Recent advancements in dermal microdialysis to assess topical bioavailability and bioequivalence

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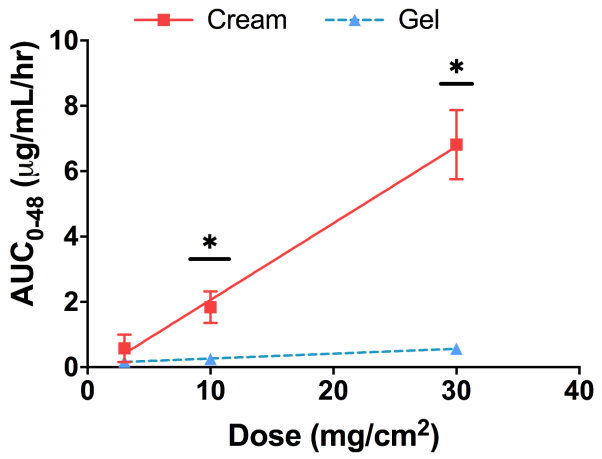

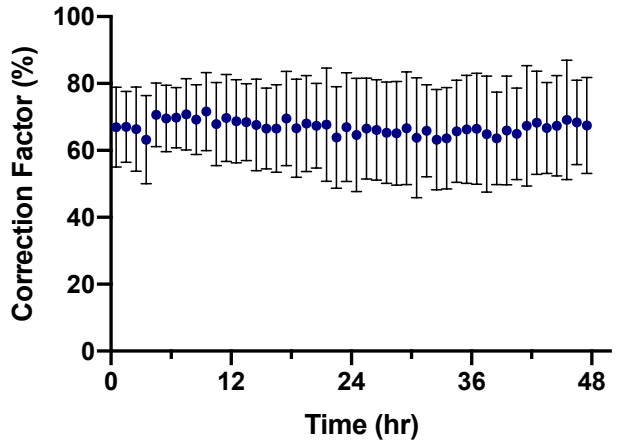

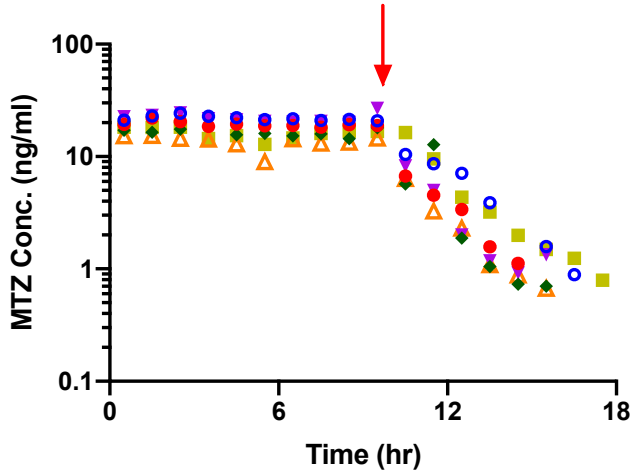

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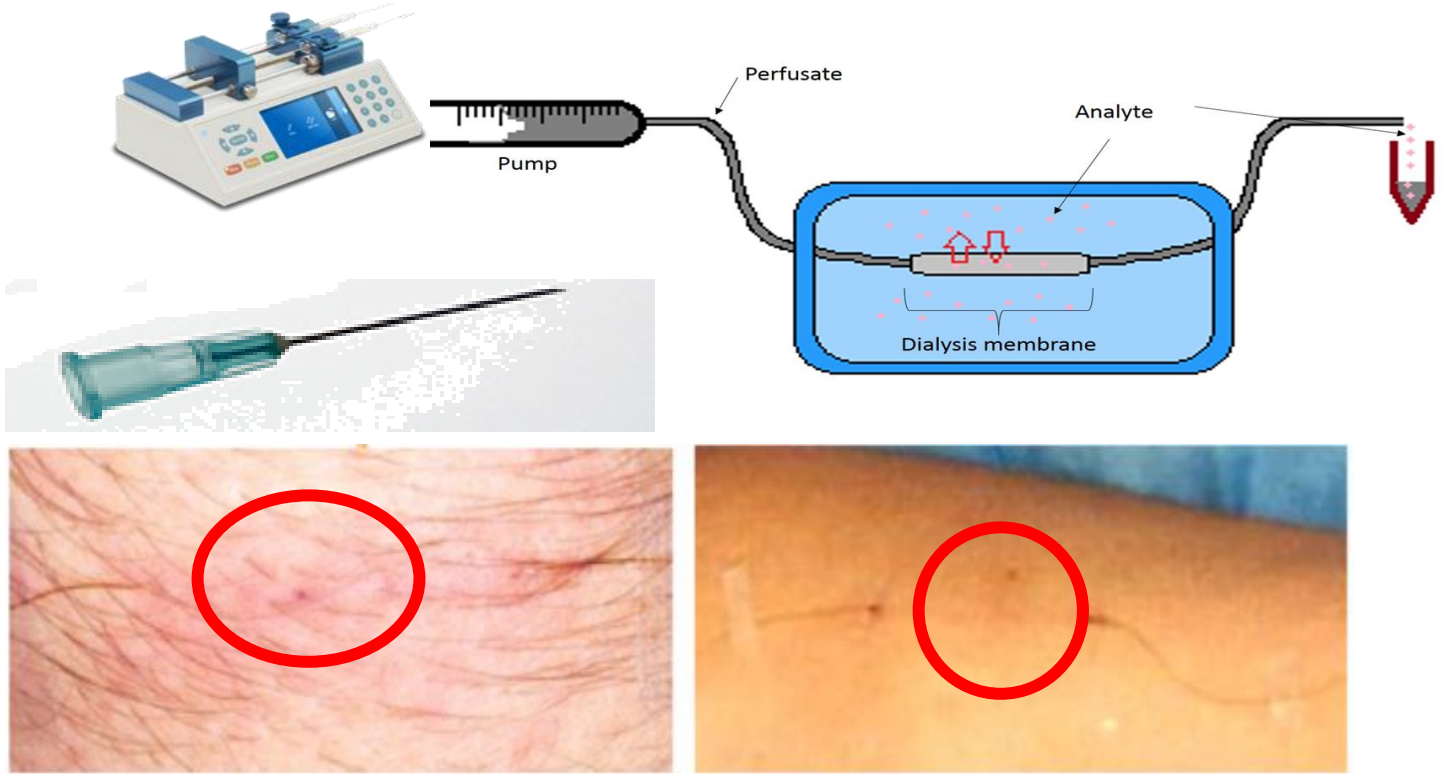
FDA Disclaimer

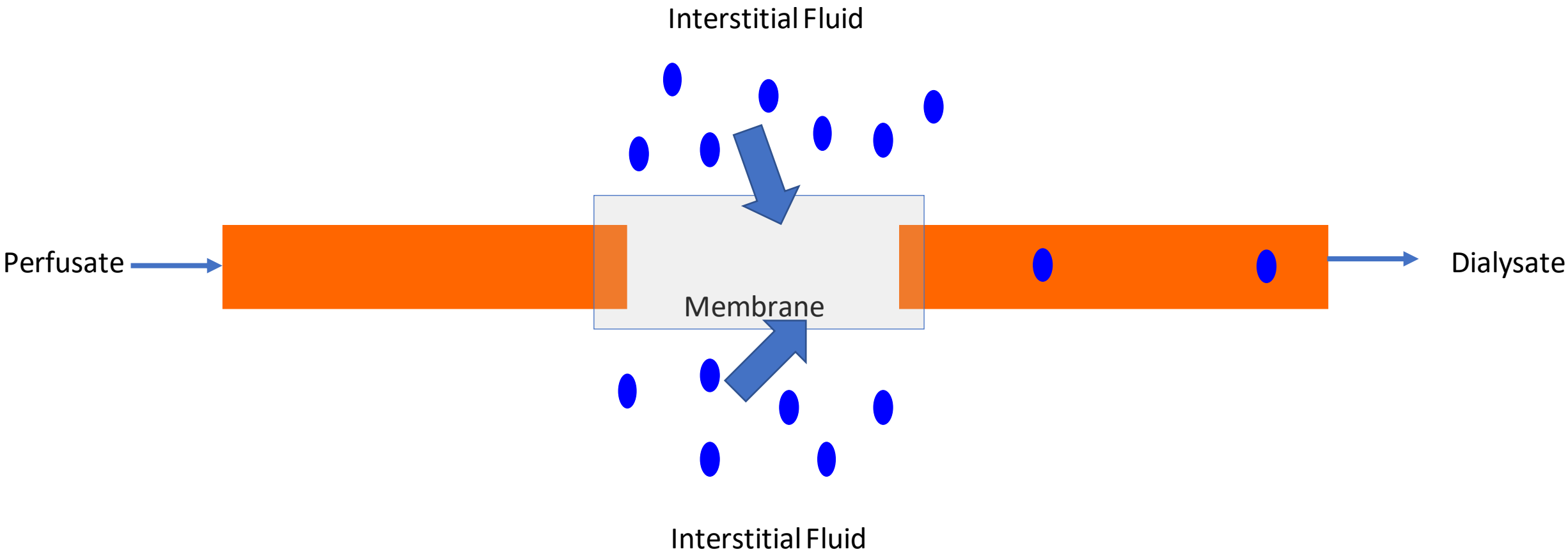
- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Dermal Microdialysis (dMD)

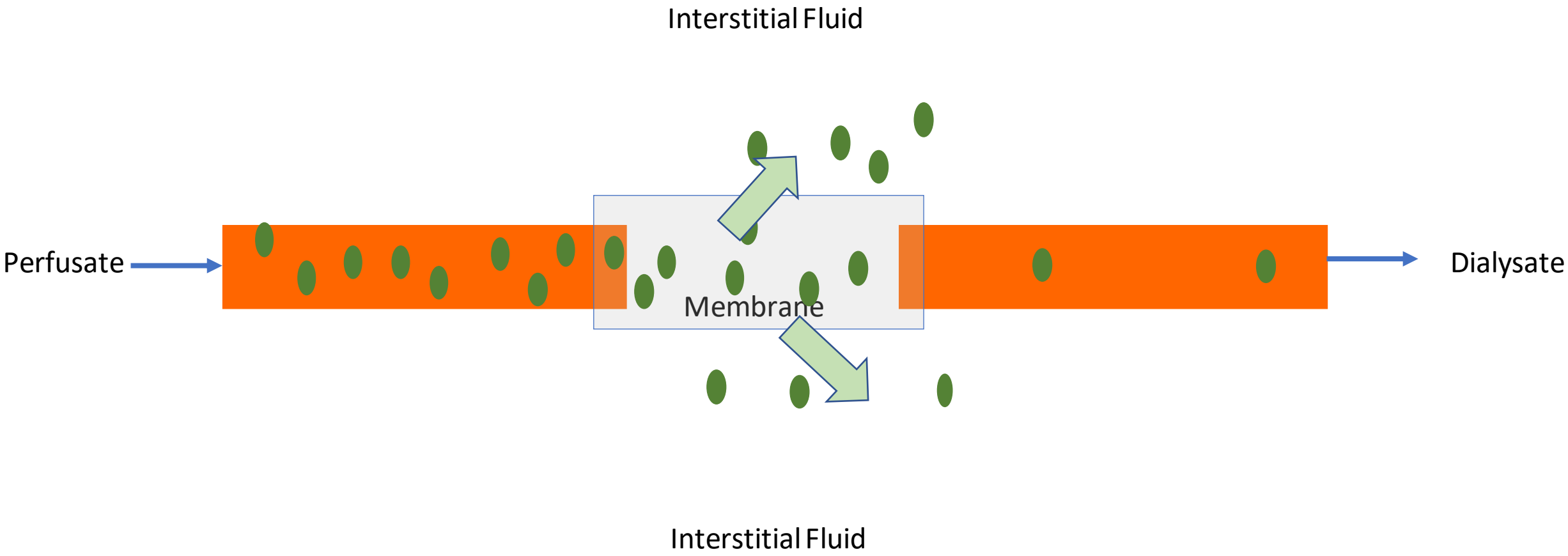
- MD is an *in vivo*, minimally invasive technique, that allows sampling of **unbound** molecules in the dermis and subcutaneous tissues



Microdialysis (*Gain*) Principle

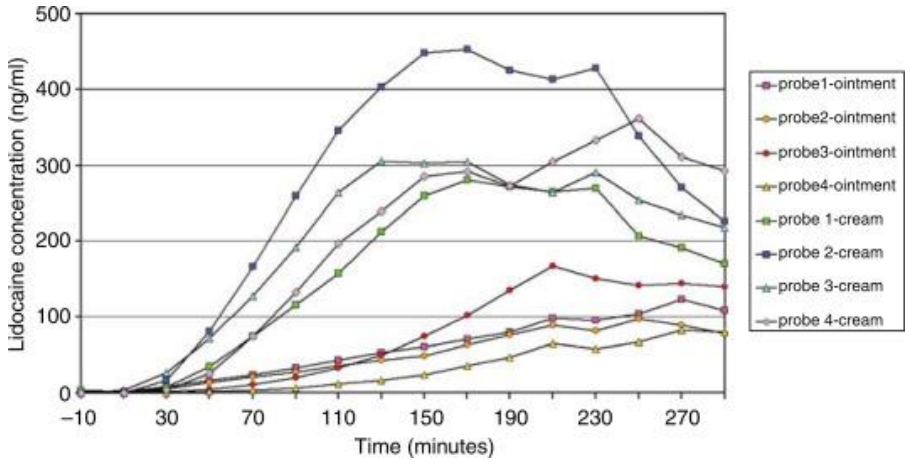


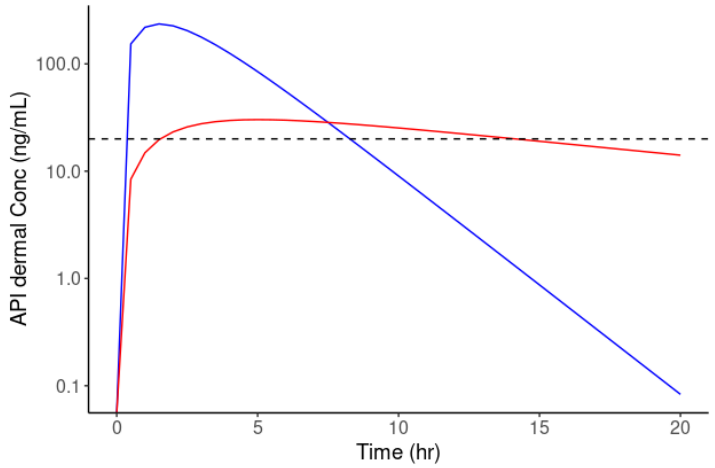
Retrodialysis (*Loss*) Principle

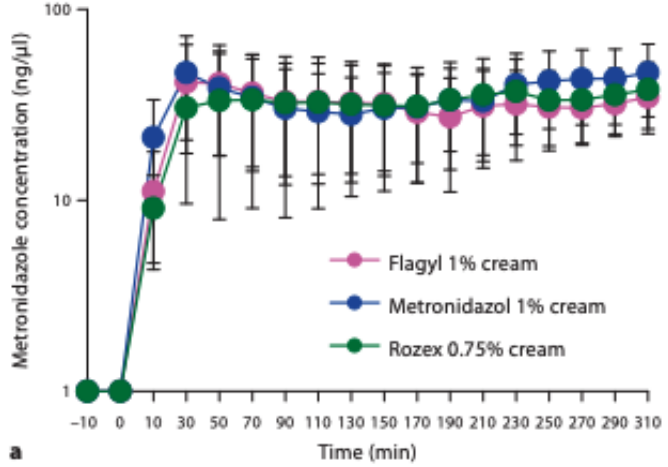


Where have we been?

- dMD has been utilized for numerous years with promising results yet more left to be desired







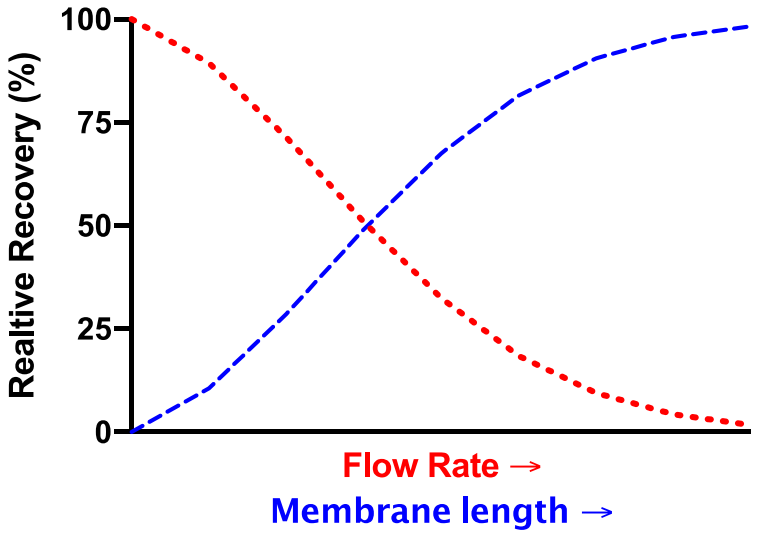
Benfeldt, Eva, et al. Journal of Investigative Dermatology 127.1 (2007): 170-178.

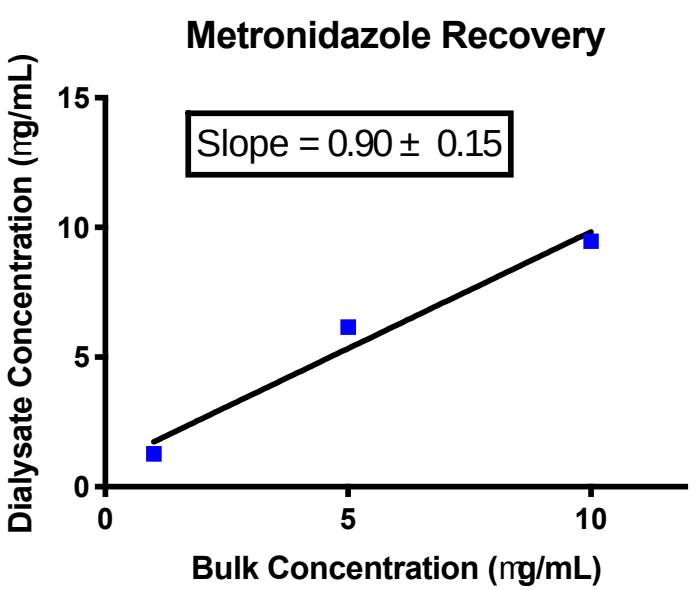
Ortiz, P. García, et al. *Skin pharmacology and physiology* 24.1 (2011): 44-53.

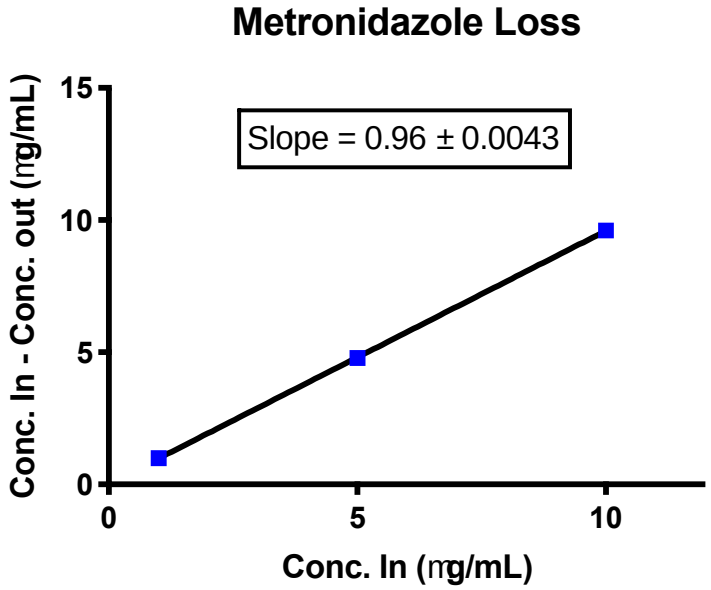
Consistency is KEY!

- Is the dMD probe stable?
- Can dMD specifically quantify topically applied drug?
- Is dMD sensitive to differences in local BA?
- Can dMD distinguish between formulations that have known differences in IVPT data?
- How reproducible is dMD?
- Are results between labs similar/dissimilar using standardized protocol?

dMD in vitro system suitability







Optimized Parameters
Flow rate: 0.5 uL/min
Membrane length: 1.7 cm

In vitro recovery ~ 90%
In vitro retrodialysis ~ 96%

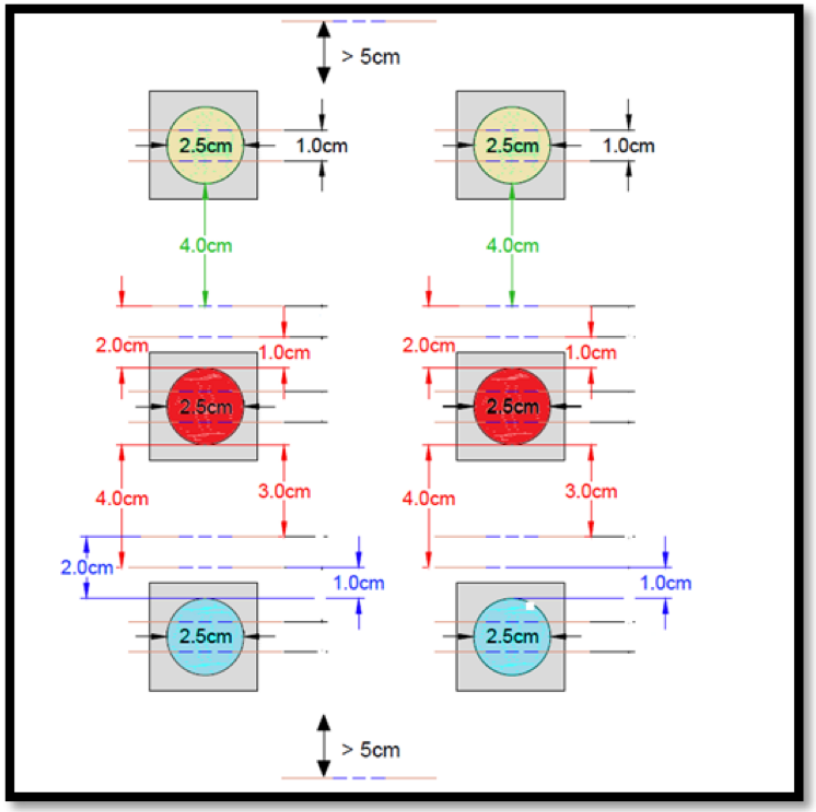
→ ✓ dMD set-up suitable for Metronidazole

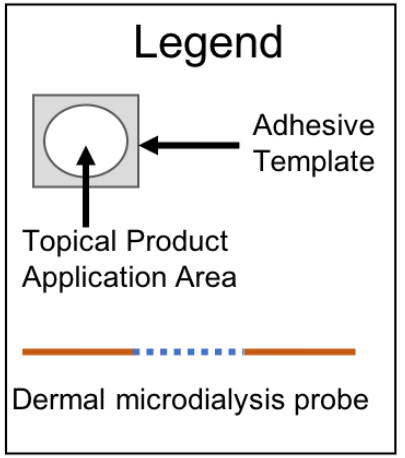
Local BA of Metronidazole (MTZ) Study

- Are dMD probes sensitive to changes in the local dermal environment?
- What is the minimum distance between application sites for no cross talk?

Formulations

- Generic Gel: MTZ topical gel, 0.75% from Tolmar
- Generic Cream: MTZ topical cream, 0.75% from Fougera Pharma





Dose:

3 mg/cm^2

10 mg/cm^2

30 mg/cm^2

Kuzma, Benjamin A., et al. *European Journal of Pharmaceutical Sciences* 159 (2021): 105741.

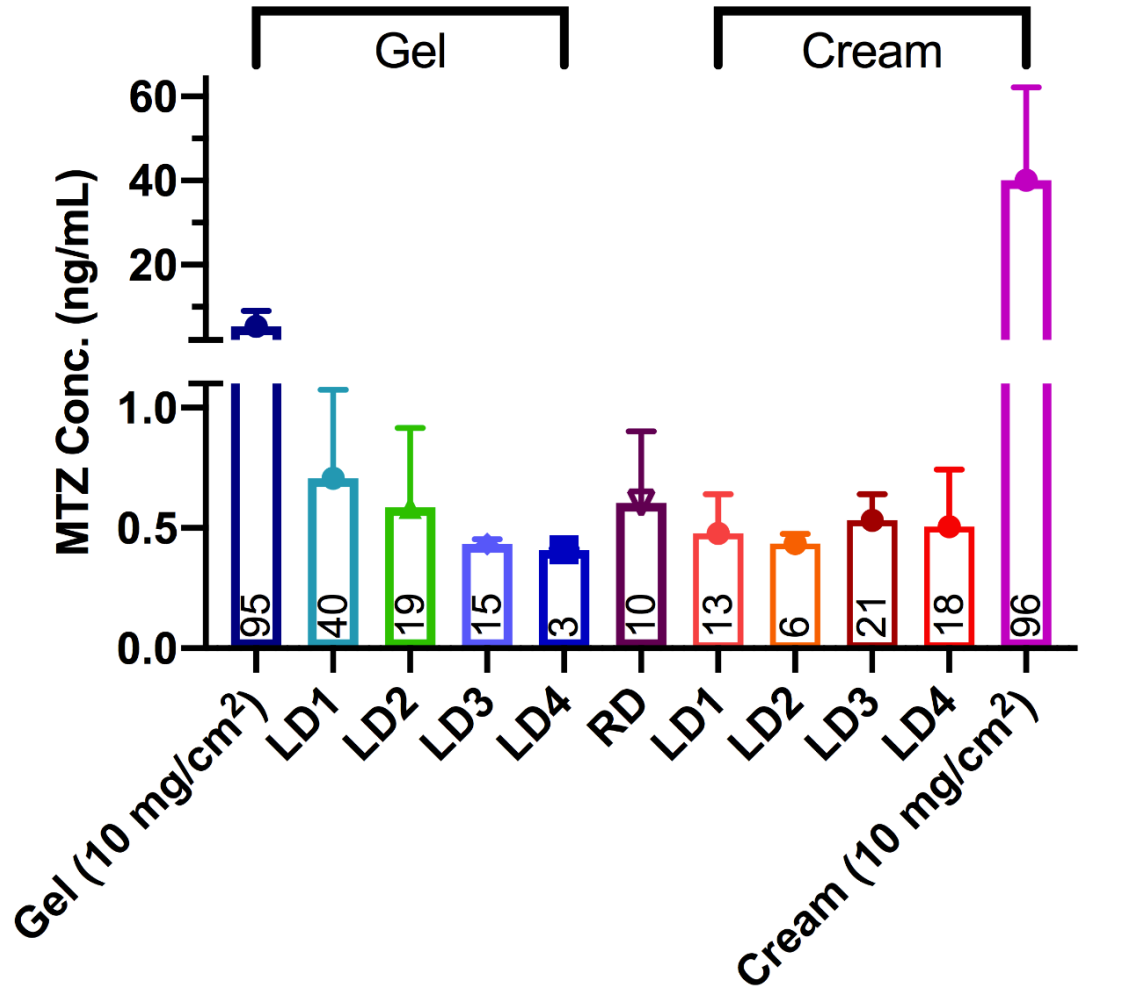
Negligible Lateral Diffusion

- Theoretical distances from clinical dose (10 mg/cm^2)

✓ Concentrations detected in LD probe were similar to those in the RD

✓ No significant trend moving away from application site

✓ No systemic redistributions – Contributions in LD probe attributed to MTZ impurity in D_3-MTZ



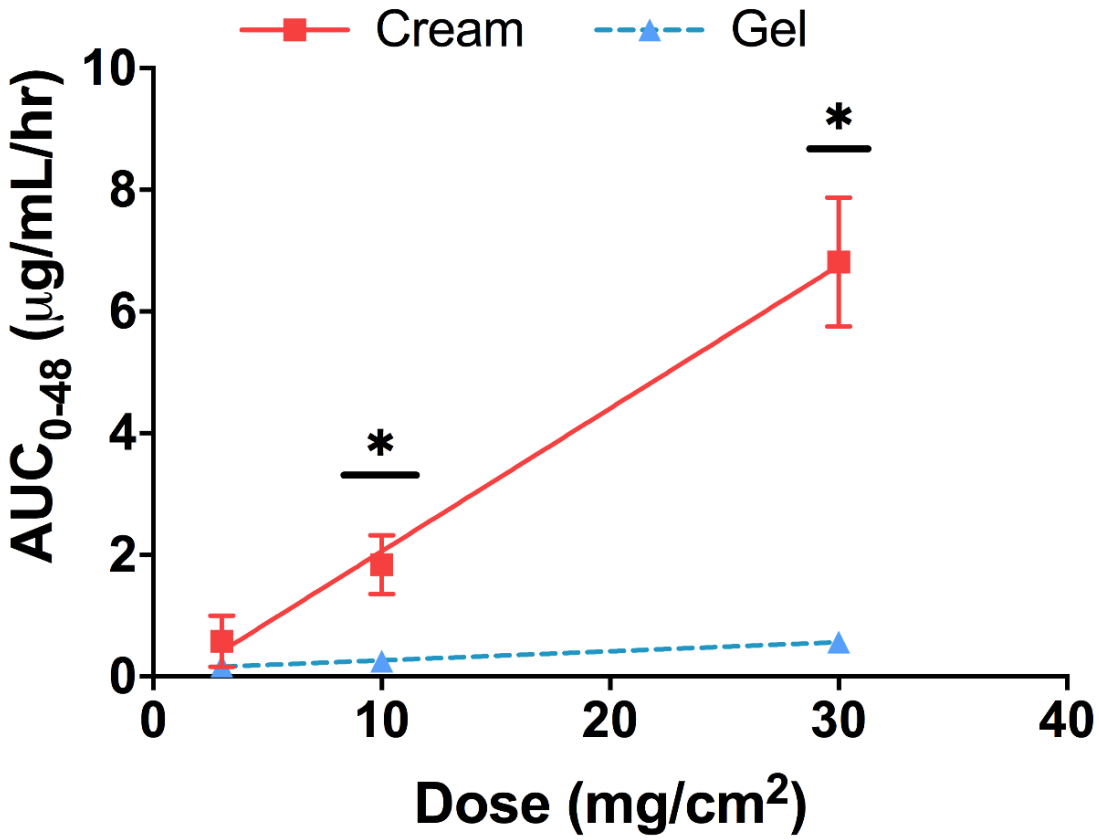
Kuzma, Benjamin A., et al. *European Journal of Pharmaceutical Sciences* 159 (2021): 105741.

Linear Dose-Response Relationship

✓ Significant exposure difference between gel and cream products at 10 mg/cm^2 ($p = 0.009$) and 30 mg/cm^2 dosing ($p = 0.0005$)

✓ Significant difference between slopes ($p = 0.0042$) with linear ($R^2>0.99$) and proportional increase in AUC_{0-48} with dose

✓ dMD able to discriminate between formulations and sensitive to different local bioavailabilities



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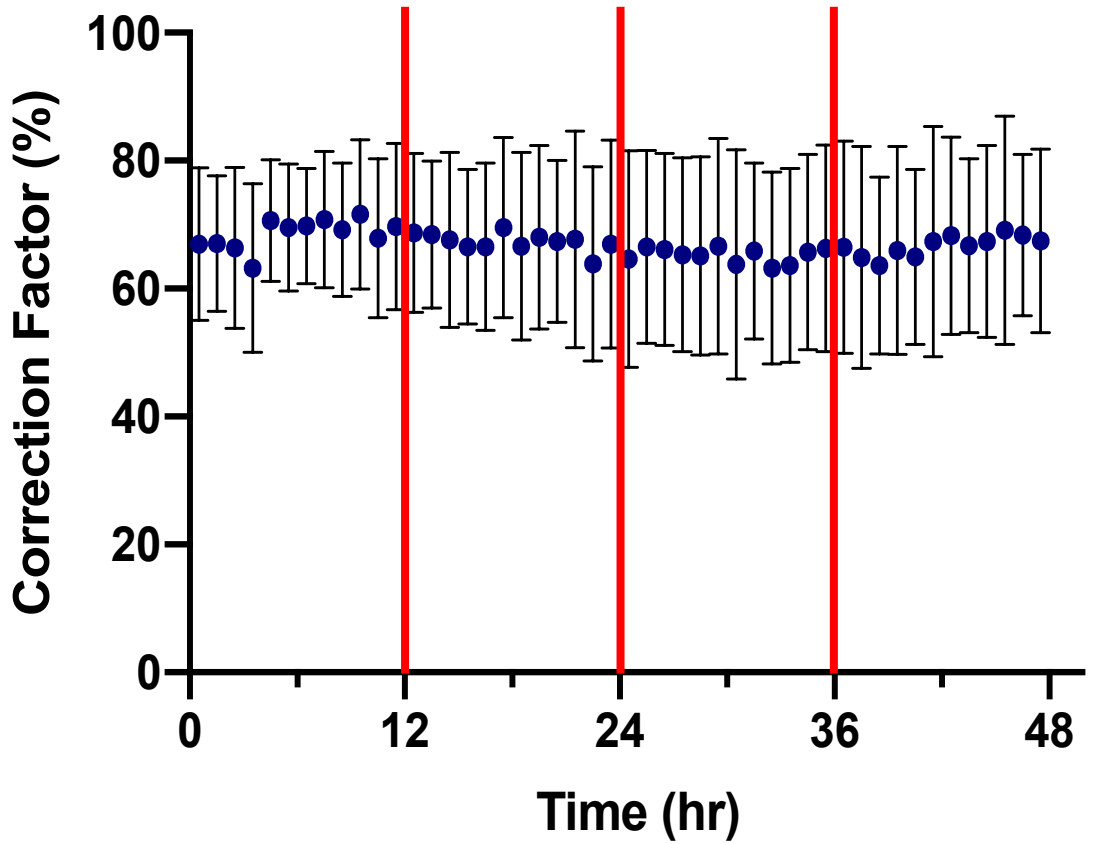
dMD Probe Stable for 48-hr

✓ Correction factor compared over 12-hr intervals indicated that 3rd 12-hr block was significantly different from the others

✓ Ability to correct concentrations by correction factor can account for random fluctuations

✓ No probe fouling or deterioration over the course of the study duration



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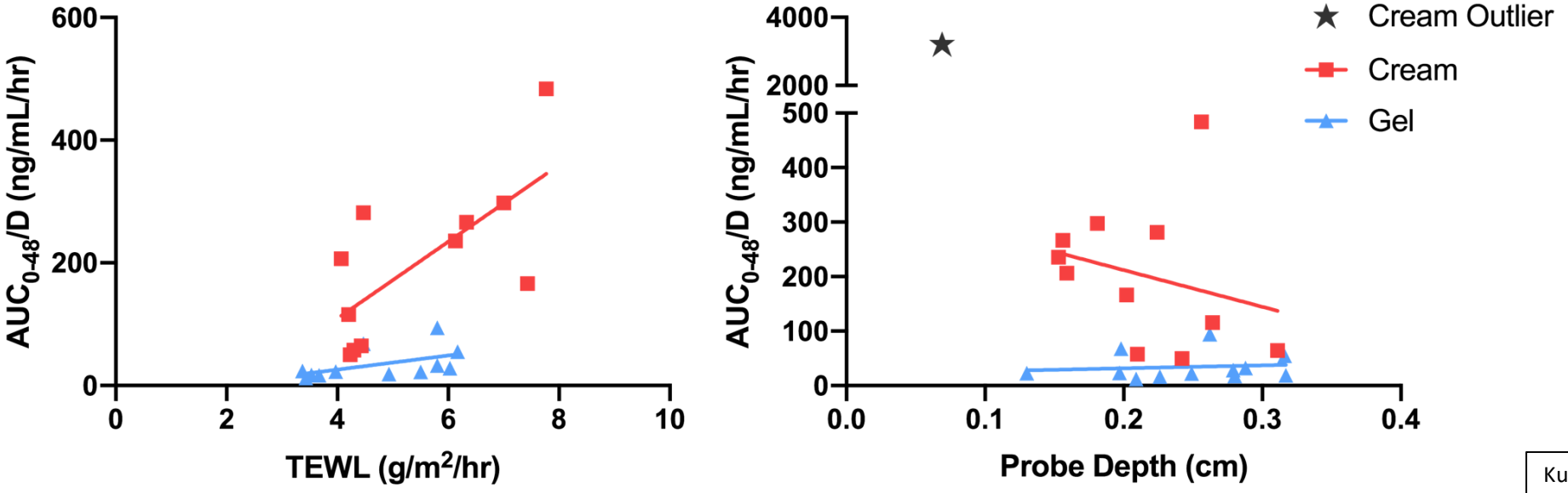
No significant covariate impact of on dPK

- ✗ TEWL has no significant correlation with dermal exposure:

  Cream ($R^2 = 0.484$), Gel ($R^2 = 0.256$)

- ✗ No correlation between $AUC_{0\text{-}48hr}/D$ and probe depth

  Cream ($R^2 = 0.068$), Gel ($R^2 = 0.0004$)



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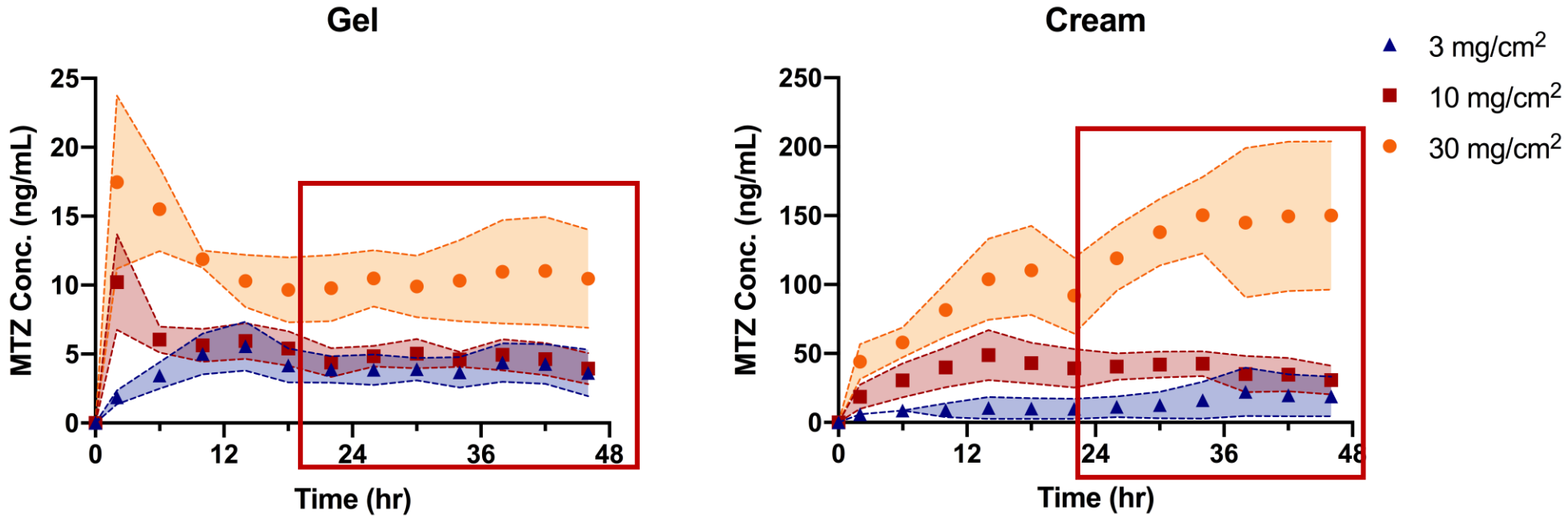
Lack of Terminal Phase

- ✕ Unable to get reliable estimate of C_{max}
- ✕ Concentrations continue to either level off or increase after 24-hr

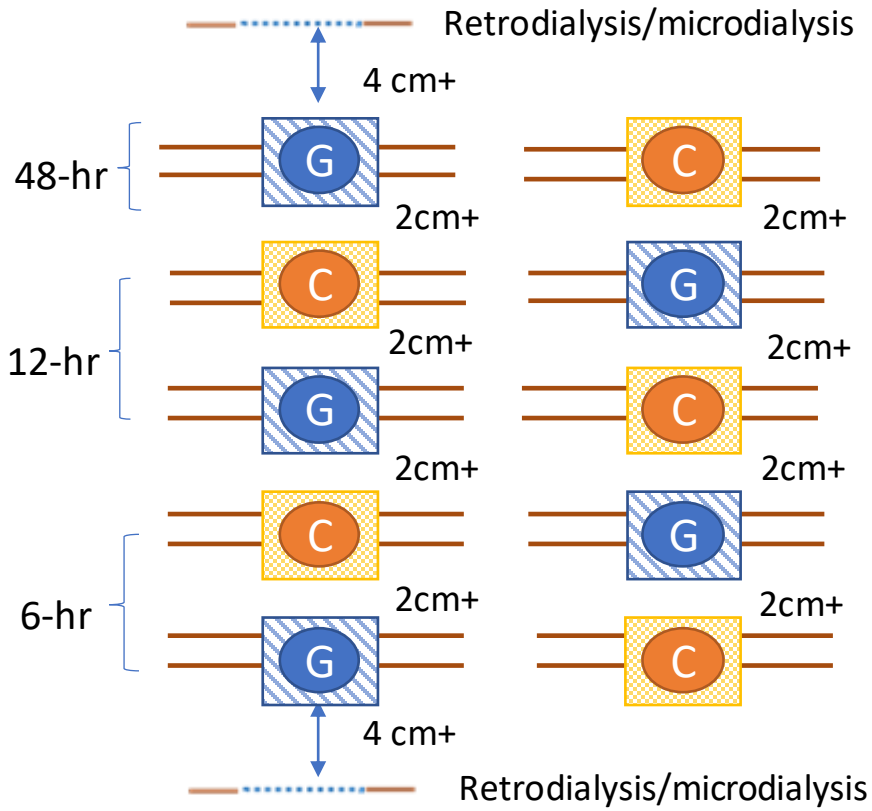


- The concentrations are plotted as the average of 4 time points with the corresponding averaged time midpoints.

Kuzma, Benjamin A., et al. *European Journal of Pharmaceutical Sciences* 159 (2021): 105741.

Dose Duration Effect on dBA Study

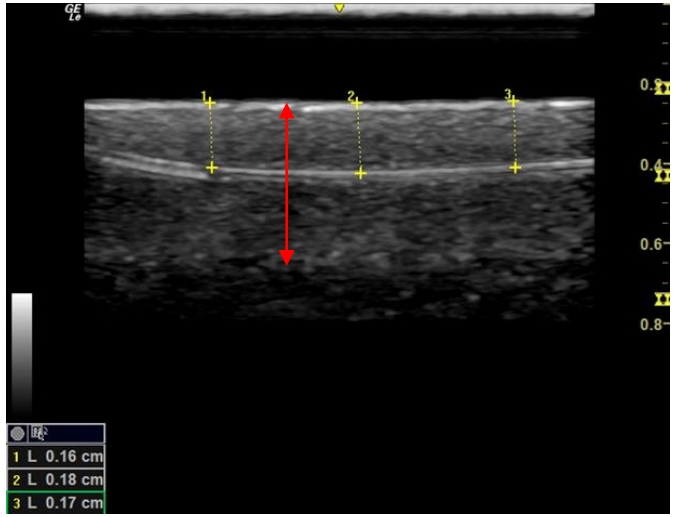
- Does the dose duration impact dermal BA?
  - Formulations applied for:
    - 6-hr
    - 12-hr
    - 48-hr (no removal)
- Can we estimate the dermal disposition of metronidazole using dMD?

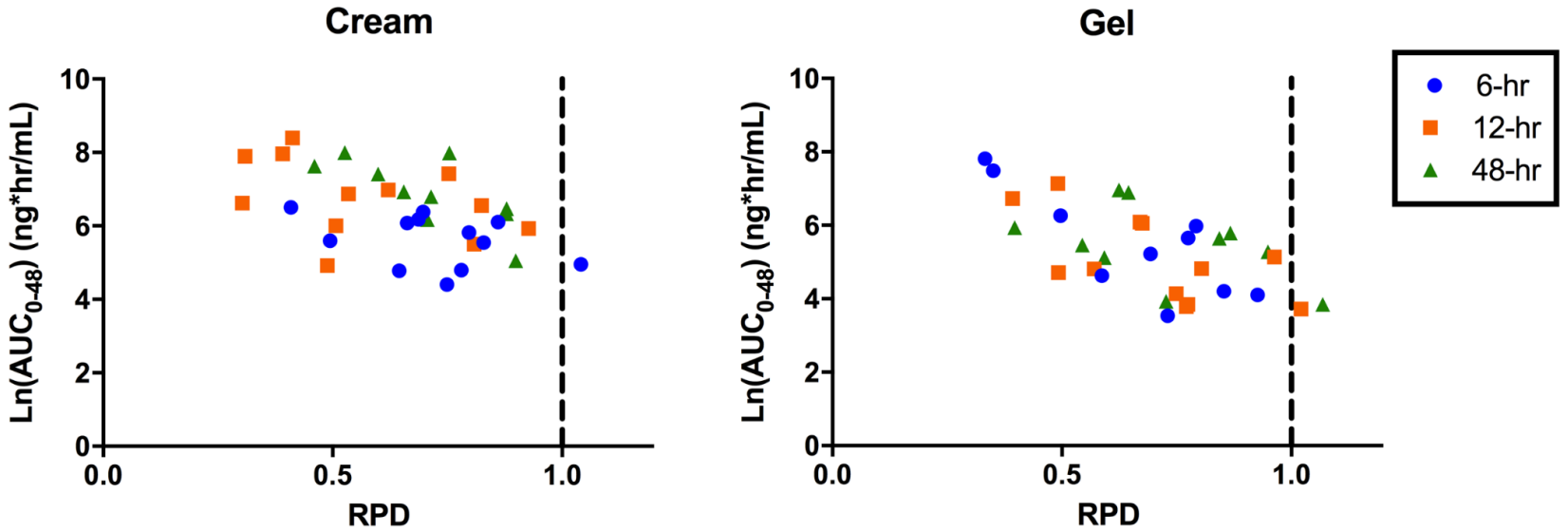


Kuzma, B.A., et al. (2018). Effect of formulation wipe-off time on topical bioavailability of metronidazole using dermal microdialysis, AAPS Annual Meeting. Washington D.C., November 2018.

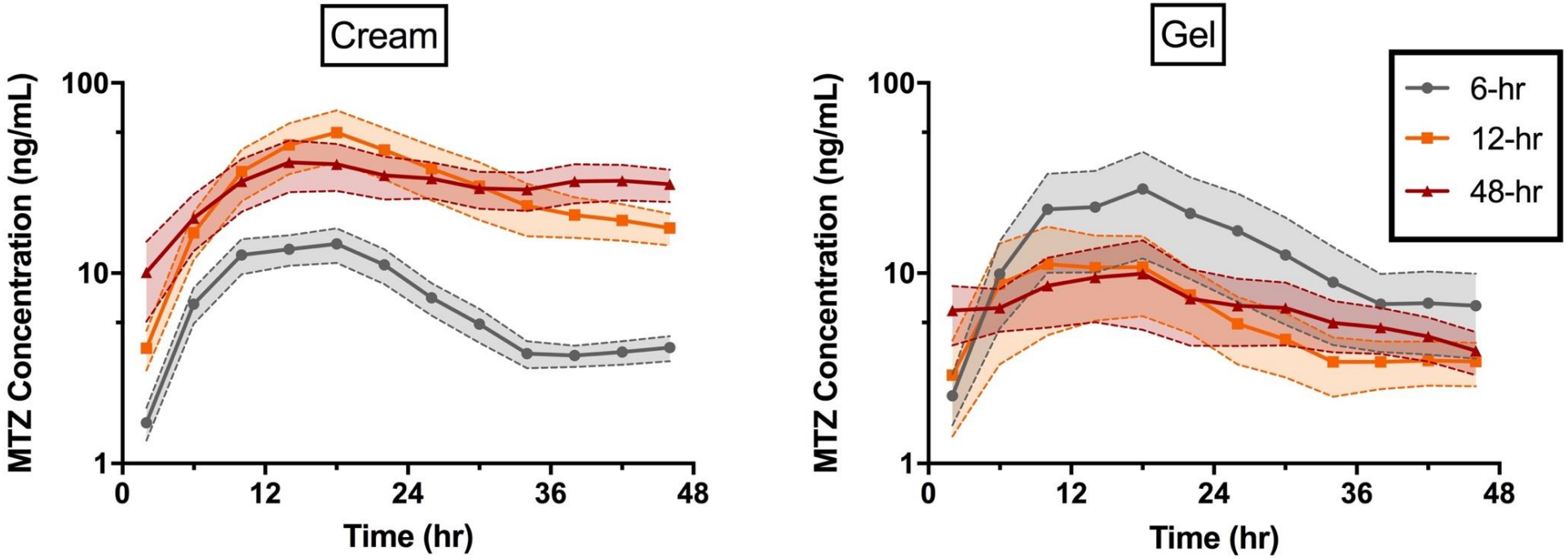
Probe Depth Relationship

- From ultrasound images we can measure both probe depth and skin thickness and arrived at a probe depth ratio (PDR)
- Only moderate correlation ($R^2 = 0.6$) for the 6-hr gel but no real correlation for other dosing schemes ($R^2 < 0.5$) comparing $Ln(AUC_{0-48})$ vs PDR





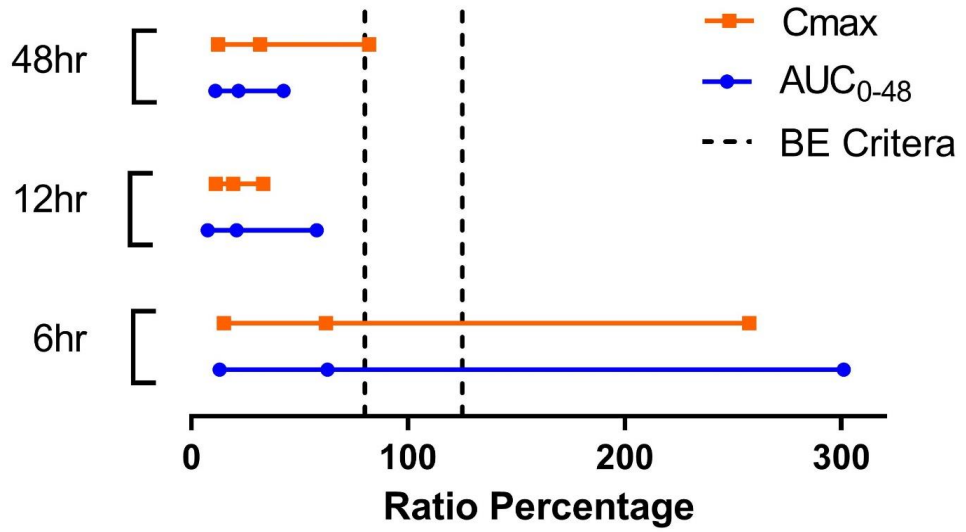
Adequate Characterization of Dermal PK

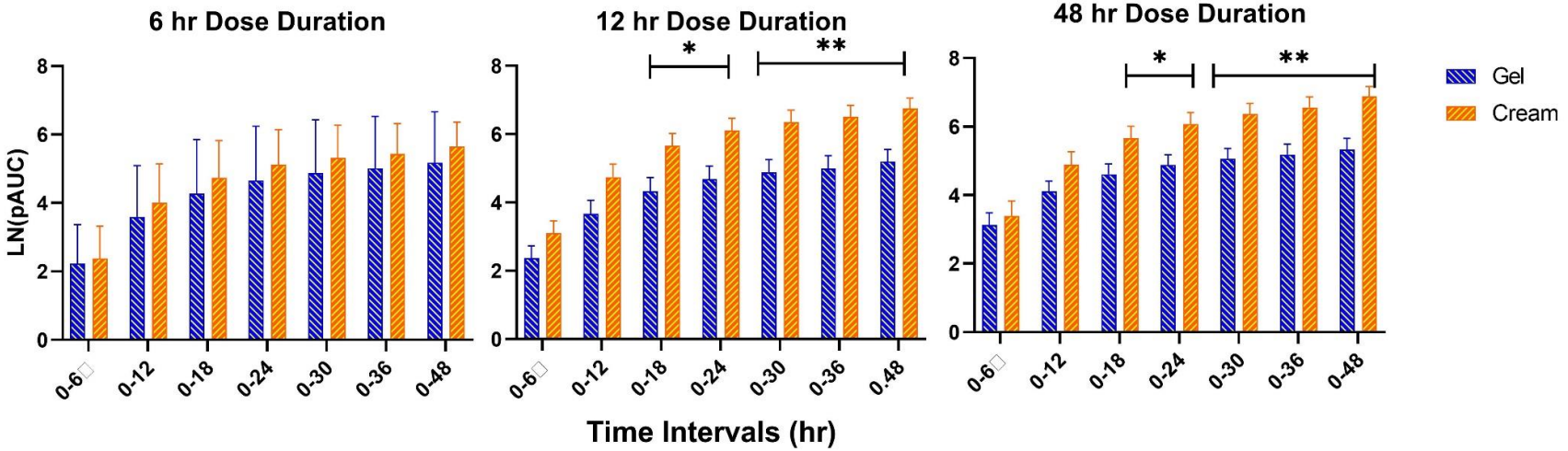


- The cream 6-hr DD was significantly different from both the 12-hr DD and 48-hr DD for AUC_{0-48}, AUC_{0-36}, and C_{max}
- Terminal phase half-life estimated for 44 of 66 probes (6 probes from preliminary study)
- 6-hr DD comparison between cream and gel indicated no significant difference in exposure

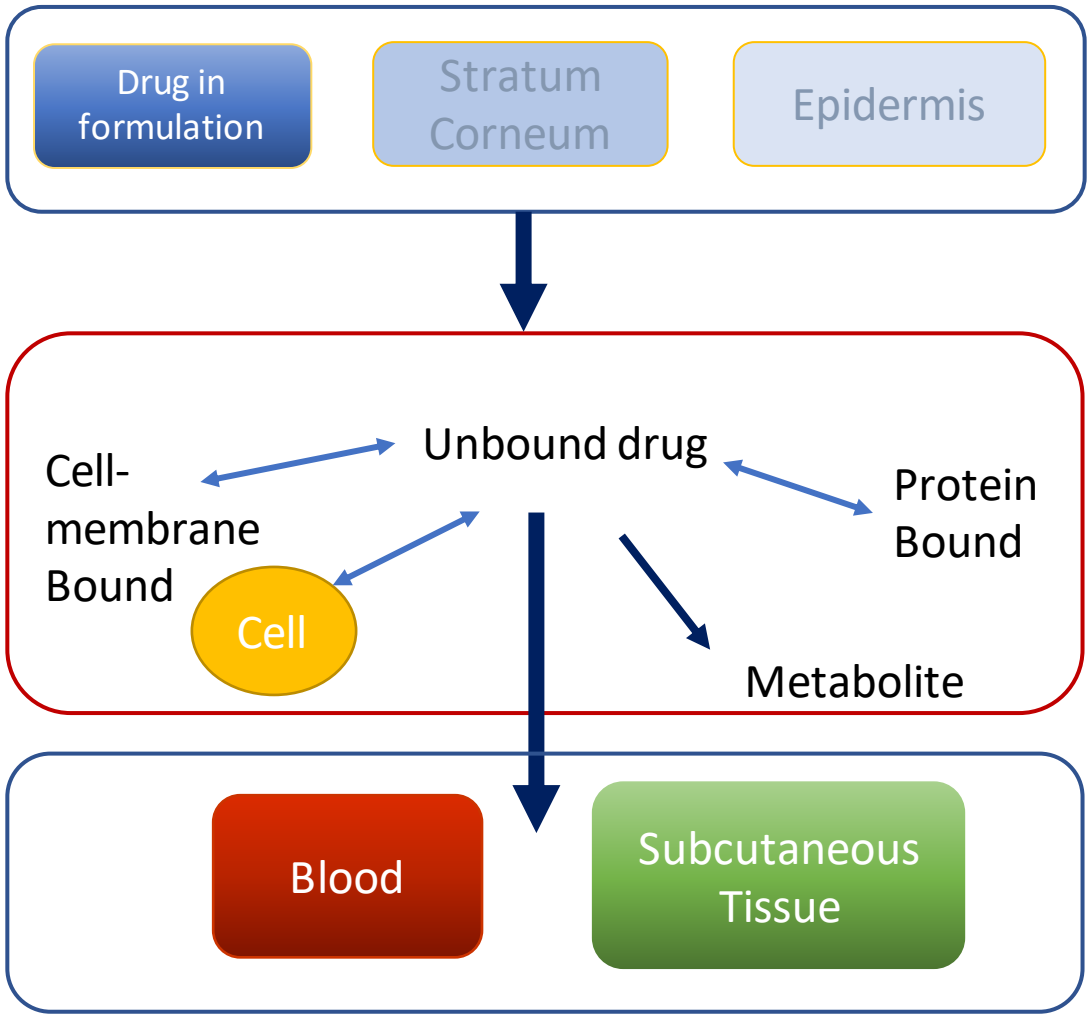
Local dBA Comparison

- Different dBA for 12-hr and 48-hr dose duration
- How long would we need to conduct studies for a difference in dBA?





The observed dermal concentration profile results from:

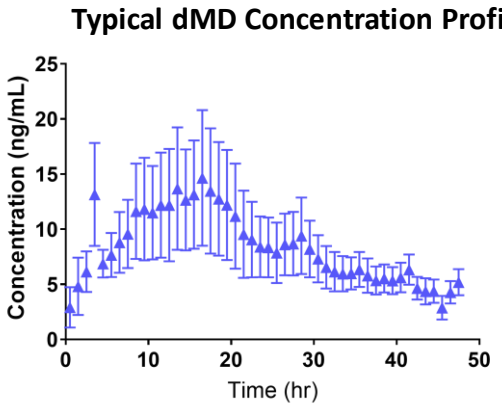


Absorption (f_t)

Distribution within dermis

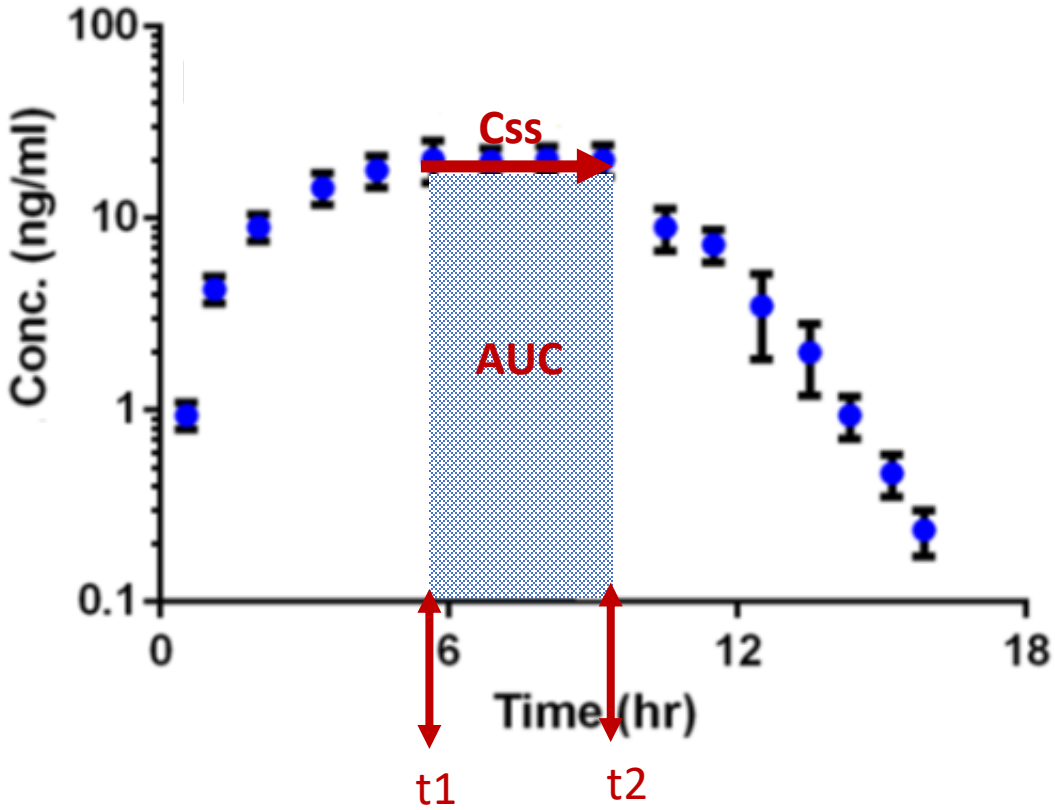
Elimination

Disposition (g_t)

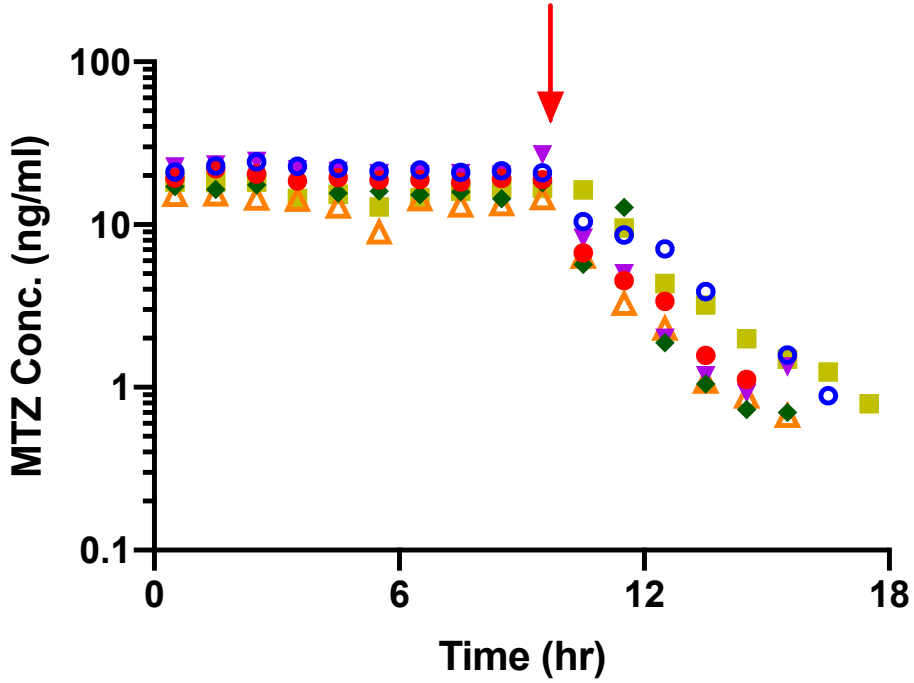


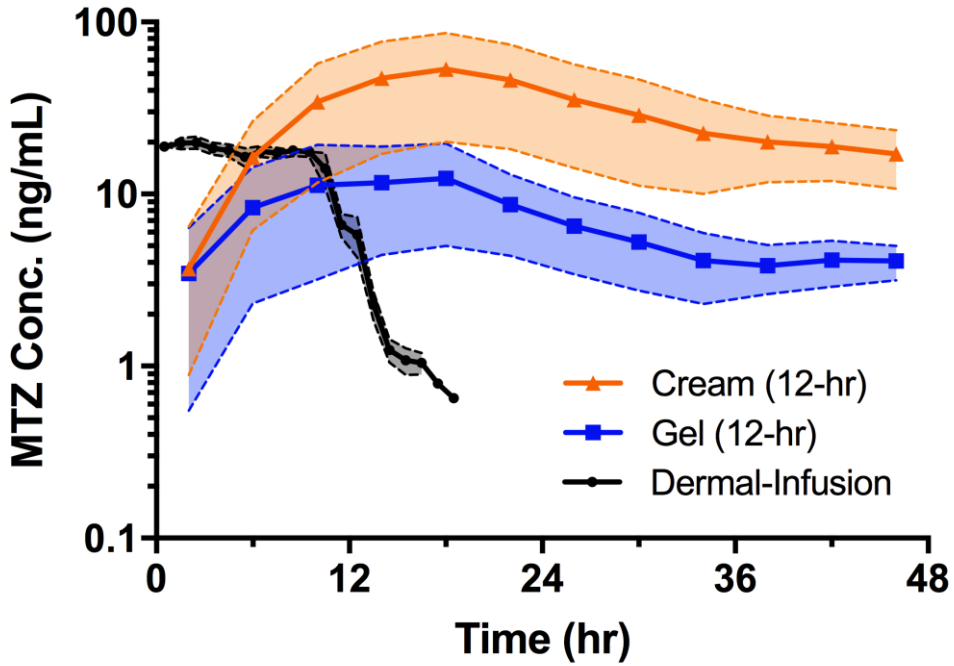
Dermal API delivery via dMD probe

- Identify steady state concentration (C_{ss})
- Measure the AUC under the selected steady state (shaded area)
- Calculate the dose delivered in that time interval:
  - $Dose_{t1-t2} = (C_{perfusate} - C_{ss}) \times V_{perfused\,(t1-t2)}$
- Calculate clearance:
  - $Cl = \frac{Dose_{t1-t2}}{AUC_{t1-t2}}$
- Fit the best poly-exponential equation to the elimination-phase data;
- Estimate V_d:
  - E.g., if mono-exponential: $V_d = \frac{Cl}{k_e}$
  - More complicated if poly-exponential



MTZ Dermal Disposition





- Dermal elimination half-life after dermal infusion was 1.47 hr (19.5) (geo. mean (CV%))
- Average dose delivered from 5.5 - 9.5-hr was 3.5 ng $\pm$ 0.8 (mean $\pm$ SD; n=6)
- Average dermal volume of distribution was calculated as 0.12 $\pm$ 0.06 mL (mean $\pm$ SD, n = 6)

Kuzma B.A., et al. (2019) Estimation Of In Vivo Skin Permeation (Flux) And Cumulative Amount Input of Metronidazole Formulations in Mini-pigs' Dermis GRS/GRC – Skin Barrier Function of Mammalian Skin, Waterville Valley, N.H. **2019**.

dUIR Calculation

- UIR for mono-exponential elimination:

$$UIR = \frac{1}{V_d} \times e^{-k_e t}$$

Where V_d has units of mL and K_e has units of hr^{-1}

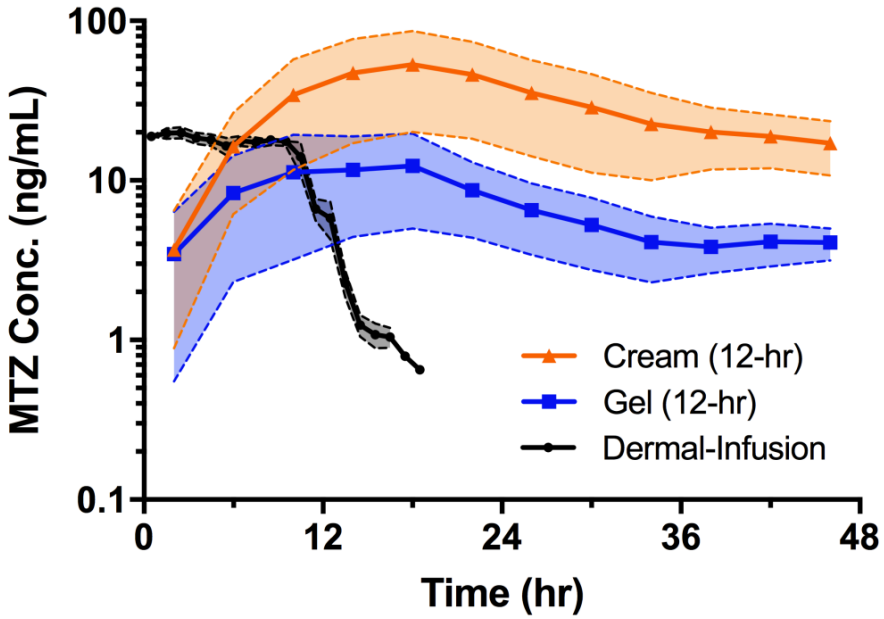
- Averaged dUIR for all probes and subjects:

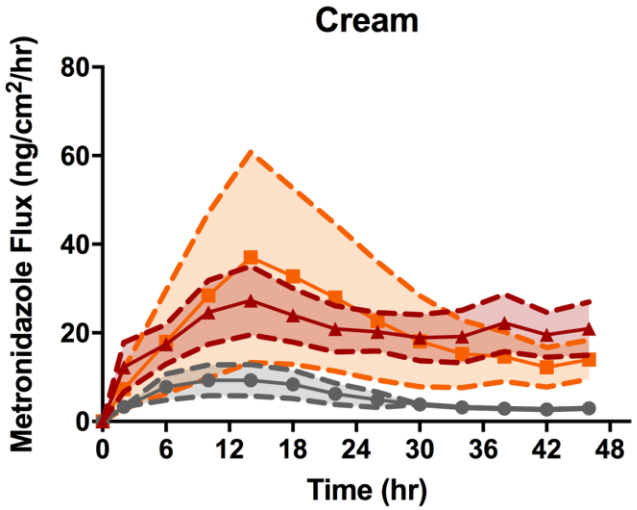
$$dUIR = 10.1 \times e^{-0.47t}$$

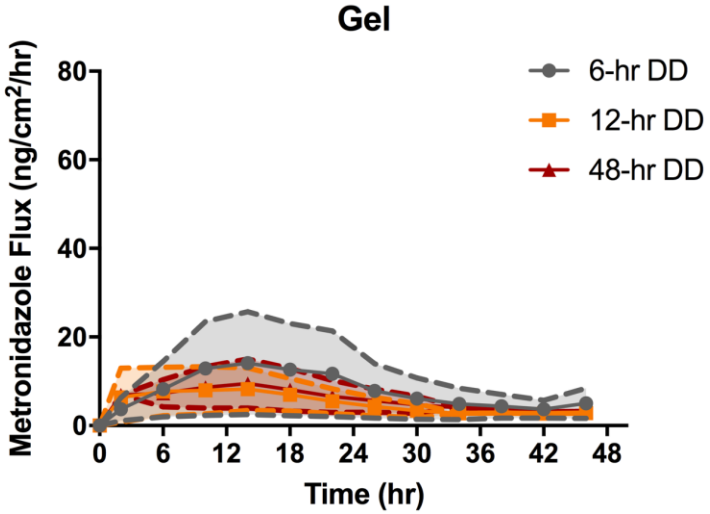
- dUIR can be used to deconvolve **dermal microdialysis concentration data**
- dUIR can also be used to convolve **in vitro permeation testing data**

MTZ dermal input kinetics

- Data indicate **flip/flop dermal PK**:
  - Absorption (permeation) from upper layer of the skin is a prolonged, sustained process







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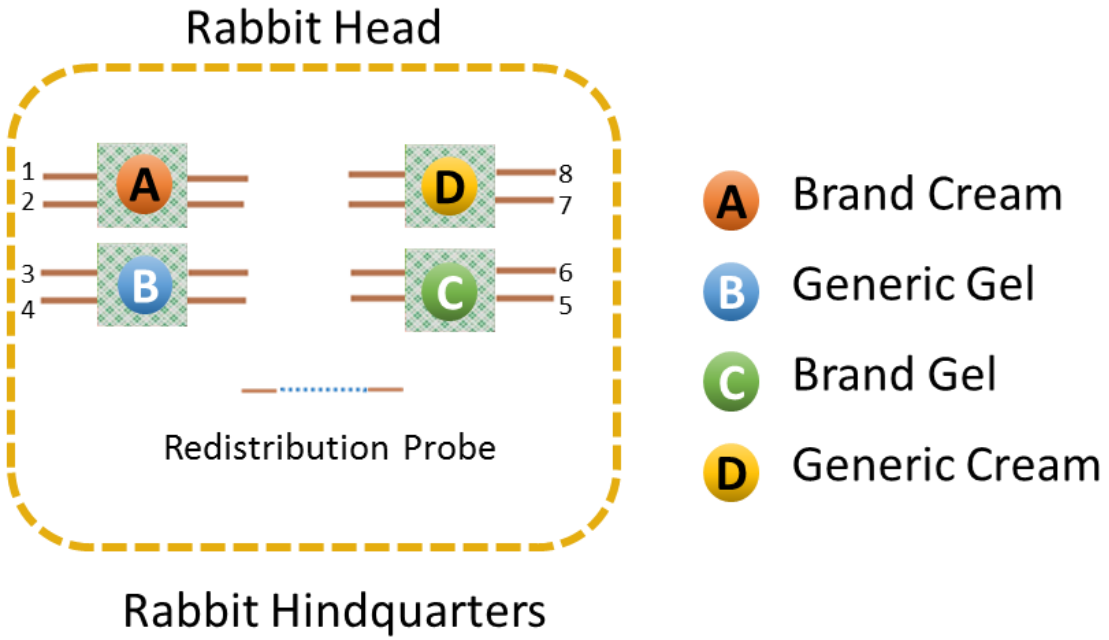
Rabbit MTZ BE study

- Can dMD be used to identify differences in local BA between:
  - Two types of vehicles (cream/gel)
  - Test vs. reference in same vehicle

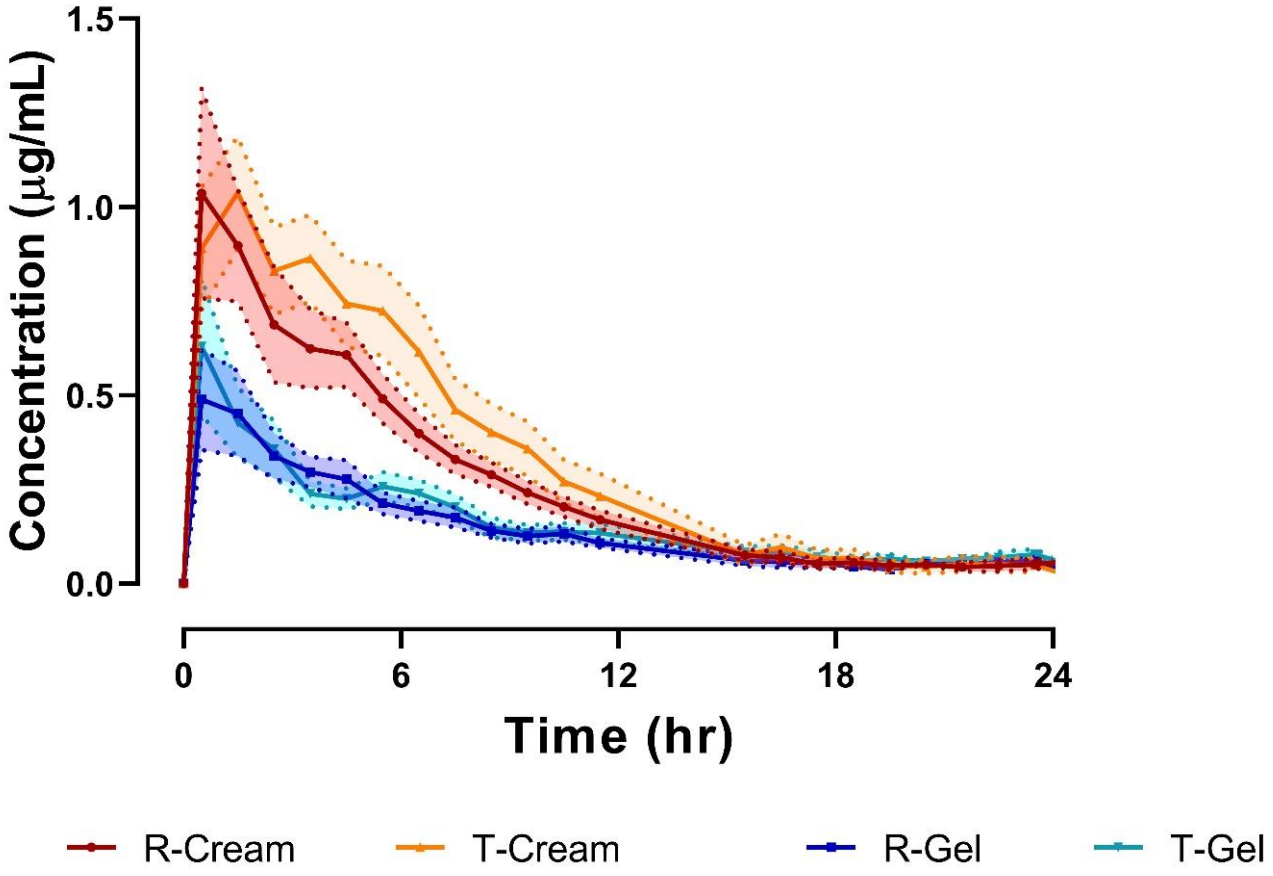


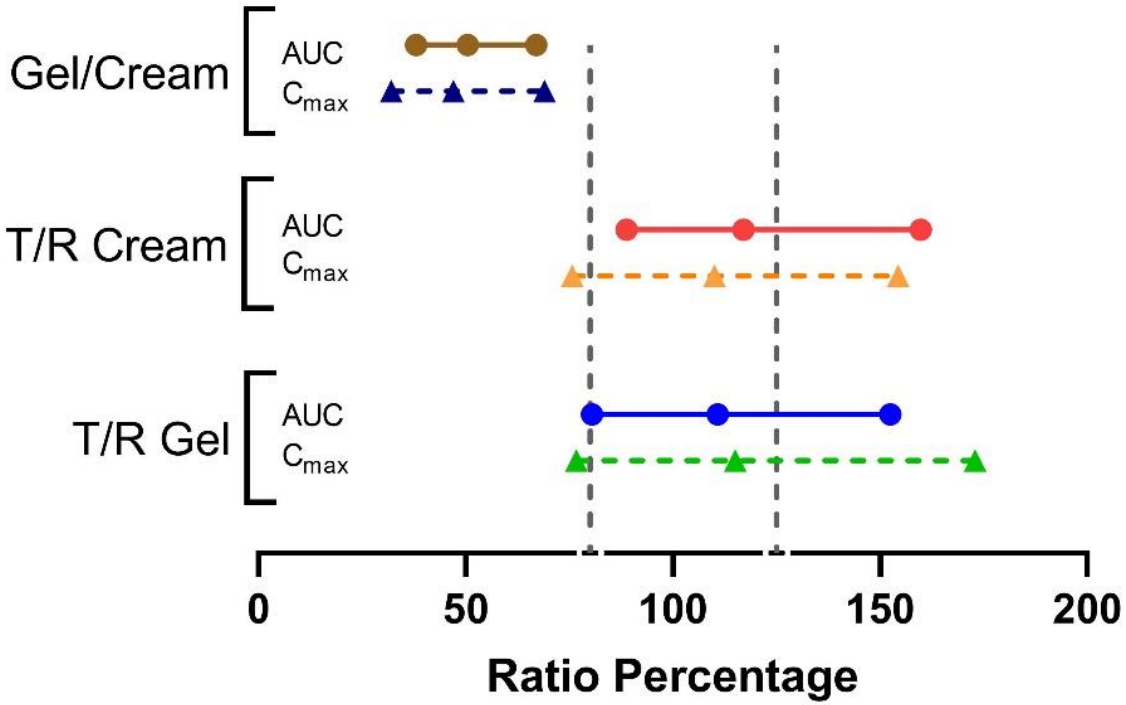
Formulations

- Brand Gel: MetroGel® topical gel, 0.75% from Prasco Labs
- Generic Gel: MTZ topical gel, 0.75% from Tolmar
- Brand Cream: MetroCream® topical cream, 0.75% from Galderma Laboratories
- Generic Cream: MTZ topical cream, 0.75% from Fougera Pharma

Senemar S, et al. (2019) Evaluating the Bioequivalence of Topical Dermatological Drug Products Containing Metronidazole Using Dermal Microdialysis: Preliminary Studies in Rabbits. AAPS 2019

Adequate BA and BE assessment

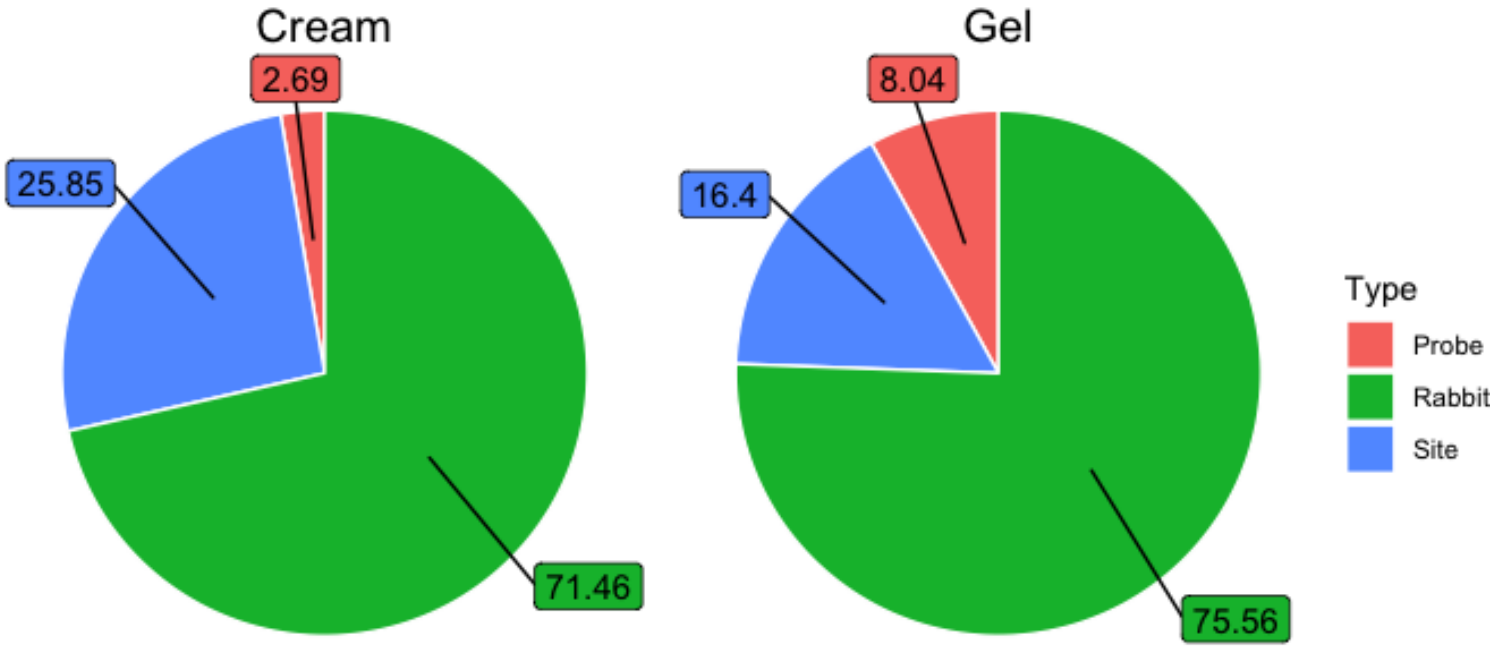




Senemar S, et al. (2019) Evaluating the Bioequivalence of Topical Dermatological Drug Products Containing Metronidazole Using Dermal Microdialysis: Preliminary Studies in Rabbits. AAPS 2019

What components contribute to the variability?

- Total CV of log(AUC_{0-24}) between 42-55%



Senemar *et al.* (Metronidazole)
Inter-subject variability – 71-76 %
Intra-subject variability – 24-28 %

Senemar S, et al. (2019) Evaluating the Bioequivalence of Topical Dermatological Drug Products Containing Metronidazole Using Dermal Microdialysis: Preliminary Studies in Rabbits. AAPS 2019

Benfeldt *et al.* (Lidocaine)
Inter-subject variability – 61 %
Intra-subject variability – 39 %

Benfeldt et al., J Invest Dermatol. 2007 Jan;127(1):170-8. Epub 2006 Jul 27

Ortiz *et al.* (Metronidazole)
Inter-subject variability – 116-223%*
Intra-subject variability – 30-39%*

Ortiz, P. García, et al. *Skin pharmacology and physiology* 24.1 (2011): 44-53.

Conclusions

- dMD methodology developed here was **sensitive, selective, stable, and reproducible**; however, ruggedness still requires investigation
- Study duration, dose-duration, topical dose, and application site location should be chosen with the utmost care
- Knowledge of the disposition function confirmed a **flip-flop PK scenario** after TDDP application
- The disposition function estimation allows for further exploration into the **in vivo absorption function** and potential IVIVRs
- dMD methodology has the potential to be implemented into BE assessment of TDDPs

Thoughts…

- The same dMD methodology developed here should be investigated by outside lab to determine its ruggedness
- Now we have a proposed method for dermal disposition – what can we do with this?
- Excipient's role in absorption and/or disposition?
- We know there is no “One Size Fits All” Approach – careful consideration into selection of tools from the *Toolbox of Methods*
- Systemic PK has tried and true fundamentals – do these carry over to cutaneous PK?

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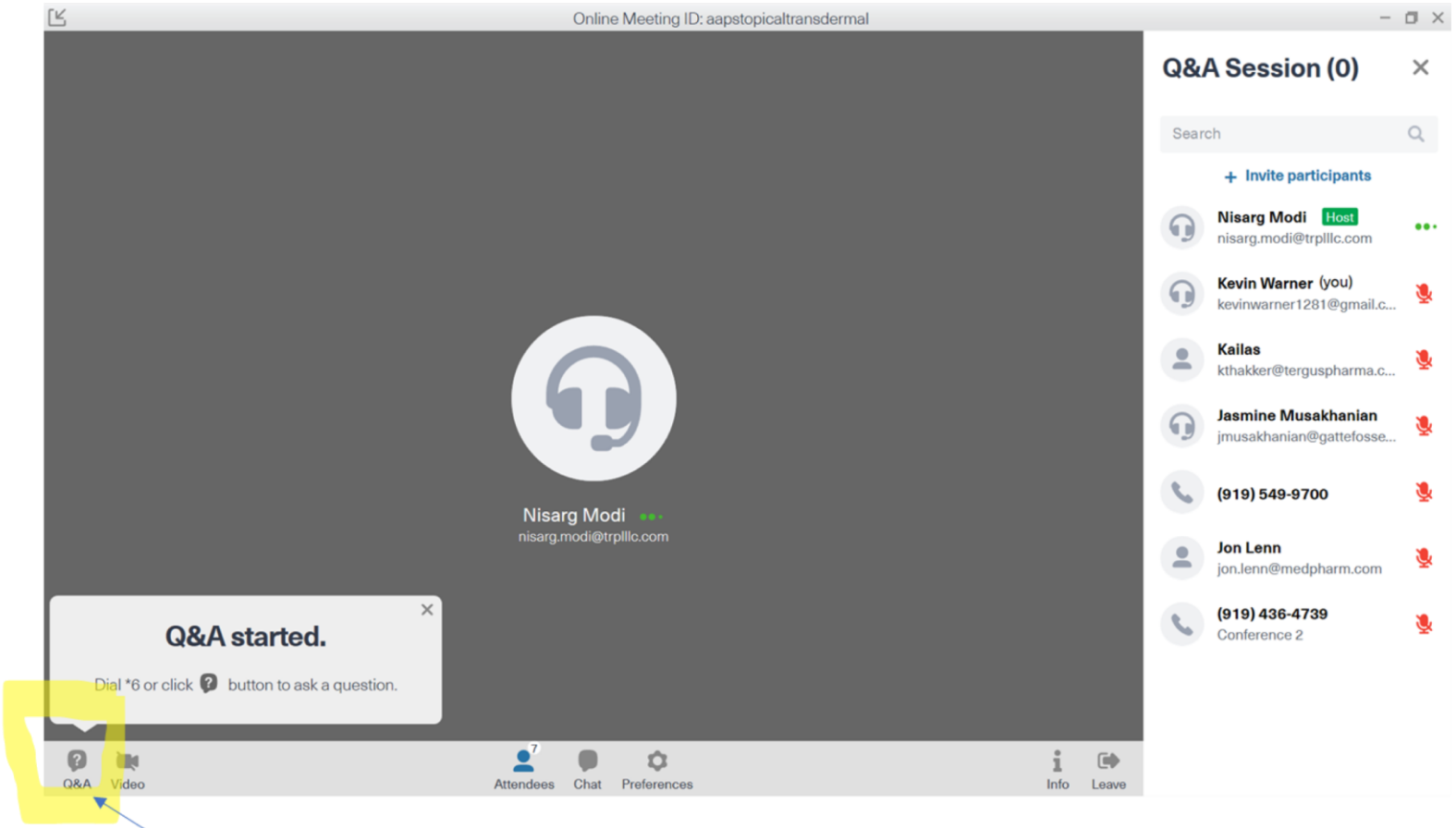
How to Ask A Question…



Click this icon or dial *6 to get in the queue to ask a question.

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