E$_2$BRN-Network-Meeting at ESDR 2019, September 18-21, Bordeaux, France

# Variability of topical penetration data from Dermal Open Flow Microperfusion might be attributed to variability in skin barrier function and follicular penetration

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## Purpose

Topical penetration studies are associated with considerable data variability.

This study aimed to investigate data variability in preclinical and clinical dOFM (dermal open flow microperfusion) studies and to determine the biological or methodological reasons for data variability.

## Methods and Data

Data enabling this research:

- Drug data from dOFM in in-vivo topical bioequivalence studies (Fig. 1) (volunteers [1], pigs)
- Drug data from dOFM in ex-vivo topical penetration studies (donor skin, pig skin)
- Demographic and skin barrier data: sex, age, weight, skin temperature, TEWL (Aquaflux 200, Biox Ltd., London) and skin impedance (3-electrode in-house approach) (Fig. 2)
- Method precision data: dOFM probe depths, flow-rates, recoveries

Characterisation of variability and identification of sources:

- Variability analysis by ANOVA, distribution analyses, statistical modelling, site-to-site and probe-pair analysis.
- Literature Search for similar findings in big data sets (IVPT, in-vivo testing)

## Results

- Predominant inter-subject variability (Fig. 3)
  - well documented
  - skewed, log-normal distribution similar to other studies
  - similar predominance as other (microdialysis) studies
  - no correlation with demographics
  - weak correlation with TEWL ($r = 0.31$, $p = 0.054$)
  - high, negative correlation with skin impedance ($r = -0.71$, $p < 0.0001$)
- Intra-subject variability was very low (Fig. 3)
  - less documented in literature
  - skewed, log-normal distribution
  - no correlation with site-to-site comparison (Fig. 4)
  - no correlation with method precision data
  - variability was only attributable to probe location

### Where does the variability come from?

- Intra-subject literature attributes such variation to skin appendages:
  - IVPT-studies with donor skin found skewed data for water soluble drugs, while IVRT-studies with membranes find normally distributed data [3].
  - Follicular-Plug-Studies and Skin-Sandwich-Studies demonstrated the role of skin microstructures for penetration of drugs with low log P <1.9. [4-6].
  - Microdialysis found distinct differences between normal and hairless rats [7].
- Analysis showed that most variability was due to individual skin barrier properties. Our in-vivo dOFM data had sufficient power and sensitivity to attribute intra-subject variability of topical penetration data to skin microstructure. dOFM probes are sufficiently small and sensitive to detect inhomogeneities in local dermal drug concentrations caused by skin microstructure. Pig dOFM data suggest that different formulations which enhance different penetration routes can be discriminated by their dOFM profile.

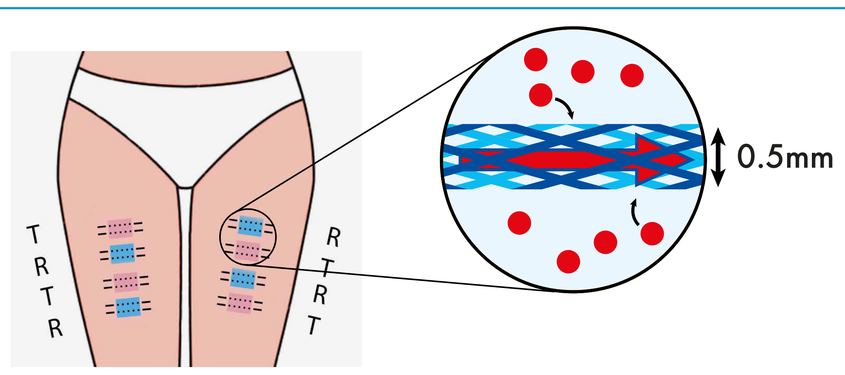


***Fig. 1: Typical bioequivalence setting with dOFM probes in the dermis.*** *Multiple treatment sites allow the simultaneous comparison of drug penetration between a test product (T) and a reference product (R).*

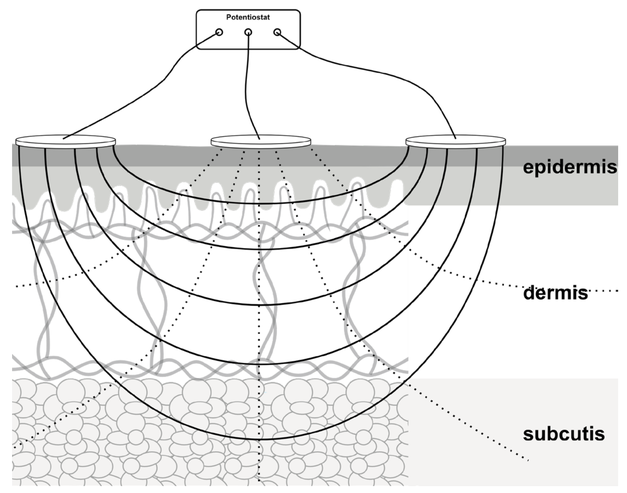


***Fig. 2: Three-electrode setup for skin impedance assessment.*** *Skin impedance at low frequencies was highly correlated with drug penetration assessed by dOFM thus confirming the utility of impedance for the characterisation of the epidermal skin barrier.*

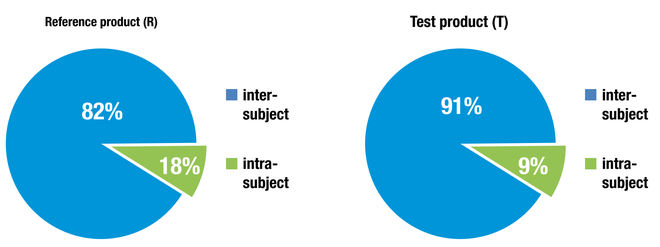


***Fig. 3: ANOVA results describing the sources of variability for the penetration of the reference and the test product.*** *The charts show the relative contributions to the total variability. Inter-subject variability is the dominant source of variability.*

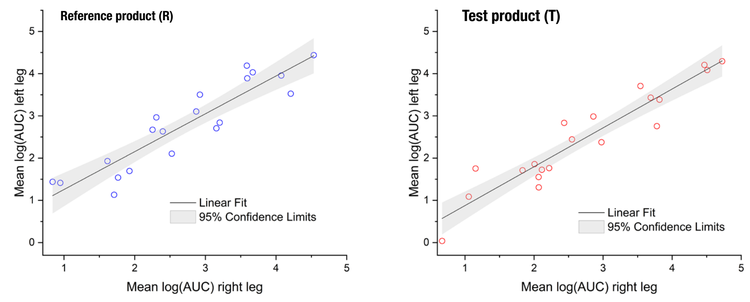


***Fig. 4: logAUCs left versus right leg in 20 volunteers for the reference and the test product.*** *dOFM data indicate good reproducibility between different test sites. Further analyses and literature indicated that also the small site-to-site variability was not due to local skin barrier variation but due to penetration through skin appendages.*

## Conclusions

- dOFM is very sensitive to detect differences in the skin barrier; it also provides information on the drug penetration behavior and the effect of different formulations.
- Skin impedance is very informative about the epidermal barrier function. Optimized skin impedance measurements might enable more efficient studies by using these data for subject stratification.
- A better understanding of the variability in skin permeation studies will be key to cost-efficient studies in preclinical and clinical topical drug development.

References

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