Prediction, assessment and optimisation of drug delivery into and through the skin

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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

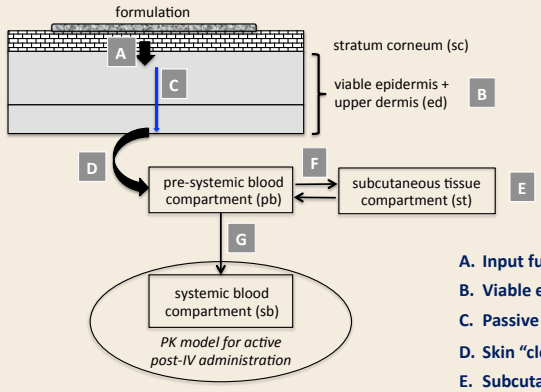
Objectives for a practical PK description of skin absorption:

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 coefficient 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:

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

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:

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

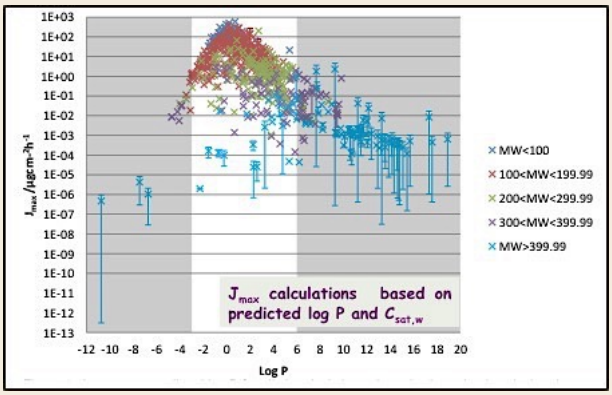
*R.O. Potts and R.H. Guy. Predicting skin permeability. *Pharm. Res.* 9, 663-669 (1992).

4

Predicting the maximum skin flux of an active

Maximum flux is achieved when the drug is applied as a saturated solution.

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



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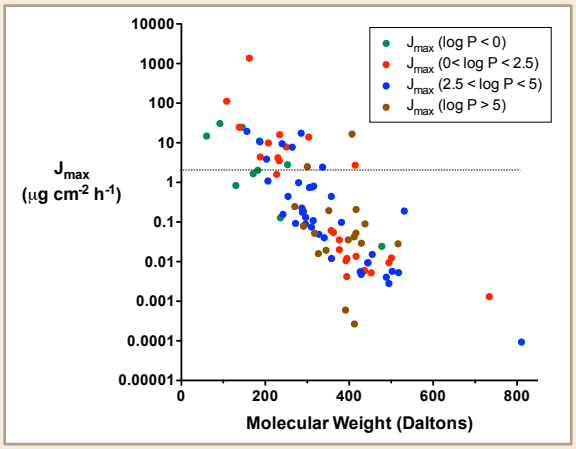
Topical and transdermal drugs (n=92)



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.

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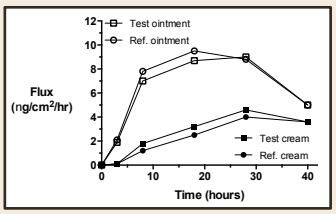
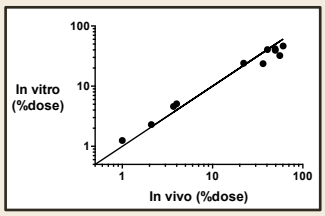
Measuring and validating drug "input kinetics" *in vitro*

- 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

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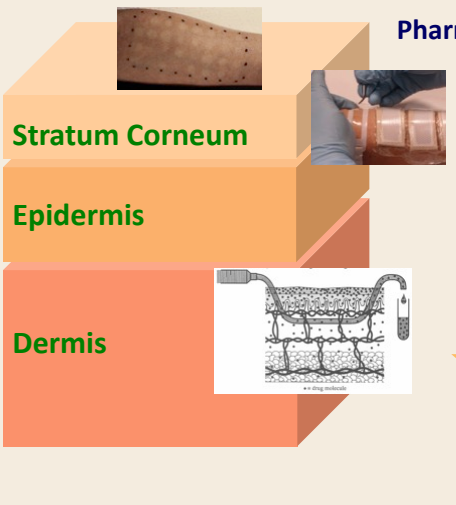
Assessing skin bioavailability *in vivo* in man



Pharmacodynamic assay

SC sampling, IR/Raman spectroscopy/imaging

Suction blister x

Microdialysis/oFM

Biopsy x

Blood levels

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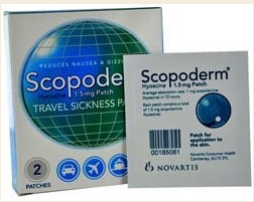
Measuring and validating drug "input kinetics"

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 <u>transdermal</u> 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).



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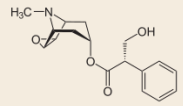
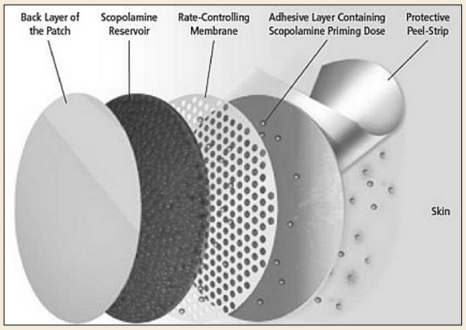
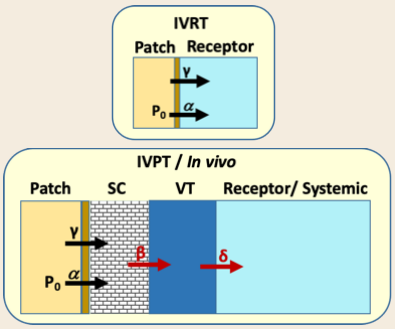
Transdermal scopolamine







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.

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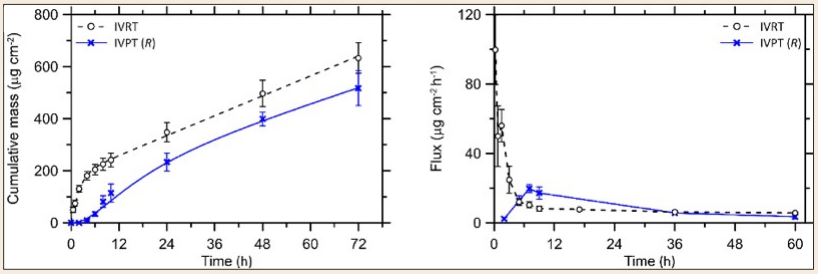
Transdermal scopolamine – in vitro skin penetration



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

Subsequently, slower, controlled delivery from the drug reservoir.

Pensado A et al. (2021) submitted.

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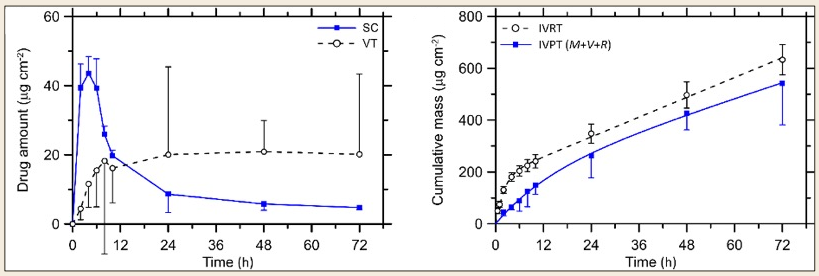
Transdermal scopolamine – SC and VT sampling *in vitro*



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

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

Pensado A et al. (2021) submitted.

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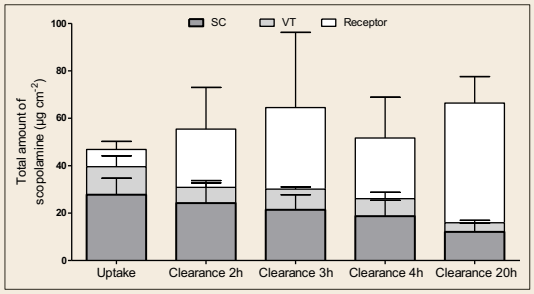
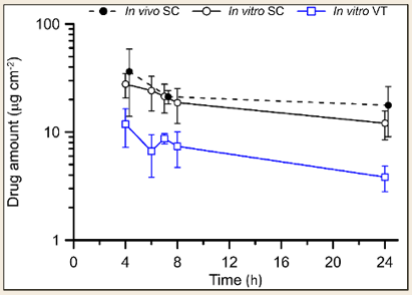
Transdermal scopolamine – *in vitro and in vivo* skin PK





Skin disposition of drug tracked after patch removal.

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

Pensado A et al. (2021) submitted.

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Stratum corneum (SC) sampling *in vivo*

what if stratum corneum is not the target?

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

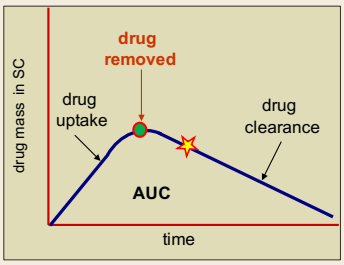
- drug/formulation specific for IVIVC
- simpler than PK; feasible when plasma levels too low
- simpler than open flow microperfusion/microdialysis

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:

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



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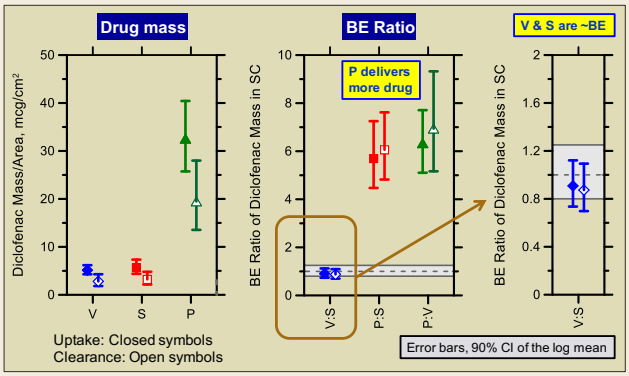
Stratum corneum (SC) sampling *in vivo*

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.

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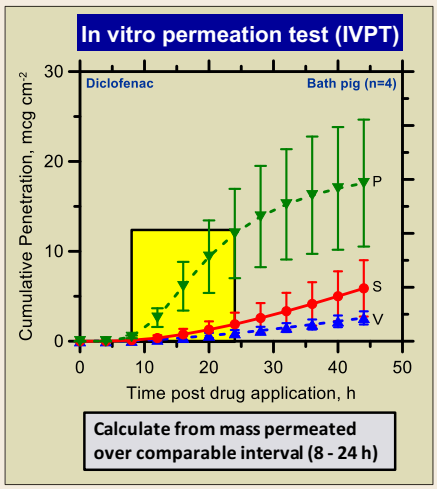
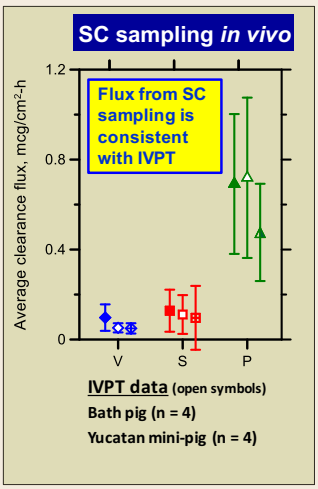
Stratum corneum (SC) sampling *in vivo*

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.

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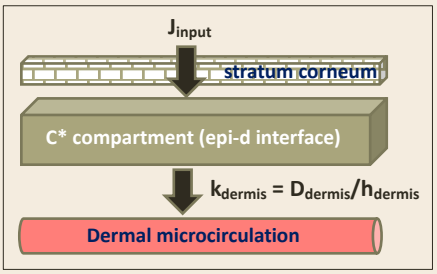
Higuchi's C* concept – concentration of active at its target



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.

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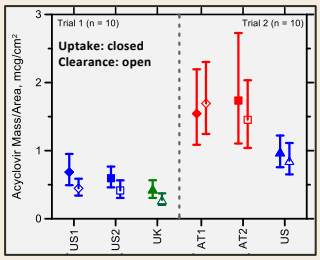
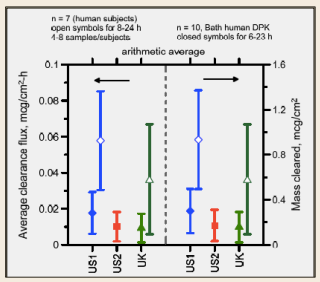
Higuchi's C* concept – acyclovir example





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

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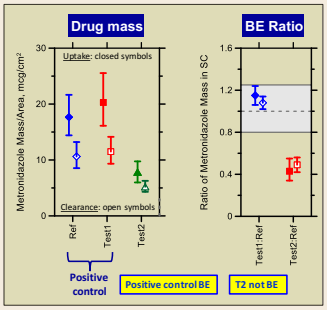
Topical bioavailability derived from SC sampling

- 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.

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AUTHOR'S PROOF

JmlID 12248_ArtID 571_Proof# 1 - 27/02/2021

The AAPS Journal ##########_
DOI: 10.1208/s12248-021-00571-3

Research Article

Assessment of Drug Delivery Kinetics to Epidermal Targets *In Vivo*

M. Hoppel,[1] M. A. M. Tabosa,[1] A. L. Bunge,[2] M. B. Delgado-Charro,[1] and R. H. Guy[1,3]

Table III. Estimation of Drug Concentrations at the Site of Action in the Viable Skin (C*) from SC Sampling Results for Nicotine Delivered from a Patch and for Lidocaine Delivered from a Medicated Plaster and from a Cream

Drug (delivery system)	$(M_{UP} - M_{CL})/\Delta t$ (μg cm^{-2} h^{-1})[a]	D_D (cm^{2}h^{-1})[b]	P_D (cm h^{-1})[c]	C* (μg cm^{-3})
Nicotine (patch)	15.2	0.0101	1.015	15.0
Lidocaine (plaster)	4.2	0.0076	0.757	5.6
Lidocaine (cream)	8.3	0.0076	0.757	11.0

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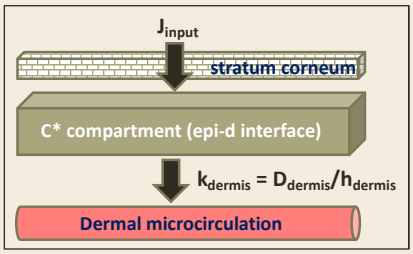
Higuchi's C* concept – concentration of active at its target



Davis, A.F., "Thermodynamic activity of drug and functional excipients in topical dermatological design". *Bulletin Technique Fondation Gattefossé*, 2013, 106, 28-40

Cordero, J.A., et al., "In vitro based index of topical anti-inflammatory activity to compare a series of NSAIDs", *Eur. J. Pharm. Biopharm.*, 2001, 51, 135-142

The steady-state model:

$J_{input} = k_{dermis} \times C^*$

may be re-expressed:

$J_{input}/IC_{50} = k_{dermis} \times (C^*/IC_{50}) = k_{dermis} \times EI$

where IC_{50} = drug's potency (expressed as in vitro IC_{50}), and C^*/IC_{50} ="efficacy index" (EI)

Hence, if EI = 1, then $C^* = IC_{50}$ and represents a threshold of useful activity.

In other words, the drug flux required to achieve a steady-state concentration at the target site equal to the IC_{50}:

$J_{input} = k_{dermis} \times IC_{50}$

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Higuchi's C* concept – estimation of drug dose

Consider hydrocortisone (IC_{50} = 5 ng/cm³) dosed at a typical amount of 2 mg of formulation per cm² of skin.

Given $J_{input} = k_{dermis} \times IC_{50}$, then (assuming k_{dermis} = 1 cm/hr), then J_{input} = 5 ng/cm²/hr.

Required quantity of HC to sustain IC_{50} over 12 hours = 12 hr x 5 ng/cm²/hr = 60 ng/cm².

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In 2 mg of formulation, 60 ng corresponds to a 'dose' of 0.003% w/w!

This is incredibly low compared to marketed products (0.5 - 1% w/w).

However, this makes sense as HC bioavailability from such products is ~1%... and 1% of a 0.5% w/w product = 0.005% w/w.

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However, this makes sense as HC bioavailability from such products is ~1%... and 1% of a 0.5% w/w product = 0.005% w/w.

Of course, estimated dose of 0.003% w/w is an absolute minimum; a reasonable starting point for loading in a formulation might be 10-fold higher at 0.03% w/w, for example.

Reduced loading important for safety, inadvertent application to impaired skin barrier, possibly reducing irritation, etc.

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Drug clearance from the skin – prediction?

Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-020-00864-8

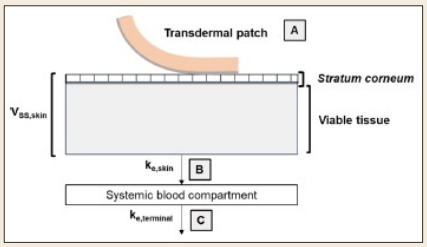
ORIGINAL ARTICLE

Predicting topical drug clearance from the skin

Maria Alice Maciel Tabosa[1] · Magdalena Hoppel[1] · Annette L. Bunge[2] · Richard H. Guy[1] · M. Begoña Delgado-Charro[1]

Accepted: 2 October 2020

Descriptor	Variance inflation value (VIF)	Derived coefficients ± standard error	*p* value
Intercept	–	− 0.921 ± 0.318	0.0110
MW	2.2	− 0.008 ± 0.002	0.0001
log *P*	2.2	0.389 ± 0.090	0.0006
TPSA	1.2	0.011 ± 0.002	0.0002



A Removal of the transdermal patch

B $k_{e,skin} = \frac{Cl_{skin}}{V_{SS,skin}}$

C $k_{e,terminal} = k_{e,skin}$

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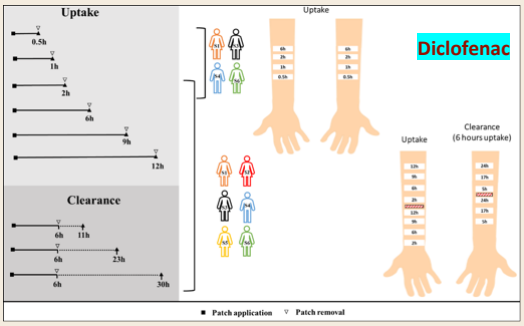
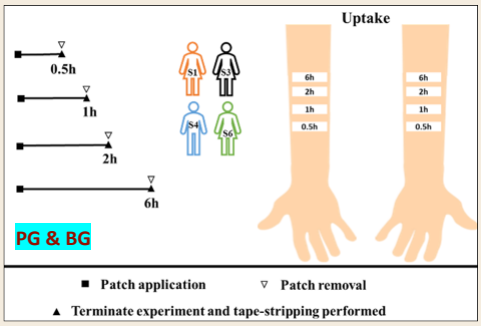
But topical bioavailability is not all about the active…

Voltarol® Medicated Plaster: active drug = diclofenac

Key excipients: propylene glycol (PG) and butylene glycol (BG)





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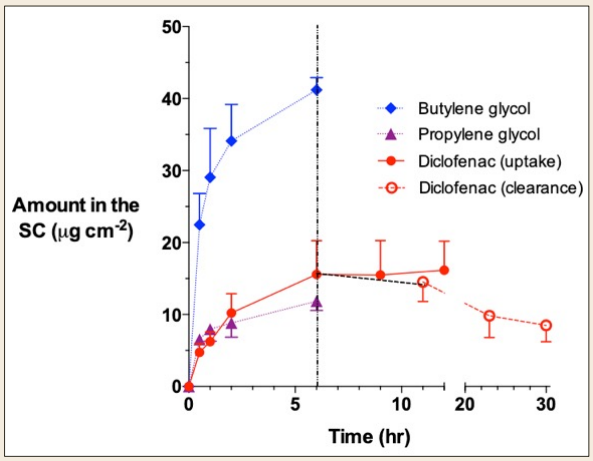
But topical bioavailability is not all about the active…



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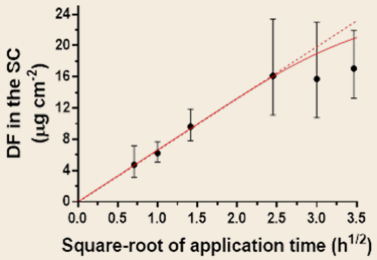
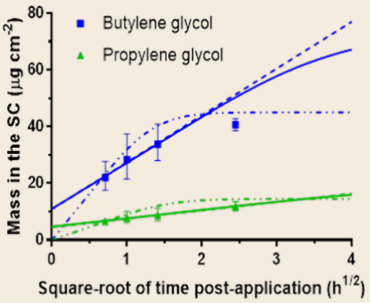
But topical bioavailability is not all about the active…





Uptake of diclofenac, PG and BG into the stratum corneum (SC) plotted as [time$^{1/2}$].

Solid lines = solution of the finite membrane model.

Dashed lines = solution of the semi-infinite membrane model.

Dot-dashed lines for PG and BG = solution of the finite membrane theory.

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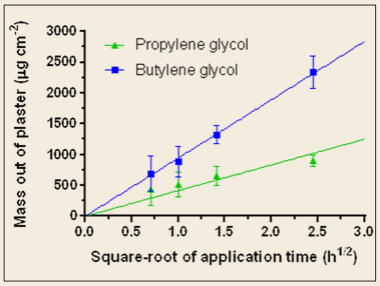
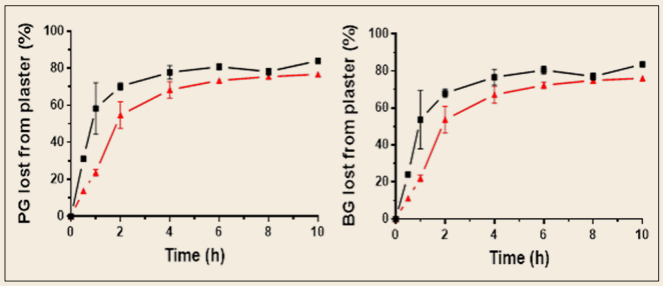
But topical bioavailability is not all about the active…



Masses of PG and BG lost from plaster during wear for 6 hours



Mass of PG and BG lost from plaster after removal from packaging either when release liner removed (black squares) or when release liner left in place (red triangles)

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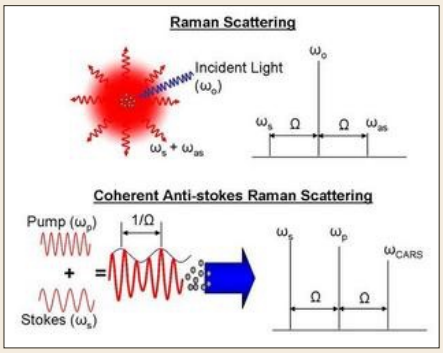
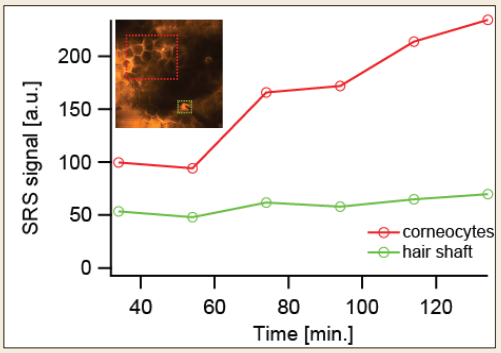
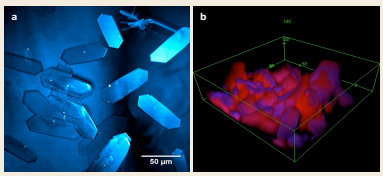
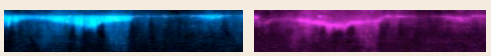
Raman imaging of skin penetration and vehicle 'metamorphosis'









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

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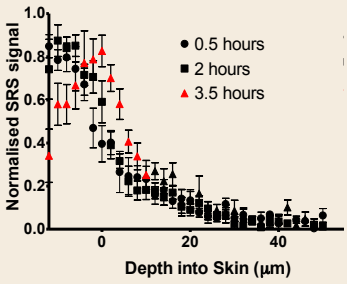
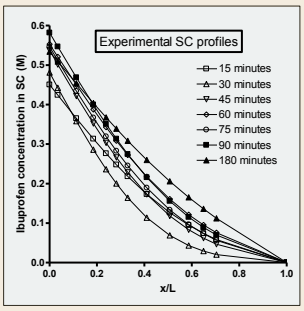
Depth-profiling analysis of skin penetration





* 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

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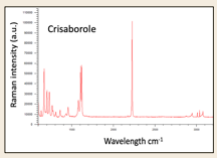
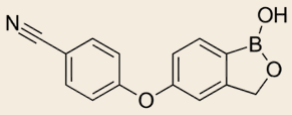
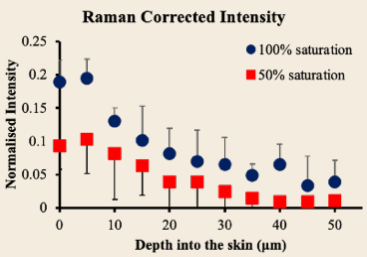
Raman – a noninvasive tool to assess topical drug bioavailability?

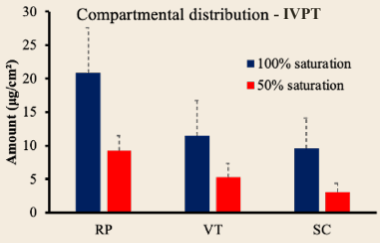




Crisaborole formulations: 100% and 50% saturated solutions in 30:70 v/v water:propylene glycol



AUC ratio (100%/50%) = 2.3 ± 0.4



Total drug uptake (100%/50%) = 2.1 ± 0.7

Zarmpi, P., unpublished data

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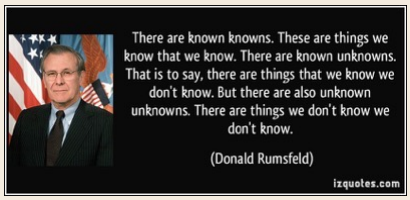
Challenges…

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?**



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