# In-Vivo Flux: A Breakthrough in IVIVC of Topical Dermatological Formulations

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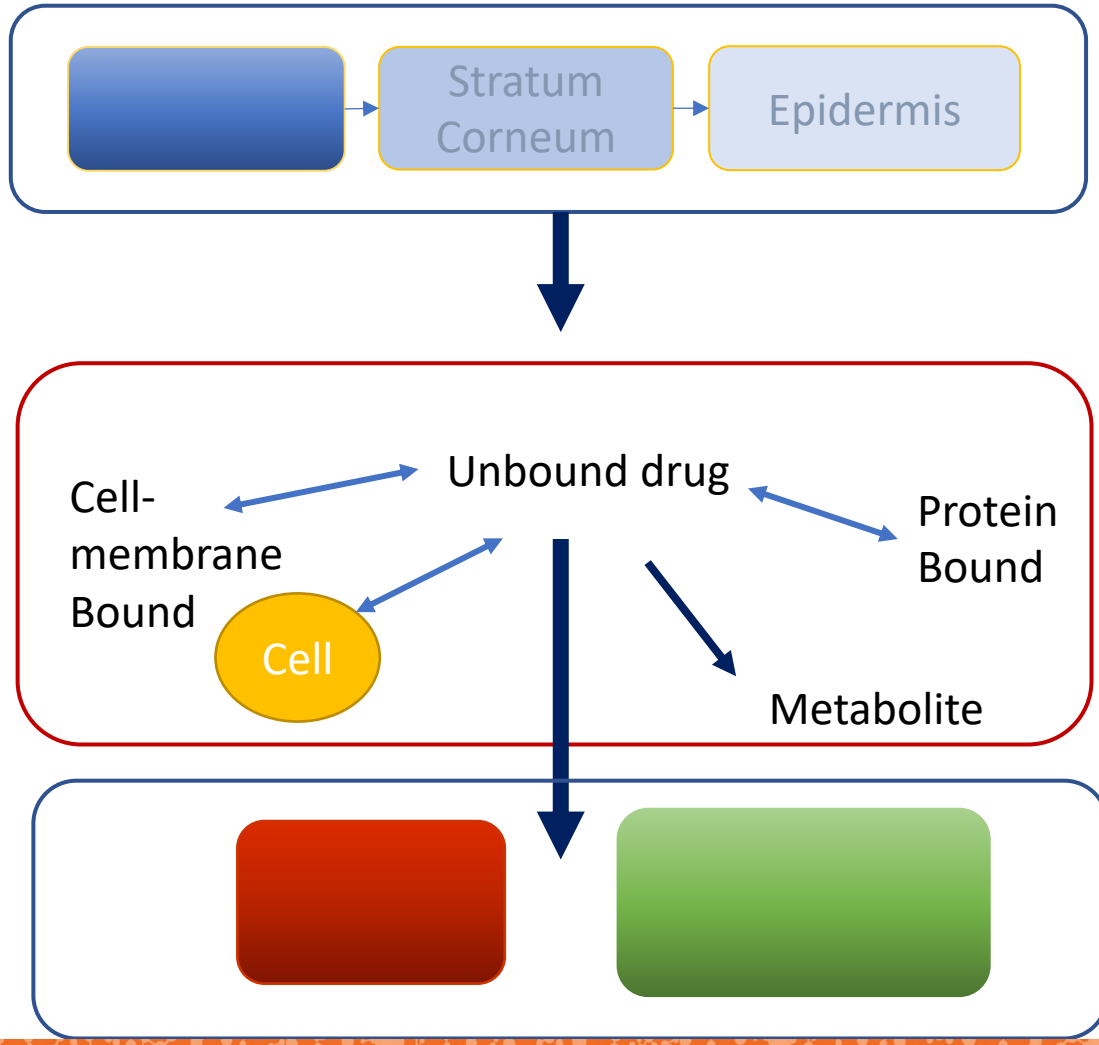
# Disclaimer

- 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.

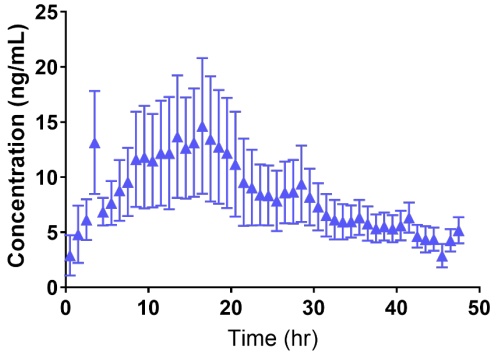
# Objectives

- Demonstrate the applicability of a retrodialysis/microdialysis approach to estimate the dermis unit impulse response (dUIR).
- Calculate MTZ flux and cumulative amount permeated.
- Development of IVIVR from in-vitro permeation testing data (IVPT) and dermal microdialysis (dMD) concentration data to predict dermis pharmacokinetics.

# The observed dermis concentration profile results from:




Absorption ($f_t$)




Distribution within dermis

Elimination

Disposition ($g_t$)

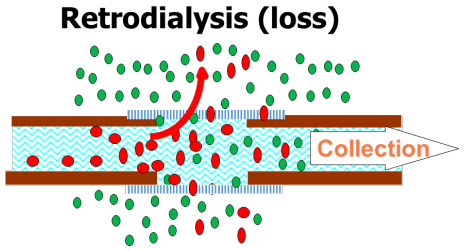
# Dermis Disposition: Unit Impulse Response (dUIR)

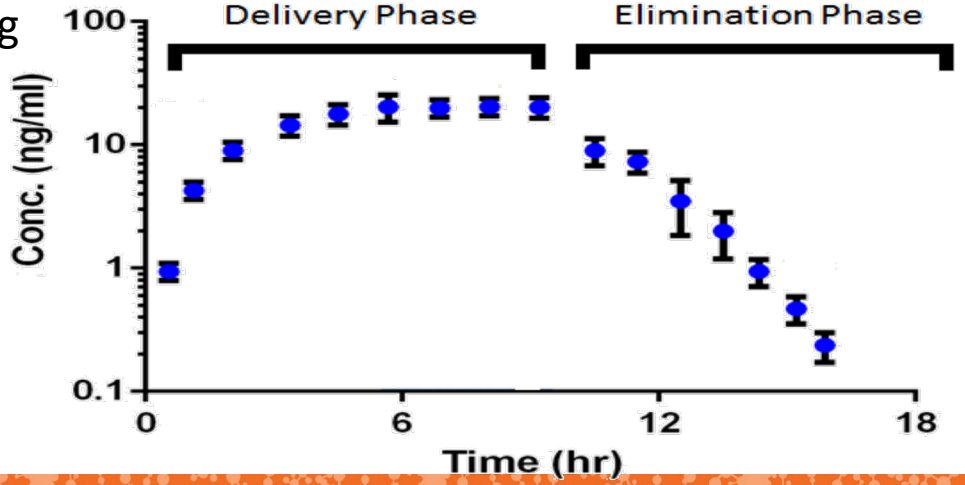
- Disposition function ($g_t$) also know as "Unit Impulse Response" (UIR) is defined as:

**The concentration deriving from the instantaneous administration of a unit amount of drug**: it accounts only for the distribution and elimination processes

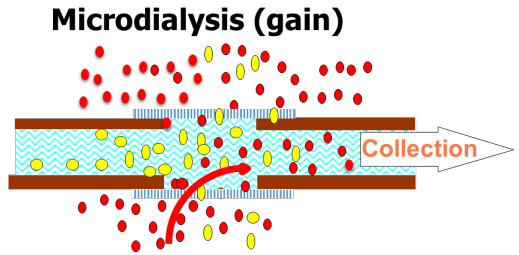
- How can we give an instantaneous administration directly in dermis?
- Idea: use a retrodialysis/microdialysis approach:

Retrodialysis (loss) to deliver drug

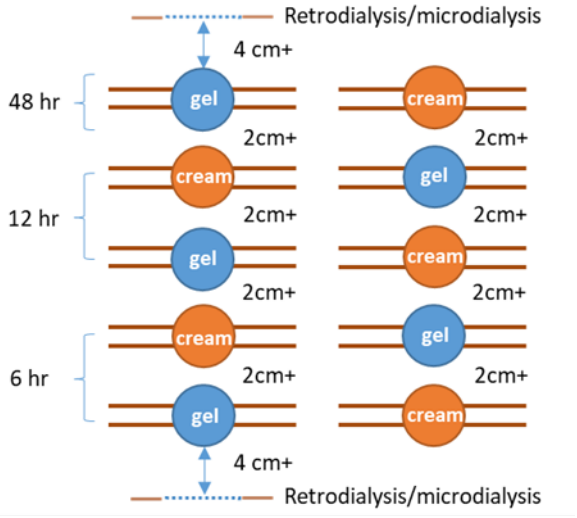


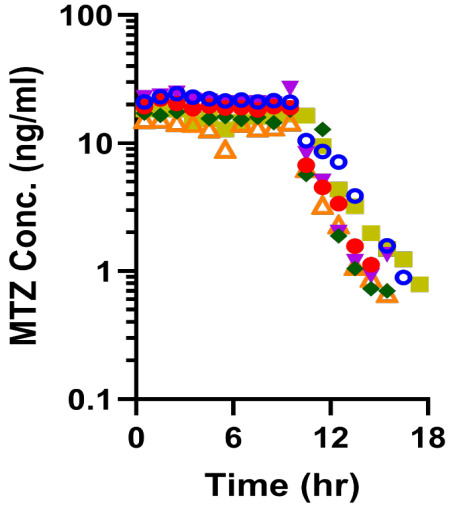




Microdialysis (gain) to sample drug



# Estimation of MTZ dUIR in Yucatan mini-pig




3 x 

- UIR for mono-exponential elimination:

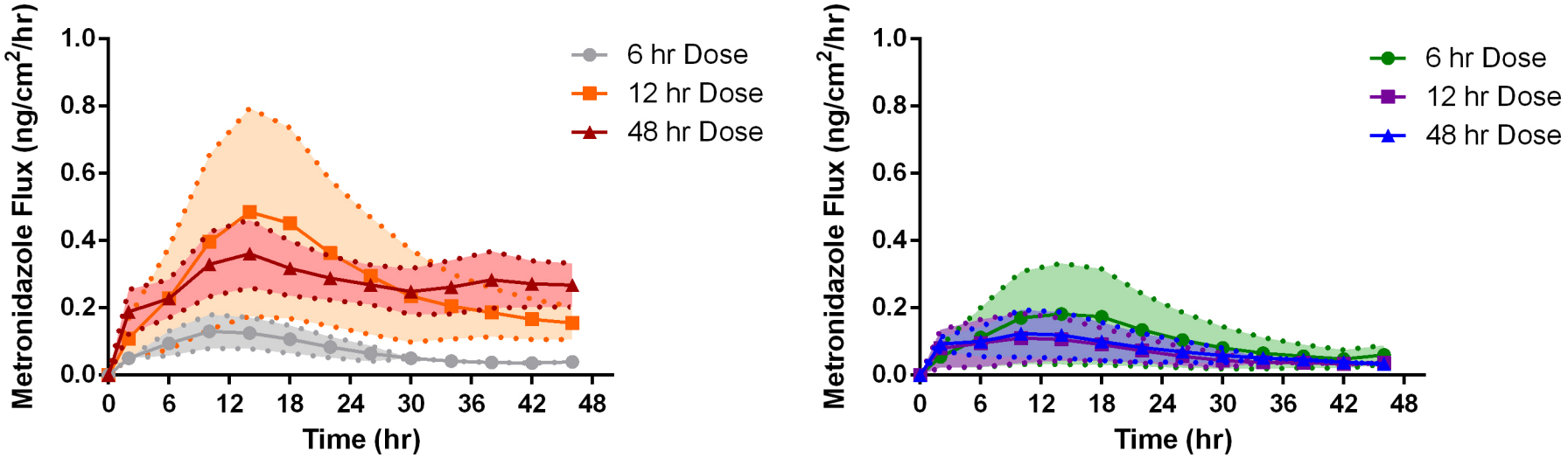
$$UIR = \frac{1}{V_d} \times e^{-k_e t}$$

- Averaged dUIR for all probes and subjects:

$$\mathrm{d}UIR = 10.1 \times e^{-0.45t}$$

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

# Deconvolution[1] of Dermis Concentrations: **In-vivo Flux**




**CREAM:** The log transform of maximum flux [Ln($J_{max}$)] for the 6-hr dose was significantly different from the 12-hr dose (p=0.019) and 48-hr dose (p=0.041). The Ln(AUC) for the 6-hr dose was also significantly different from the 12-hr dose (p=0.018) and 48-hr dose (p=0.013).

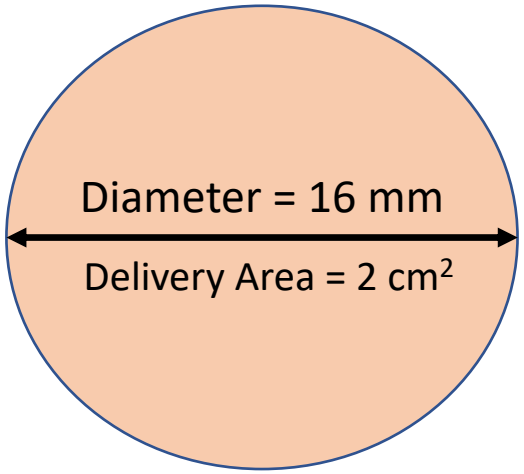
**GEL:** There was no significant difference amongst the different formulation wipe off schemes for Ln($J_{max}$) (p>0.739) and Ln(AUC) (p>0.833)

**CREAM/GEL:** Comparison between the cream and the gel at the different dose schemes indicated that both Ln($J_{max}$) and Ln(AUC) for the 48-hr dose were significantly different, *p*=0.010 and *p*=0.005, respectively; also at the 12-hr dose scheme the Ln($J_{max}$) and Ln(AUC) were significantly different between the formulations, p=0.02 and p=0.02, respectively; whereas at the 6-hr dose scheme there was no difference between the two formulations.

[1] Numerical Deconvolution performed with Phoenix®, Certara, Princeton, NJ

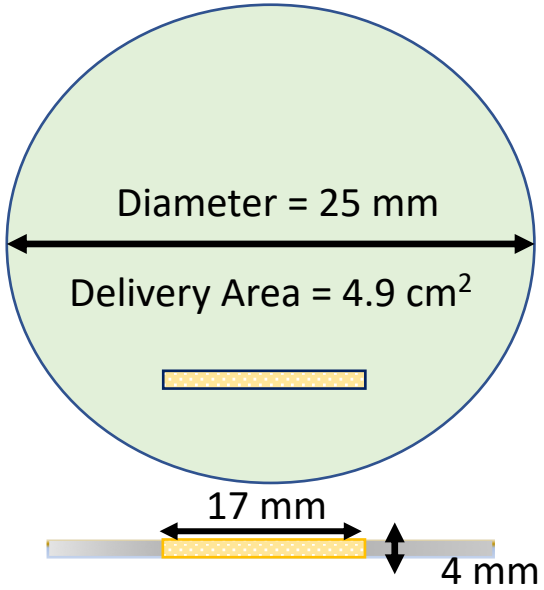
# How can we relate IVPT and dMD?

Dose applied: 10 mg/cm$^2$




Area in contact with formulation = 2 cm$^2$

Dose applied: 10 mg/cm$^2$




Area on top of sampling dMD membrane = 0.0068 cm$^2$

# Levy Plot: **Non-linear Time scaling**

Is time scaling required?

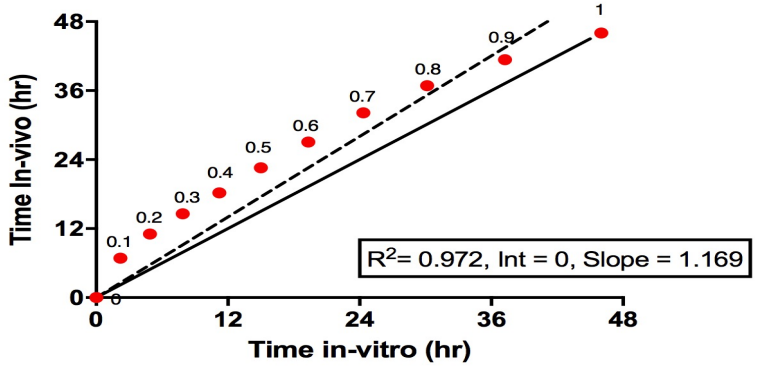
YES

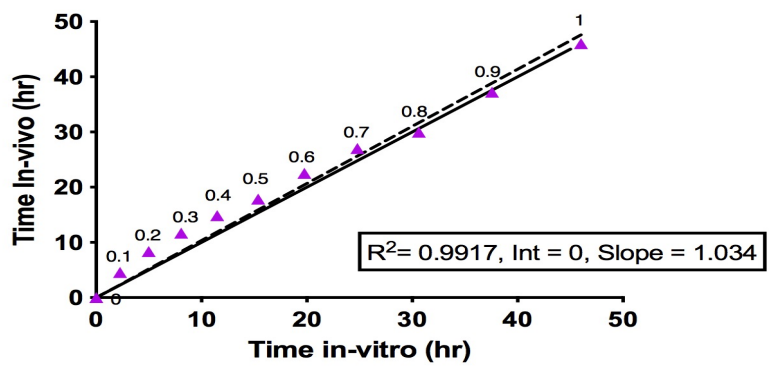
Inverse Release Function

$$TS = \left( -Ln\left( \frac{-absorb}{Finf} + 1 \right)^{\frac{1}{b}} \right) \times MDT$$

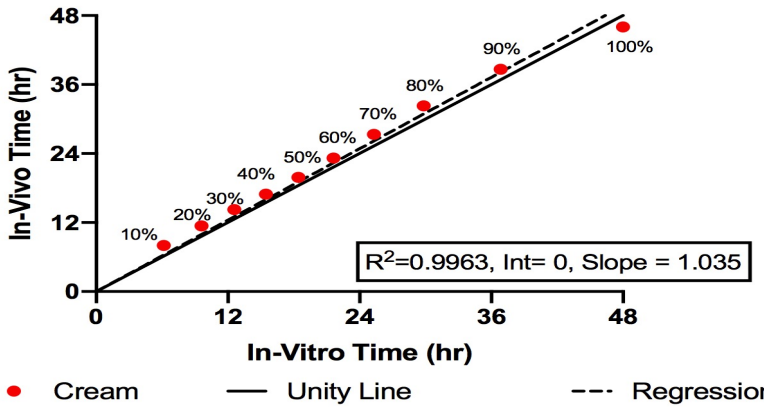
Cardot et al. AAPS J. (2018)

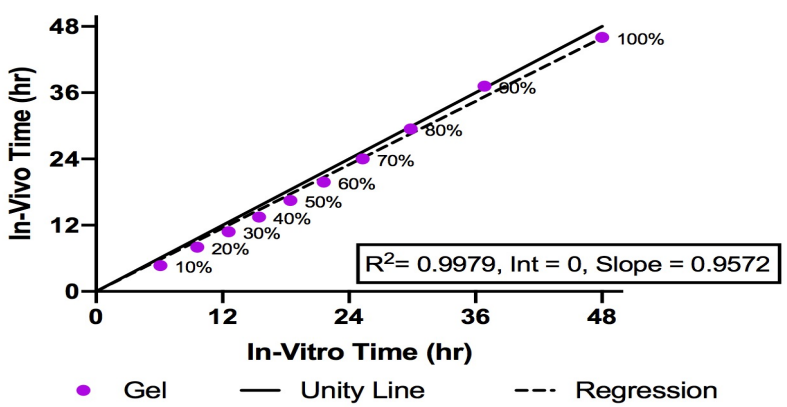
**Before** TIme-Scaling



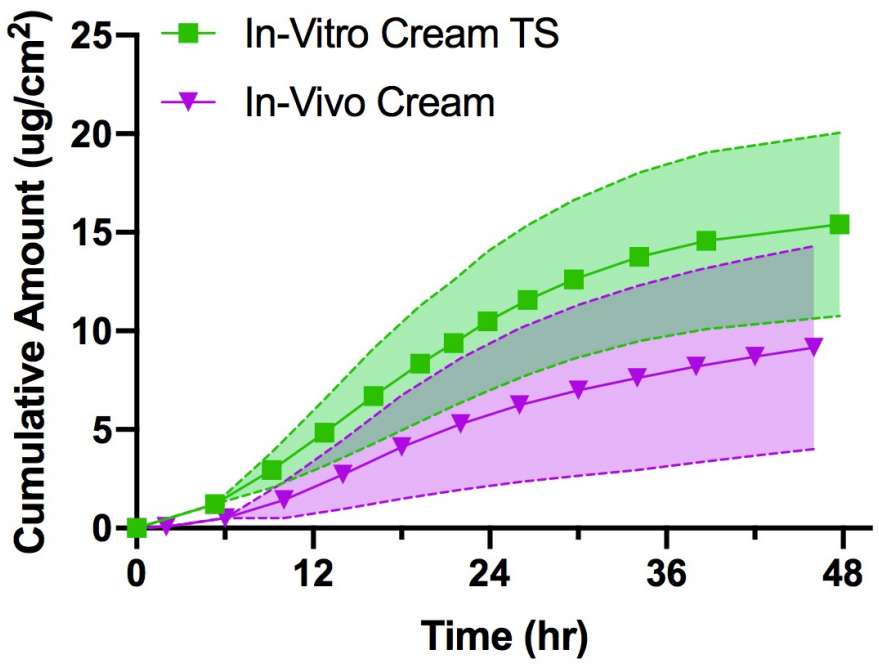



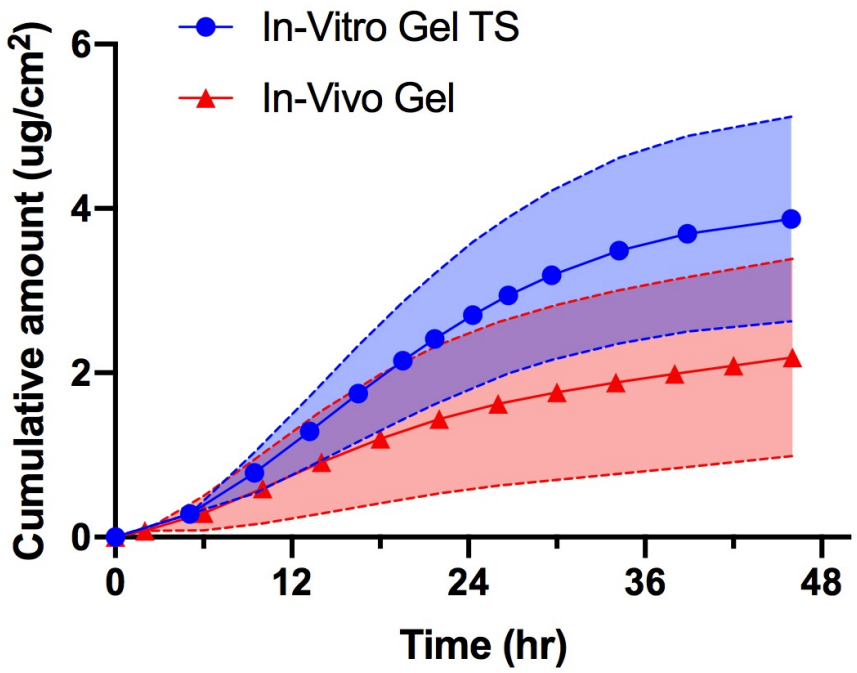

**After** TIme-Scaling



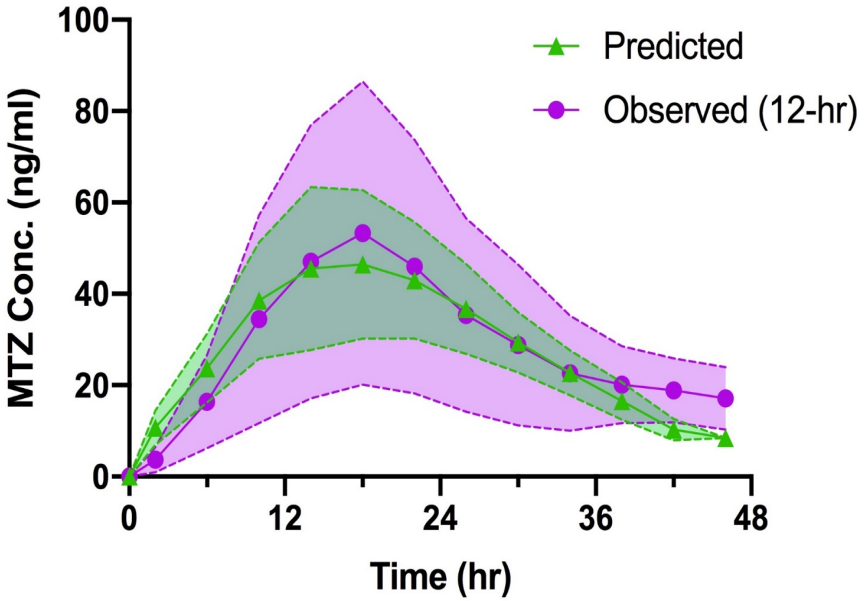
After non-linear time scaling data with Inverse Release Function and correcting the in-vivo dMD data by the area of **0.0068cm²**, we arrive here:

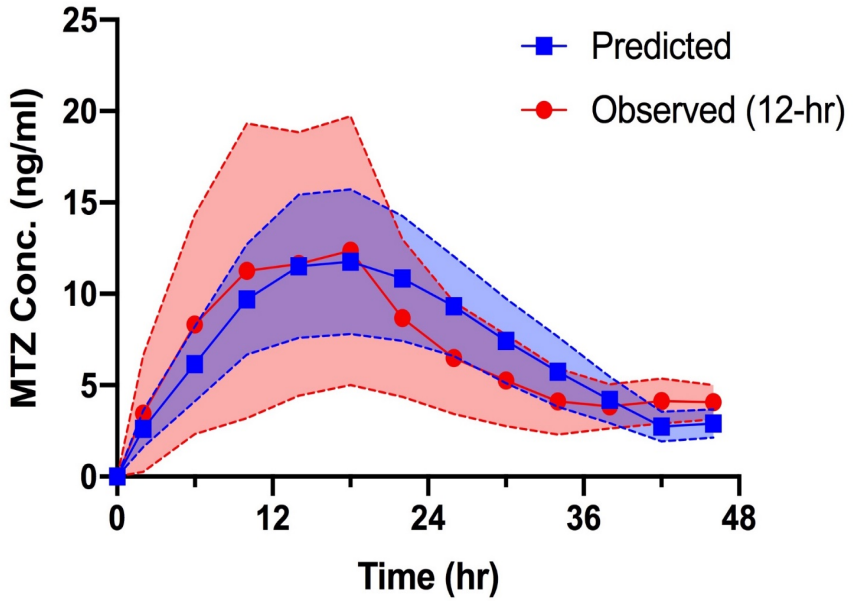



An 'absorption scaling factor' is required to relate IVPT and dMD

# Convolution of Time Scaled and Absorption Scaled IVPT data:




**Absolute Prediction Errors:**

$AUC_{all}$ – 3.4% ✓

$AUC_{0\text{-}36}$ – 5.1% ✓

$C_{max}$ – 15.1% ✓

# Conclusions

- The deconvolution of the PK profiles utilizing the dermal disposition of MTZ allowed for the characterization of the absorption process in vivo: **in-vivo flux** and **cumulative amount input**.
- Accounting for the sampling area allows for the comparison of drug permeation between IVPT data and dMD data
- Comparison of the in-vitro and in-vivo cumulative amount plots clearly shows a consistent higher MTZ permeation from the cream compared to the gel and the **non-linear time-scale** helped to account for the differences between the in-vitro and in- vivo cumulative amounts.
- The comparison of the observed and predicted in vivo concentration profiles after convolution with the dUIR demonstrates that a **reasonable IVIVR has been established**.
- These results offer a **promising starting point** for further exploration of the microdialysis/retrodialysis approach to study the disposition of drug molecules in the dermis, which can be useful for the development of a quantitative IVIVR for topical dermatological products. Additional research studies are warranted to **further evaluate** the utility of this **approach**, its **assumptions**, and **outcomes**.

# Acknowledgments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# Questions

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- **Dr. Grazia Stagni Lab Posters:**
  - **Sharareh Senemar** – M1430-09-57 - Evaluating the Bioequivalence of Topical Dermatological Drug Products containing Metronidazole using Dermal Microdialysis: Preliminary Studies in Rabbits.
  - **Benjamin A. Kuzma** – T1130-09-59 - Estimation of in-vivo percutaneous permeation (flux) and cumulative amount input of metronidazole formulations in mini-pigs' dermis

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