FDA U.S. FOOD & DRUG ADMINISTRATION

Characterizing In Vivo Cutaneous Pharmacokinetics of Topical Lidocaine Prilocaine Cream Using Dermal Open Flow Microperfusion and Dermal Microdialysis

Session: Skin and Mucosal Delivery

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THE FUTURE OF DELIVERY SCIENCE

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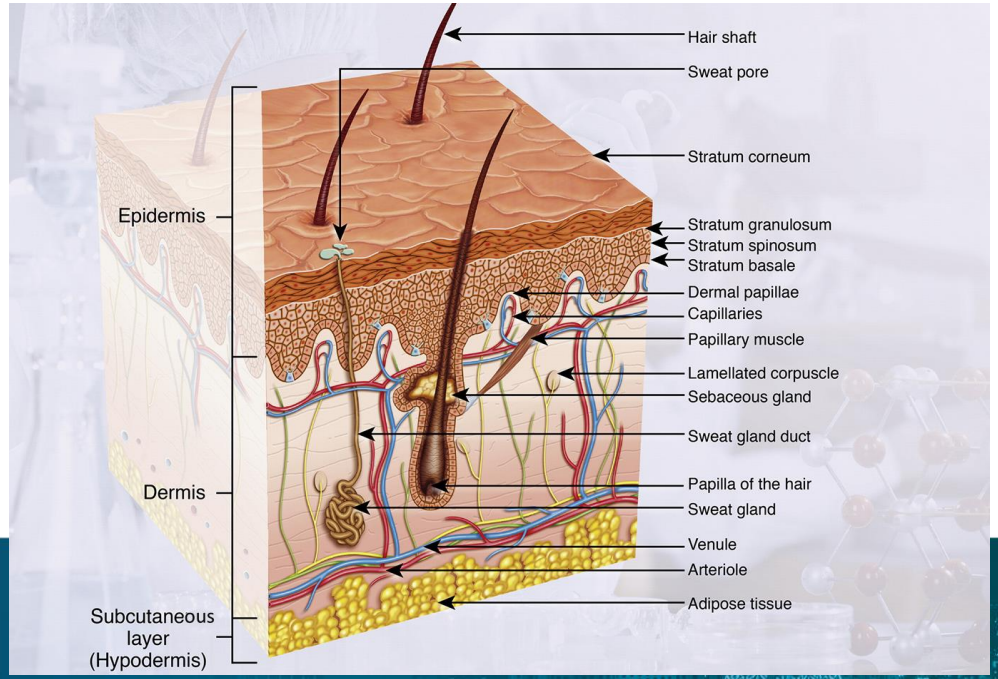
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

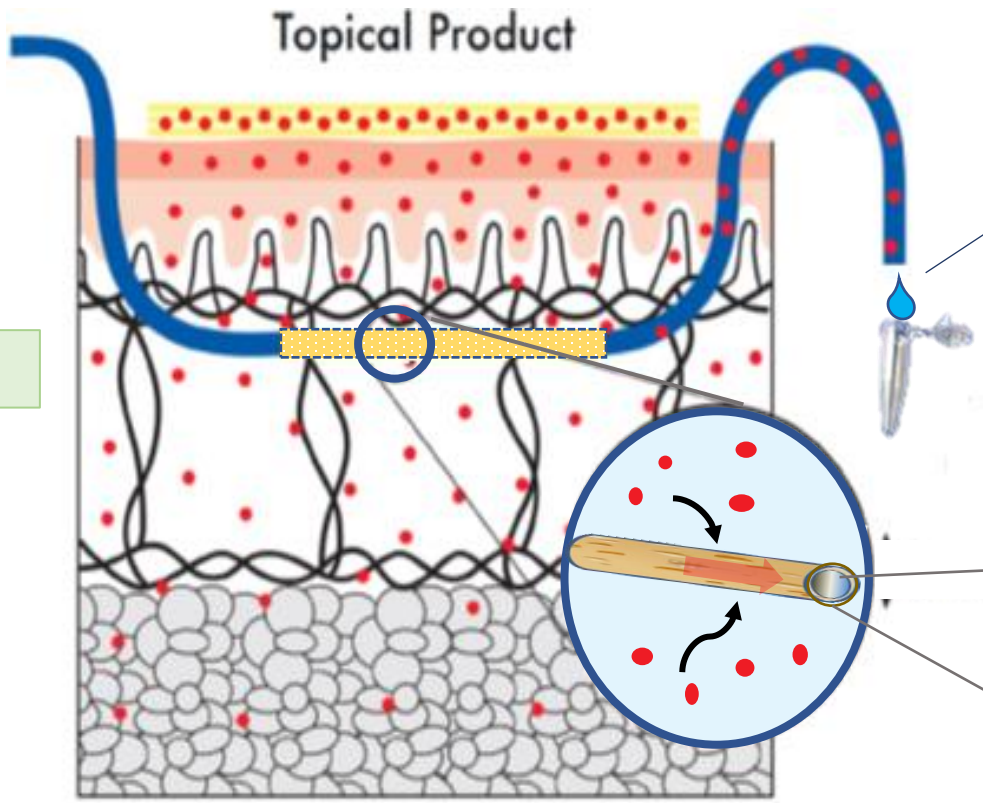
Cutaneous Pharmacokinetic Techniques

- Epidermal pharmacokinetics (PK)
  - Tapestripping “Dermatopharmacokinetics” (DPK)
  - Epidermal and/or Dermal Pharmacokinetic Tomography e.g., Raman based methods
  - In vitro Permeation Testing (IVPT)
- Dermal PK
  - Dermal Open Flow Microperfusion (dOFM)
  - Dermal Microdialysis (dMD)



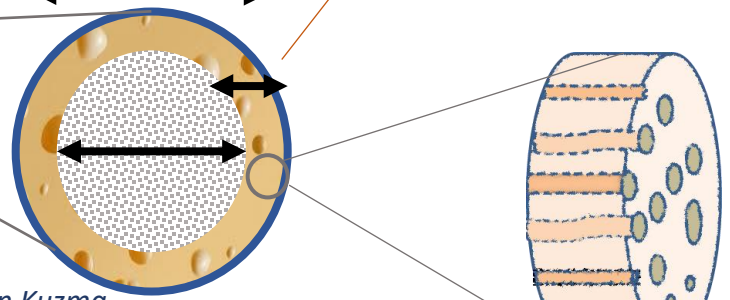
dMD

Isotonic fluid:



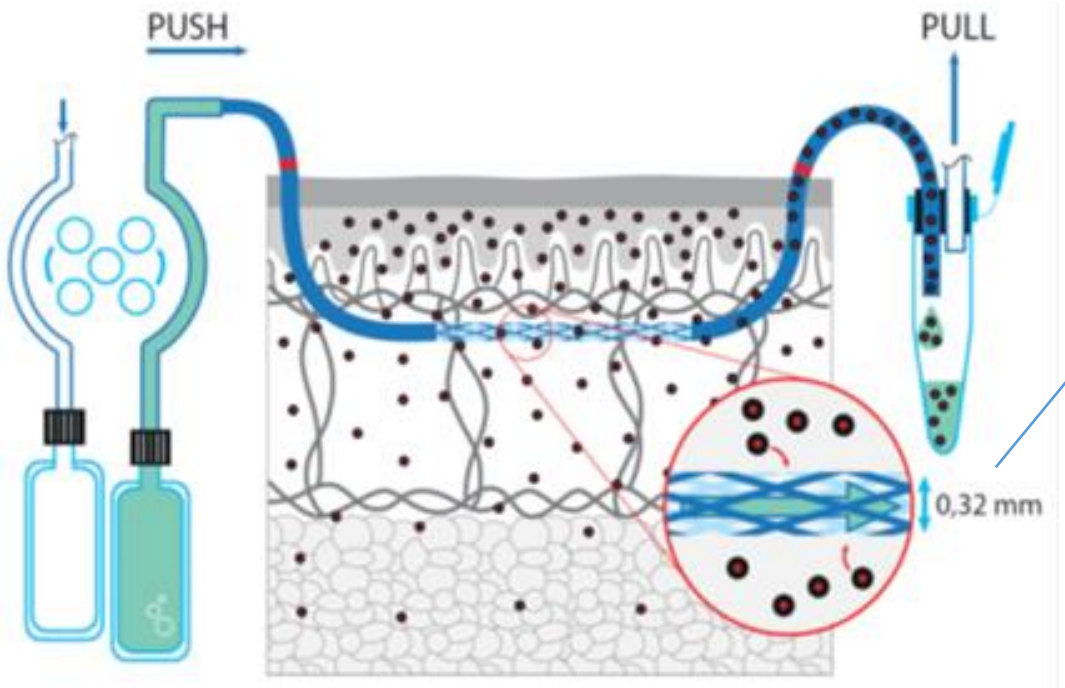
Collected sample concentration is proportional to the interstitial fluid concentration

Tubular hollow dialysis fiber from an artificial kidney

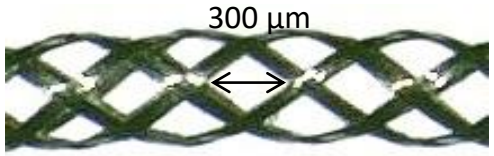


Adapted from: Bodenlenz, Manfred, et al. Clinical pharmacokinetics 56.1 (2017): 91-98 and courtesy of Dr Ben Kuzma

dOFM



Metal mesh design



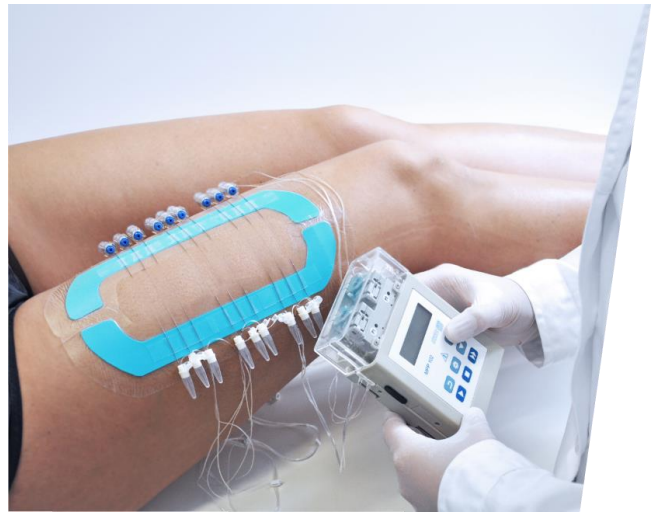


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

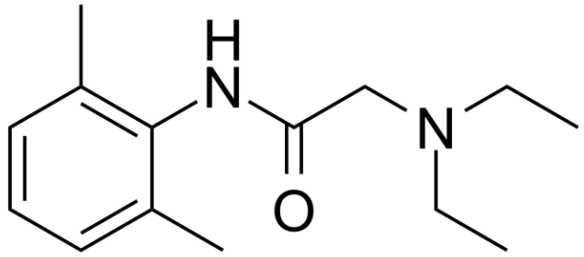
Traditional Limitations and Challenges

- Limited utility for certain classes of drugs
- High variability in the data
- Immobilization of study participants while connected to pumps and tubing during the study
- Study duration too brief (e.g., 4-5h) for adequate comparison of the products

Goals of the Study

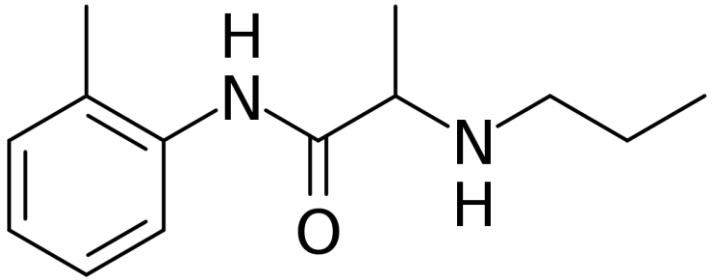
- Can dMD be used for lipophilic drug molecules?
- Can dMD and dOFM measure and distinguish bioavailability (BA) of two similarly structured drug molecules?
- Can these techniques demonstrate bioequivalence (BE) of a topical cream to itself?

Lidocaine



$C_{14}H_{22}N_2O$ molecular weight 234.3

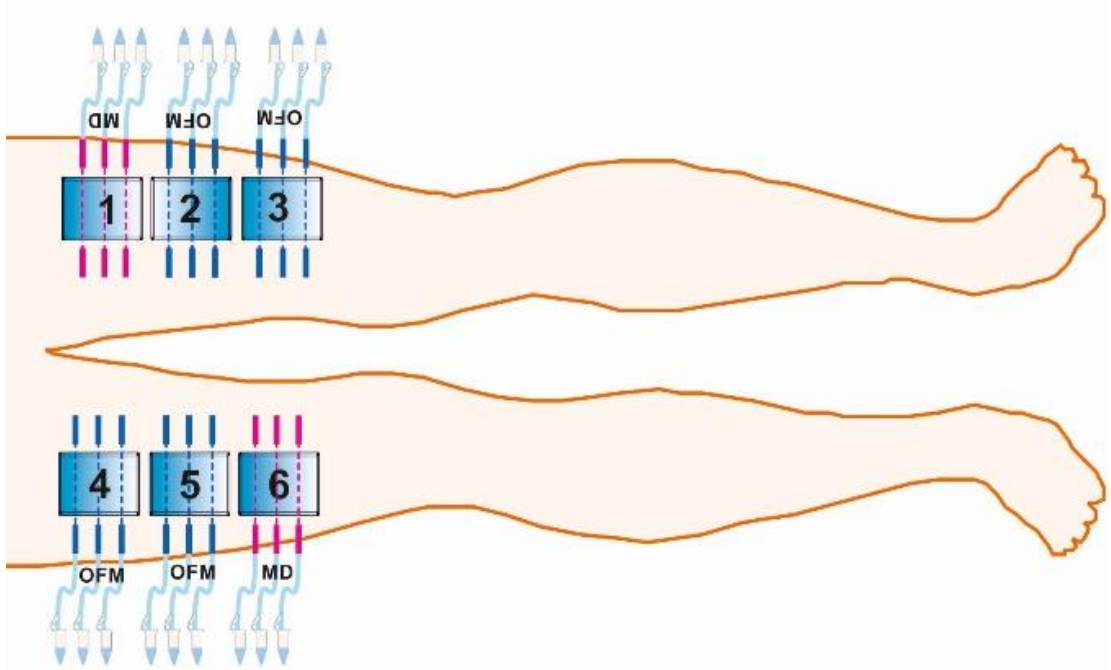
Prilocaine



$C_{13}H_{20}N_2O$ molecular weight 220.3

Clinical Study Design

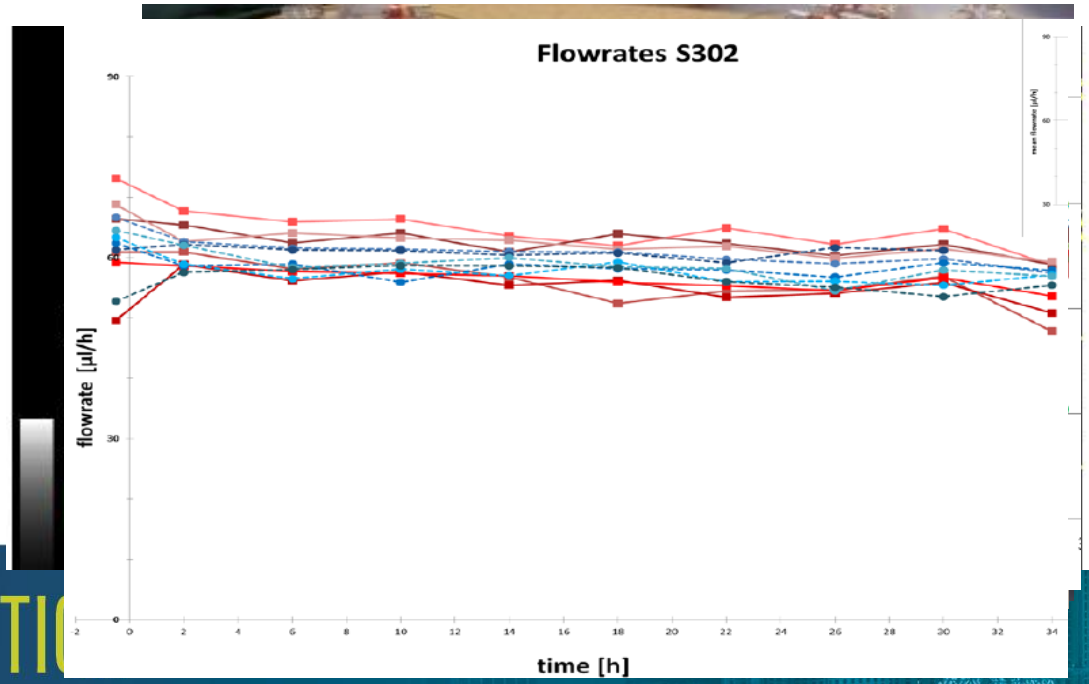
- Product used: Emla (lidocaine;prilocaine) topical cream, 2.5%;2.5%
- 20 healthy subjects
- Dose: 150 mg/cm^2
- Continuous sampling for 12 hours



The blue and purple lines represent dOFM and dMD probes, respectively.

Study Controls

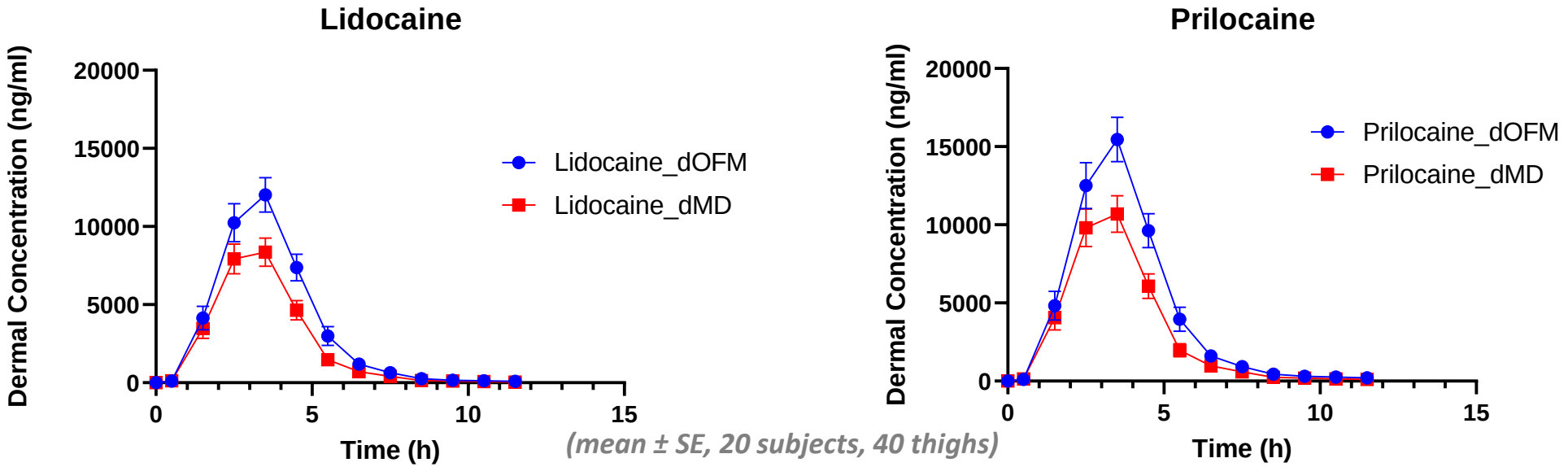
- Application site: controlled by application template
- Probe depth: monitored by ultrasound
- Barrier integrity test: transepidermal water loss (TEWL)
- Local blood flow
- Flow rates



Data/images provided courtesy of Dr. Frank Sinner, Joanneum Research

dOFM vs dMD

- Despite moderate lipophilicity of both drugs, the dermal concentration profiles of lidocaine and prilocaine were nicely captured using dMD and dOFM.



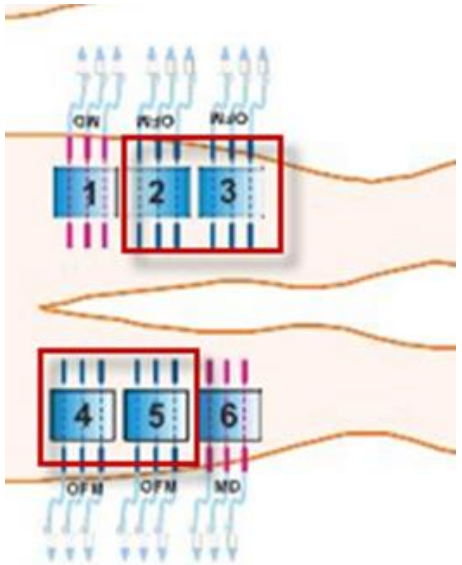
(mean ± SE, 20 subjects, 40 thighs)

Data provided courtesy of Dr. Frank Sinner, Joanneum Research

BE Verification

- The BE of Emla cream to itself was established at dOFM application sites, for 40 thighs in 20 subjects.

Parameter	Analysis variable	Point Estimator (Test/Reference)	Upper bound of the 95% scaled confidence interval	Scaled average BE-criterion satisfied
Lidocaine	LogAUC	1.20	-0.0440	Yes
Prilocaine	LogAUC	1.18	-0.0476	Yes
Lidocaine	LogCmax	1.15	-0.0498	Yes
Prilocaine	LogCmax	1.15	-0.0593	Yes



Outcome Summary

- Both dMD and dOFM collected higher levels of prilocaine compared to lidocaine in the dermis, which can be due to differences in either the permeation or protein/tissue binding between the two drugs.
- On average, lidocaine and prilocaine levels and their BA measured by dOFM were higher than those from dMD. This observation could be potentially attributed to differences in recovery of protein-bound drug between the two techniques.
- The T_{max} and shape of the PK profiles were very similar for both drugs measured by dMD vs dOFM.
- Both techniques can be used to compare and characterize the cutaneous PK of topically applied lidocaine and prilocaine.

Conclusions

- With adequate study controls and suitable perfusate(s) and equipment, both dMD and dOFM can reliably evaluate cutaneous BA of moderately lipophilic drugs like lidocaine and prilocaine.
- dMD and dOFM have both the potential to be used as a tool for BE assessment of topical drug products applied to the skin.

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