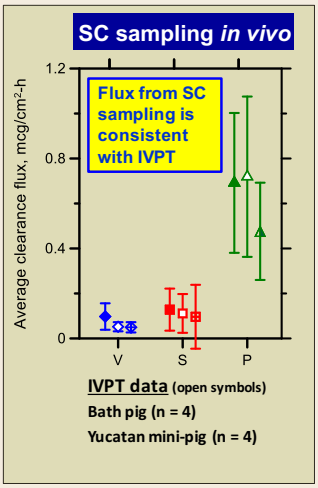
Cordery SF *et al. Int J Pharm.* 529 (2017) 55-64.

16

Stratum corneum (SC) sampling *in vivo*

Diclofenac: compare in vitro and in vivo delivery rates to skin





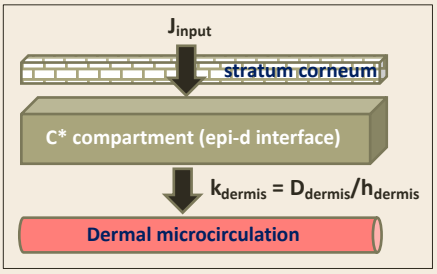
J_{input} from:

$$\frac{(M_{Up} - M_{Clear})/A}{t_{Clear} - t_{Up}}$$

Cordery SF *et al. Int J Pharm.* 529 (2017) 55-64.

17

Higuchi's C* concept – concentration of active at its target



C* is effective concentration of active at site of action (e.g., basal cells of epidermis)

At steady-state:

Rate of active delivery (μg/cm²/h) to target = J_{input}

Rate of active depletion (μg/cm²/h) from target = k_{dermis} x C*

where $k_{dermis} = D_{dermis}/h_{dermis}$

D_{dermis} = diffusivity of active in dermis

h_{dermis} = distance from C* compartment to microcirculation

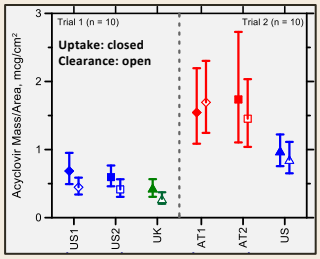
⇒ $J_{input} = k_{dermis}$ x C* and $C^* = J_{input}/k_{dermis}$

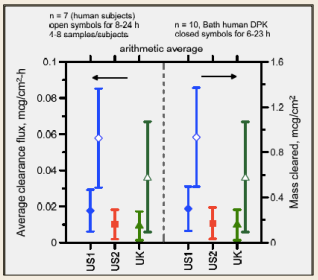
Binding of active in SC and skin "1st-pass" is captured in J_{input}; binding in dermis by D_{dermis}.

Imanidis G et al., Pharm. Res. 11 (1994) 1035-1040. Mehta SC et al., J. Pharm. Sci. 86 (1997) 797-801.

18

Higuchi's C* concept – acyclovir example





SC sampling *in vivo* in man after 6 h uptake and 17 h clearance.

J_{input} into epidermis deduced from: $\frac{(M_{Up} - M_{Clear})/A}{t_{Clear} - t_{Up}}$

$J_{input} \simeq 15$ ng/cm²/h

$D_{dermis} \simeq 7 \times 10^{-3}$ cm²/h[a]

$h_{dermis} \simeq 150 \times 10^{-4}$ cm[a]

⇒ C* = 30 ng/cm²

⇒ C* is below the target concentration deduced from animal studies[b]

[a]Krestos K et al., Inter. J. Pharmaceut. 346 (2008) 64–79.

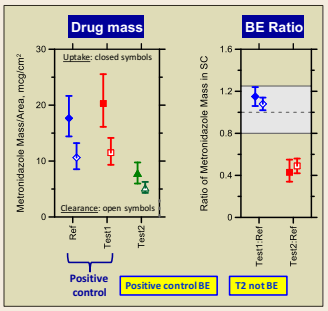
[b]Mehta SC et al., J. Pharm. Sci. 86 (1997) 797-801.

Pensado A et al. (2019) Pharm. Res. 36:180

19

Topical bioavailability derived from SC sampling

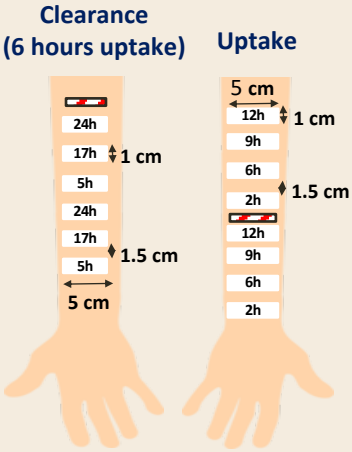
- Both *in vivo* and *in vitro* methods showed that topical bioavailabilities of diclofenac and acyclovir from different products were not necessarily equivalent.
- Excellent *in vivo : in vitro* correlation for drug permeation observed.
- This suggests, at least for these two drugs, that
  - *in vitro* skin penetration measurements are useful proxies for *in vivo* measurements, and
  - quantitative rates of active delivery to tissues beneath stratum corneum can be derived from tape-stripping.



Pedon de Araujo, T. et al., Int. J. Pharm. 541 (2018) 167–172.

20

But topical bioavailability is not all about the active…



Voltarol® Medicated Plaster - Diclofenac

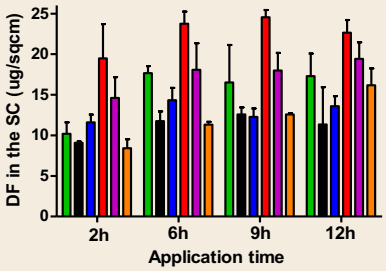
Uptake (n = 6):
Patch application: 2, 6, 8, 12h

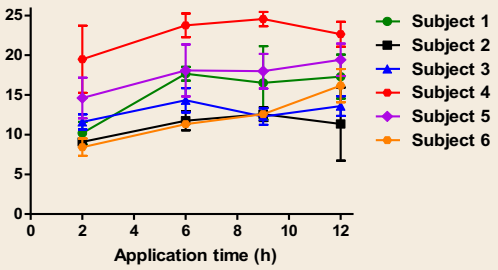
Clearance (n = 6):
Patch application: 6h
Time of clearance: 5, 17, 24h.

Maciel Tabosa MA et al. (2017) Ph.D. thesis

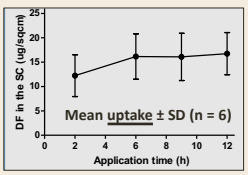
21

But topical bioavailability is not all about the active…





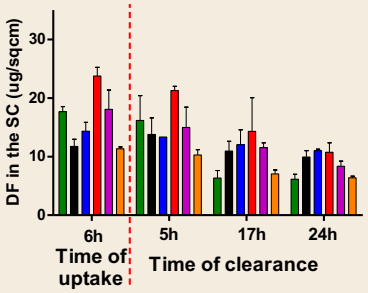
SC uptake does not increase significantly after 2 hours

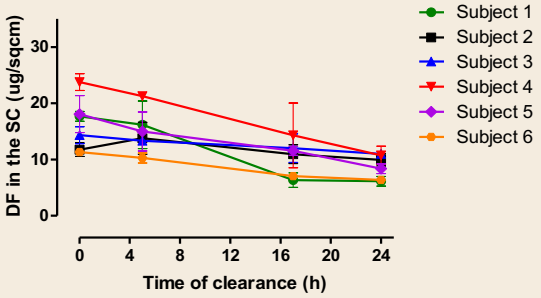


Maciel Tabosa MA et al. (2017) Ph.D. thesis

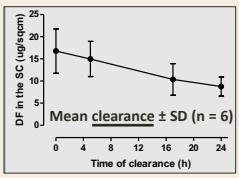
22

But topical bioavailability is not all about the active…





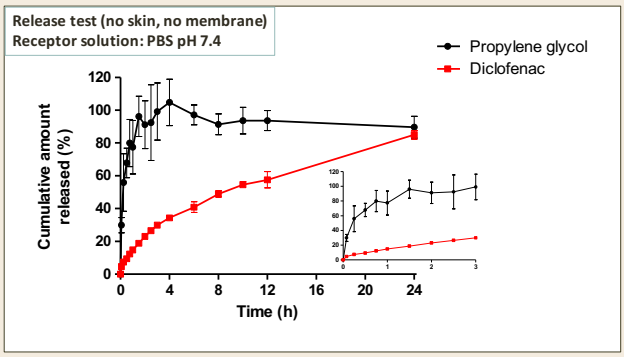
SC clearance of drug is slow



Maciel Tabosa MA et al. (2017) Ph.D. thesis

23

Diclofenac and propylene glycol: *in vitro* release test



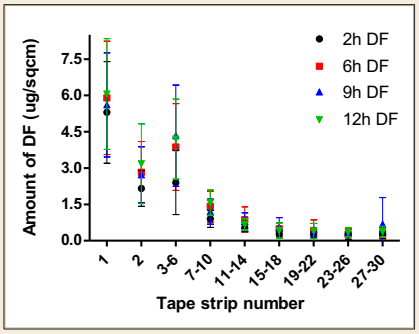
Amount of **DF** remaining in patch after 24 hours = **14 ± 3.9 %**

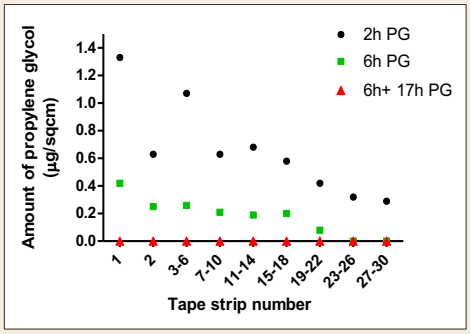
Amount of **PG** remaining in patch after 24 hours = **2.5 ± 1.2 %**

Maciel Tabosa MA et al. (2017) Ph.D. thesis

24

Diclofenac and propylene glycol: SC sampling *in vivo*



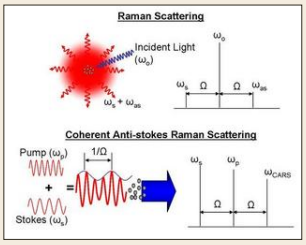


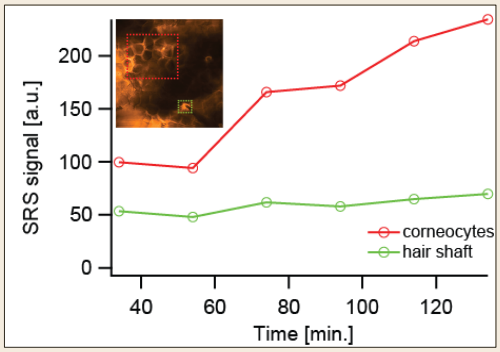
SC profiles of propylene glycol indicate significant depletion of cosolvent during 6 hours application of patch and rapid clearance after its removal

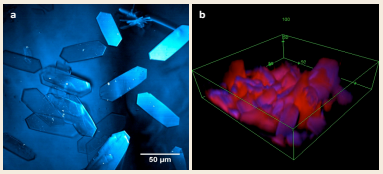
Maciel Tabosa MA et al. (2017) Ph.D. thesis

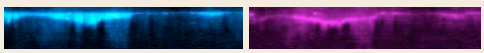
25

Imaging skin penetration and vehicle 'metamorphosis'





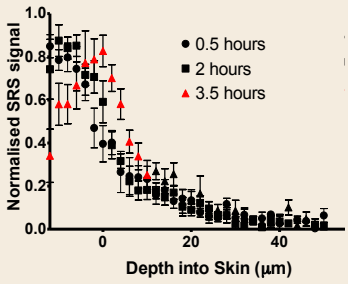


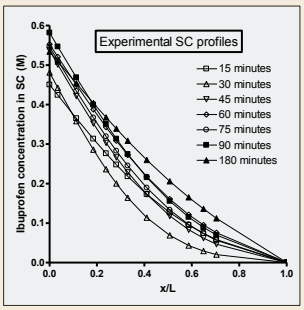


BG Saar, LR Contreras-Rojas, XS Xie, RH Guy, Molecular Pharmaceutics 8, 969-975 (2011)

26

Depth-profiling analysis of skin penetration





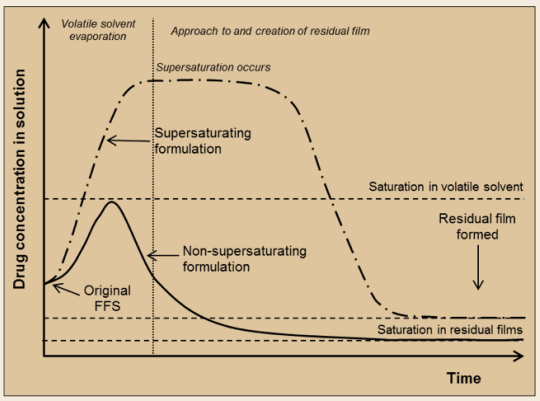
* Qualitative agreement between SRS measurement of NSAID uptake into porcine skin ex vivo and human skin vivo determined by stratum corneum tape-stripping.

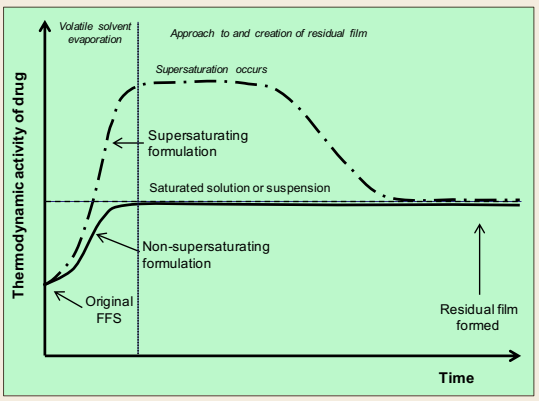
* PG permeation is faster relative to that of NSAIDs…

N. Belsey et al., J. Control. Release 174 (2014) 37-42

27

Metamorphosis of topical drug products





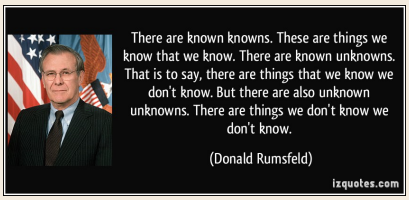
Frederiksen K et al. Exp. Opin. Drug. Deliv. 13, 349–360, 2016.

28

Challenges…

In terms of ADME in the skin, knowledge gaps remain in terms of:

1. **Bound versus unbound active; where is binding occurring?**
2. **Importance of skin metabolism; when is this not a secondary phenomenon?**
3. **Disposition of active: cellular distribution, uptake into (e.g.) hair follicles, sebaceous glands, etc.?**
4. **Clearance of active from the skin; dermal diffusivity, blood/lymph flow?**
5. **Effects of multiple dosing (same and different products), enhancement technologies, etc.**
6. **Metamorphosis of formulations and impact on drug input kinetics and subsequent PK?**



29