SAMPLING THE STRATUM CORNEUM TO QUANTIFY DRUG UPTAKE FROM TOPICAL PRODUCTS

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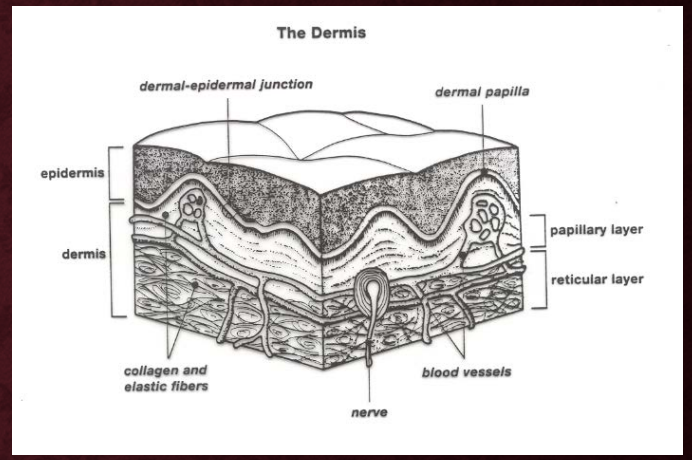
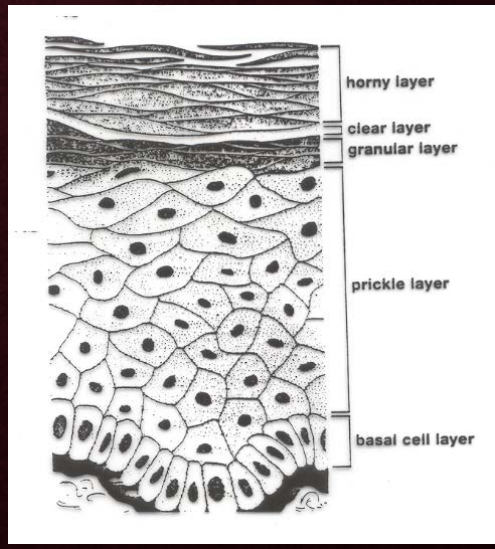
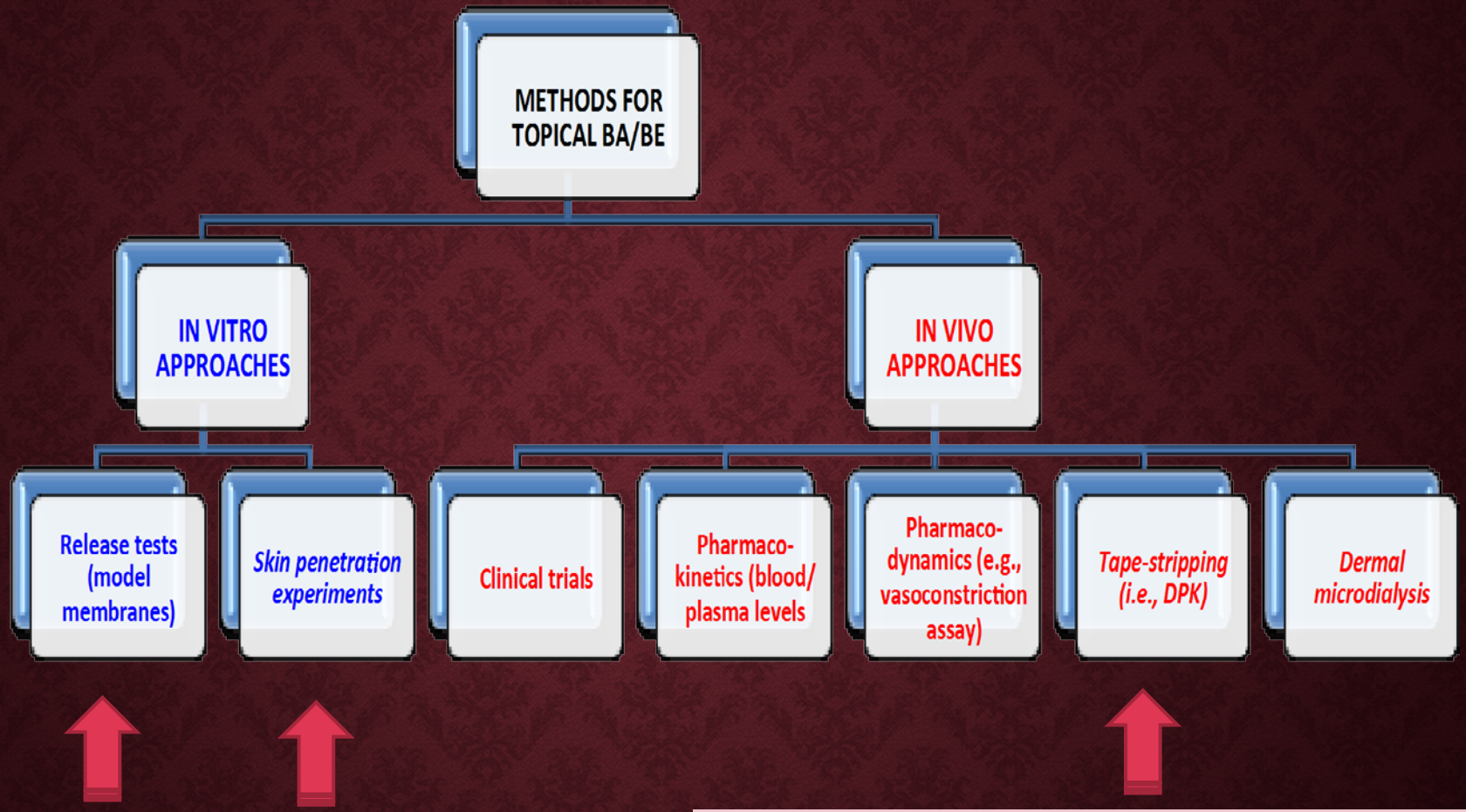
BIOEQUIVALENCE OF TOPICAL PRODUCTS

- Clinical trials required for:
  a. approval of generic products
  b. replacement of approved product following compositional changes.
  - ✓ exception: corticosteroids (vasoconstrictor assay)
- 🙁 Relatively insensitive, time-consuming and costly.



- ? Can topical BE be assessed through use of appropriate *in vitro* and/or *in vivo* surrogate tests.
- All surrogate tests have limitations but that they do not all have the same limitations:
  - the results of one test complement those of another.





Tape stripping study

Diclofenac Sodium

Solaraze gel (3%), Voltaren gel (1%) and Pennsaid solution (2%).

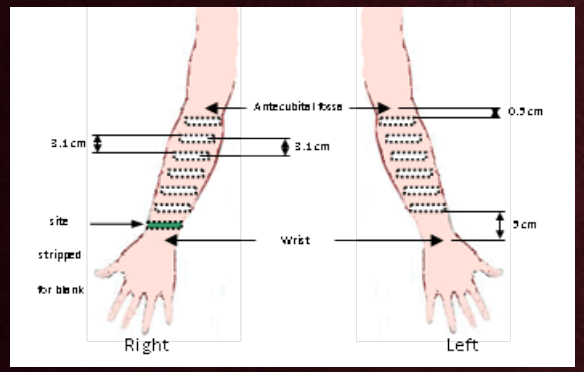
Optimizing metrics for the assessment of BE between topical producs
N'Dri-Stempfer et al., Pharm. Res. 25 (2008)

1. Ethics approval by RIHSC and REACH
2. Target: 14 healthy adults for interim analysis. Current N=12
3. (2 uptake + 2 clearance) skin sites /formulation).

4. SC depth sampled determined by TEWL

&

30 tapes /site maximum.



6 hours uptake

Formulations removed from ALL sites

Uptake sites tape-stripped

Clearance sites protected

17 hours clearance

Clearance sites tape-stripped

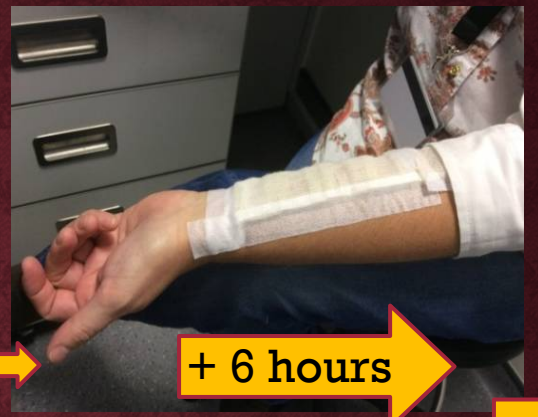
Tapes cut & weighed

Tape stripping

Tapes weighed

Tapes grouped & extracted

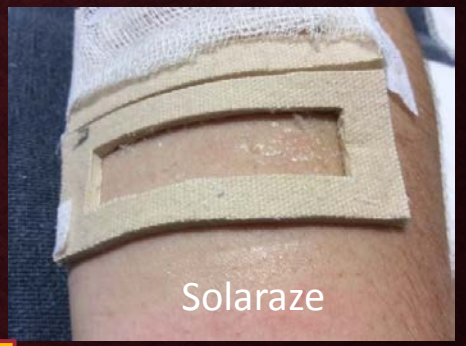
HPLC UV

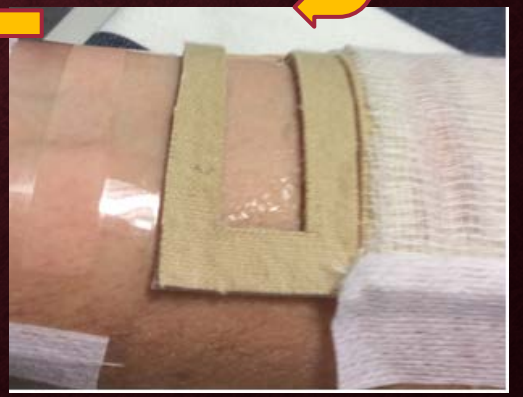


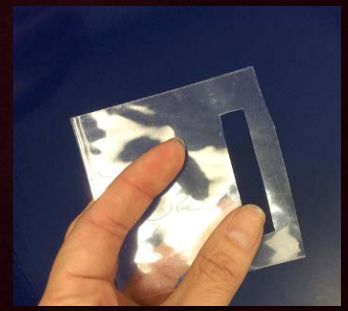
Formulation removal:

1. dry cellulose tissue paper +
2. two IP 70%. wipes Each wipe passed three times.

Formulation applied (mg)	Solaraze 3%	Voltaren 1%	Pennsaid 2%
Uptake	162.4 ± 8.3	84.9 ± 5.9	82.1 ± 6.8
Clearance	158.5 ± 17.8	84.9 ± 4.9	81.4 ± 5.1
Target formulation	165	82.5	82.5
Drug applied per site (mg)	4.95	0.825	1.65



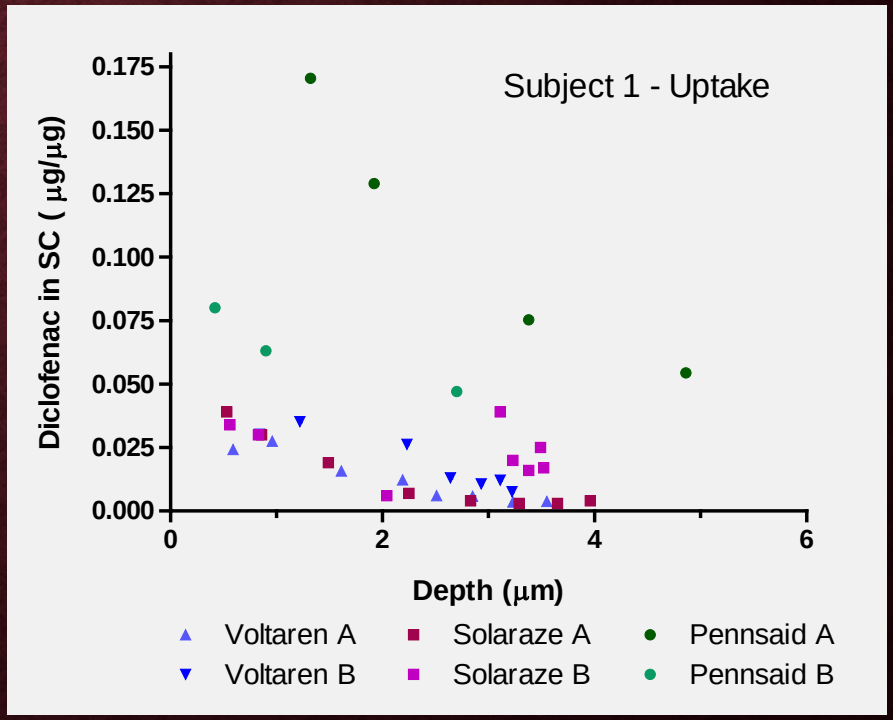


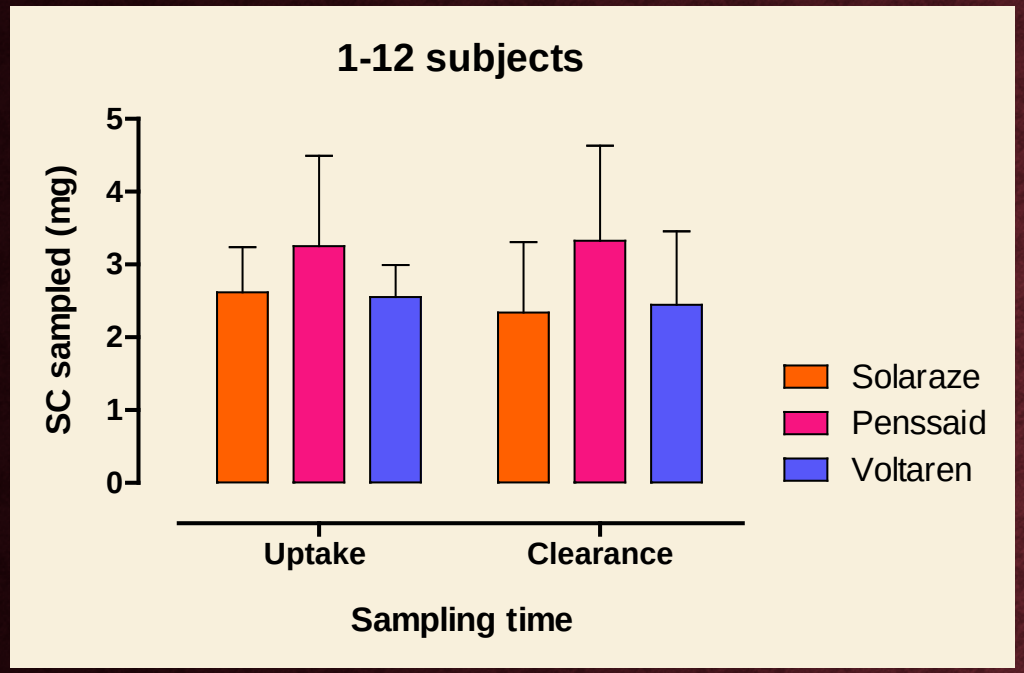


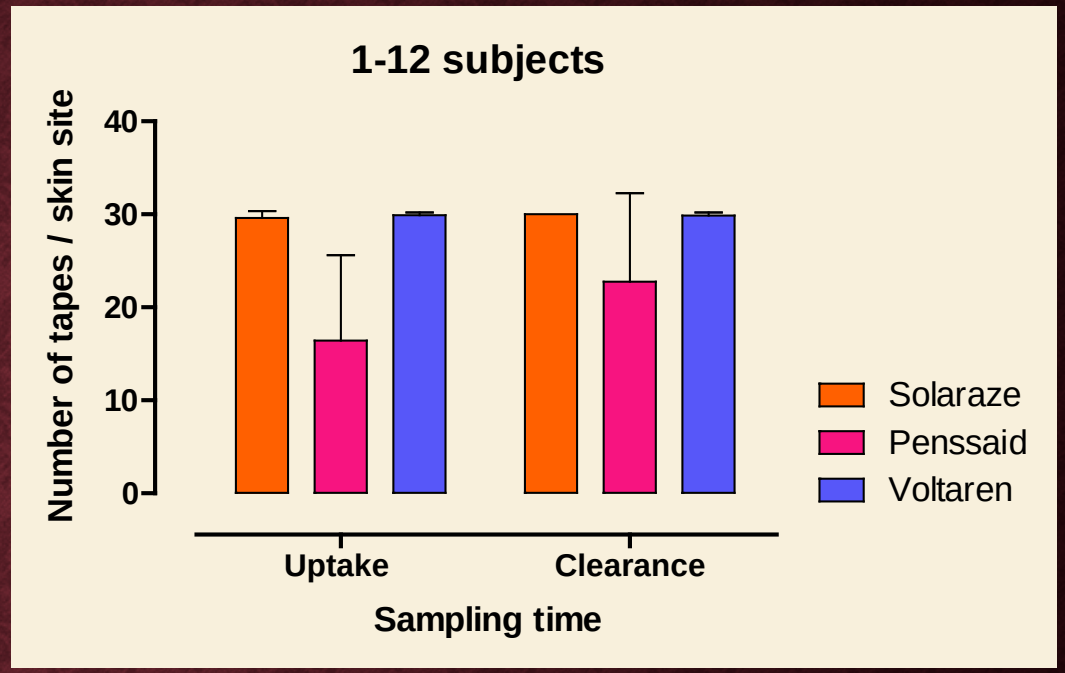
SC removed (mg)	Solaraze	Voltaren	Pennsaid
Uptake	2.62 ± 0.62	2.55 ± 0.44	3.25 ± 1.24
Clearance	2.34 ± 0.97	2.45 ± 1.01	3.32 ± 1.31

SC depth (µm)	Solaraze	Voltaren	Pennsaid
Uptake	5.24 ± 1.24	5.10 ± 0.89	6.50 ± 2.48
Clearance	4.68 ± 1.94	4.89 ± 2.03	6.65 ± 2.62

Final TEWL ($g.h^{-1}.m^{-2}$)	Solaraze	Voltaren	Pennsaid
Uptake	25.7 ± 12.5	30.7 ± 20.5	62.1 ± 21.8
Clearance	21.6 ± 9.8	24.2 ± 17.4	49.7 ± 14.0







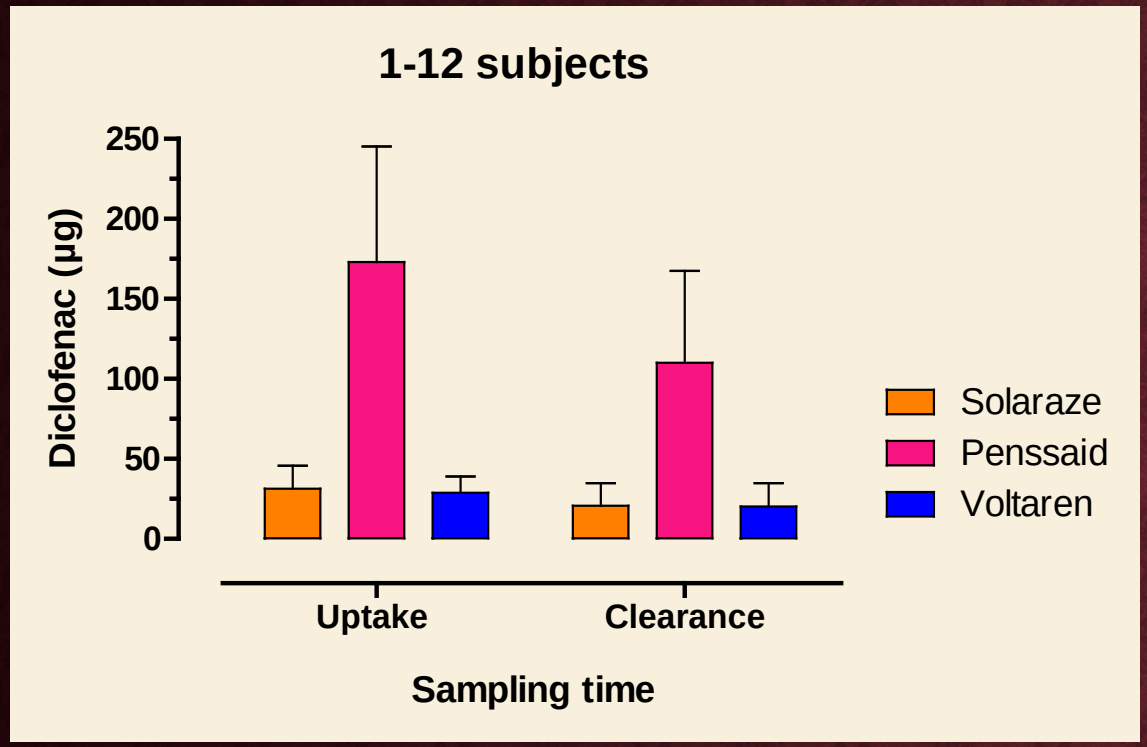
Two-way ANOVA:

- Formulation: ($p < 0.025$)
  - Pennsaid ≠ Solaraze ($p < 0.05$ clearance)
- Uptake/Clearance and Interaction: n.s.
- Pairing effective: $p < 0.04$

Two-way ANOVA:

- Formulation: ($p < 0.0001$)
  - Pennsaid ≠ Solaraze and Pennsaid ≠ Voltaren both: ($p < 0.001$ uptake and $p < 0.01$ clearance)
- Uptake/Clearance, Interaction and pairing : n.s.

DICLOFENAC RECOVERY



Diclofenac	Solaraze 3%	Voltaren 1%	Pennsaid 2%
Applied per site (mg)	4.95	0.825	1.65
Uptake recovery (µg)	31.4 ± 14.3	28.7 ± 10.4	173.0 ± 72.4
Clearance recovery (µg)	20.7 ± 14.2	20.4 ± 14.5	110.0 ± 57.5
% recovery (uptake)	0.63 ± 0.29	3.48 ± 1.26	10.48 ± 4.39
Clearance / Uptake	0.78 ± 0.72	0.69 ± 0.45	0.67 ± 0.32

Two-way ANOVA:

- Formulation: ($p < 0.0001$)
  - Pennsaid ≠ Solaraze ($p < 0.001$; uptake and clearance)
  - Pennsaid ≠ Solaraze ($p < 0.001$; uptake and clearance)
  - Voltaren = Solaraze
- Uptake/Clearance: $p < 0.0001$
- Pairing effective: $p < 0.0001$
- Interaction: $p < 0.0007$

CONCLUSIONS

- DPK (tape-stripping) approach differentiated formulations of diclofenac expected to provide different drug absorption and topical bioavailability.
- Uptake and clearance data led to similar conclusions.
- Pennsaid sites:
  - Higher (~ double) TEWL
  - Required less (16-22) tapes than other formulation sites (29-30)
  - Greater amount (~1.3 fold) and deeper (~1.3 fold) SC removed
  - Higher (~ 5-6 fold) diclofenac recovery from tapes.
- Local side effects (redness, skin irritation) consistent with tape-stripping and the formulation's composition.
- Methodological issues (formulation application and removal, tape-stripping procedure, TEWL measurements, tapes grouping and extracting) need careful consideration when DPK is used to establish BE of topical products.

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Thanks for your attention!