Skin Integrity testing

There are two methodologies that are currently employed to asses skin integrity for IVPT studies. However, there is not standardized criteria that are available to assess viable skin membranes for use in IVPT

1. The transepidermal electrical resistance (ER)
   - The measured resistance is dependent on the device, ie., applied frequency, resulting current, ionic strength of the solution as well as the surface area of the skin sample. Actual readings, measured in kΩ, is difficult to correlate with the data that has been reported in various existing literature.
   - It was determined that the skin sections that showed resistance values less than 3 times of baseline (without skin membrane, solution reading) had compromised barrier and rejected for the study. Alternatively, those skin section with resistance readings higher than 20 times of the baseline resistance, were with keratinized epithelium and also rejected from the study
2. The transepidermal water loss (TEWL)
   - Furthermore as the supporting data we measured the transepidermal water loss (TEWL) with a VapoMeter (Delfin Technologies Ltd., Finland), the standard limited value as suggested in various literatures <15 g $m^{-2}h^{-1}$ was used.

However the criteria that has been used for skin selection for the IVPT studies in many cases exhibited with quite different flux profiles within the same and different donors

More research is need to standardized skin integrity testing procedures in qualification of the viable skin membranes used IVPT studies.

The complete vs partial receptor volume removal/replacement at each time points

Advantages of complete volume removal/replacement

- Simplify flux calculation
- Close to In Vivo situation
- Help solubilize a hydrophobic analyte and maintain sink
- Avoiding the occurrence of negative flux values as sometimes occurs with slow/low penetrating compounds when aliquot sampling is used

Adventives of partial volume removal/replacement

- Easy to handle sample collections during manual operation
- Giving opportunity to use automated diffusion cells systems
- Sink condition is maintain
- Cumulative amounts are detectable in low level drug presented at early time points samples

More research is required to compare skin absorption profiles obtained with complete and partial volume replacement in IVPT studies

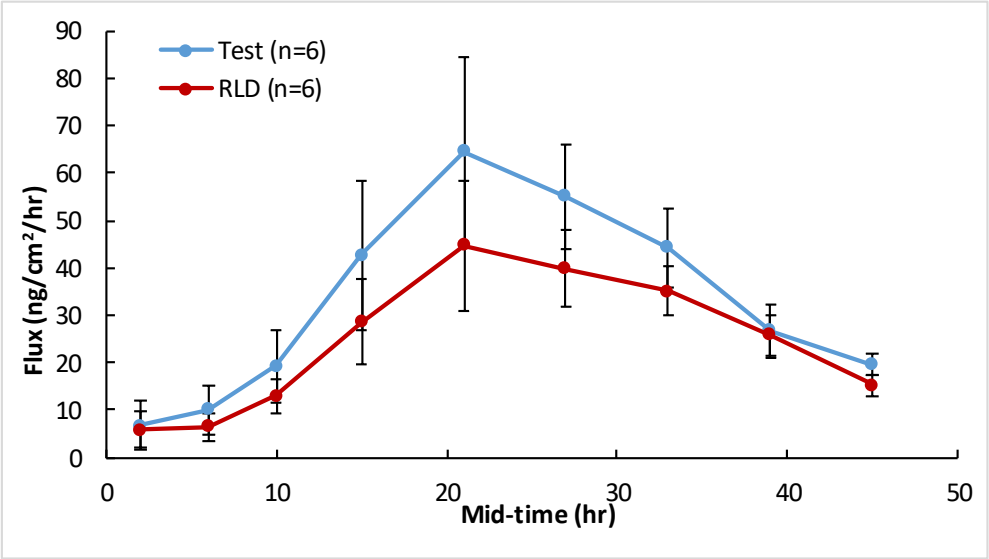

Fig. 1 Mean Flux (µg/cm²/hr) Results: Partial volume (0.5 mL) volume withdraw/ replacement at each time points. Across Donor Summary Percutaneous Absorption of low permeable anayte through exvivo Human Torso Skin over 48 hours from a Single Application.(Mean ±SD, n=6 Donors)

Unconventional Flux Profiles

For some of topical formulations we observed unconventional flux profiles when no maximum peak, Jmax was identify across multiple subsequent time points even 72hrs or 98hrs IVPT duration.

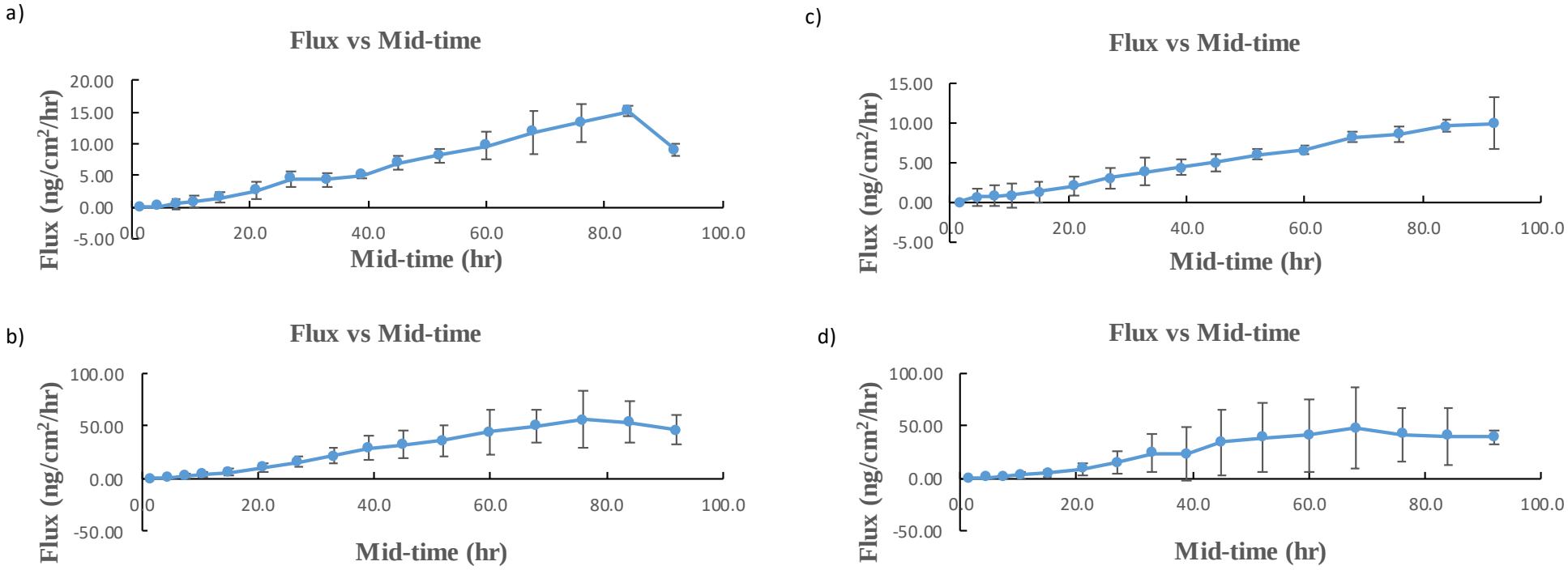

Fig1 The Percutaneous Absorption of low permeable analyte through ex vivo Human Torso Skin over 96 hours from a single application on individual donors. Mean on of n=3 skin pieces for each donor is presented. a) donor 1, with 5 mg/cm^2; b) donor 1, with 15 mg/cm^2; c) donor 2, with 5 mg/cm^2; d) donor 2, with 15 mg/cm^2;

There is a need to determine:

- How such profiles can be used in pharmacokinetic endpoints calculation
- If the dose duration method is applicable for such cases