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Open flow microperfusion for bioequivalence testing of topical drug in the dermis

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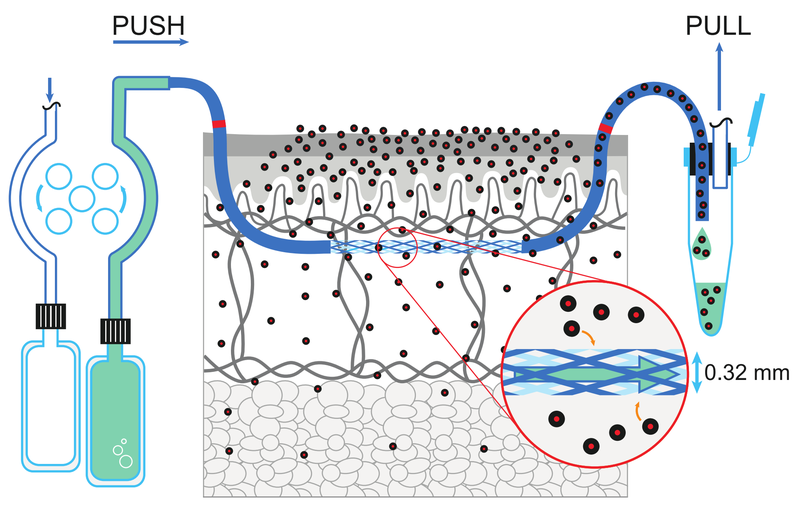
Background

Bioequivalence testing in the skin is a major challenge due to time-consuming clinical endpoint studies. Minimally invasive dermal open flow microperfusion (dOFM) can be used to continuously collect diluted interstitial fluid direct in the dermis to sample lipophilic and high-molecular weight substances such as large antibodies.



Schematic drawing of the OFM sampling system: *The dOFM probe is inserted into the dermal layer of the skin, connected to the OFM pump and the sampling vial. Acyclovir is applied to the surface of the skin and the active agent penetrates into the skin. The dOFM probe is continuously perfused with perfusate. Through the large openings of the probe, there is direct exchange between perfusate and dermal interstitial fluid.*

The aim of this proof-of-concept study was to test the feasibility of dOFM for bio-equivalence assessment in the skin.

Methods and Material

Topical acyclovir test products

- Zovirax ointment 5% (Valeant, Canada)
- Zovirax cream 5% (GlaxoSmithKline, Austria)
- Aciclobene cream 5% (Ratiopharm, Austria)
- Aciclostad cream 5% (STADA, Austria)

OFM –System

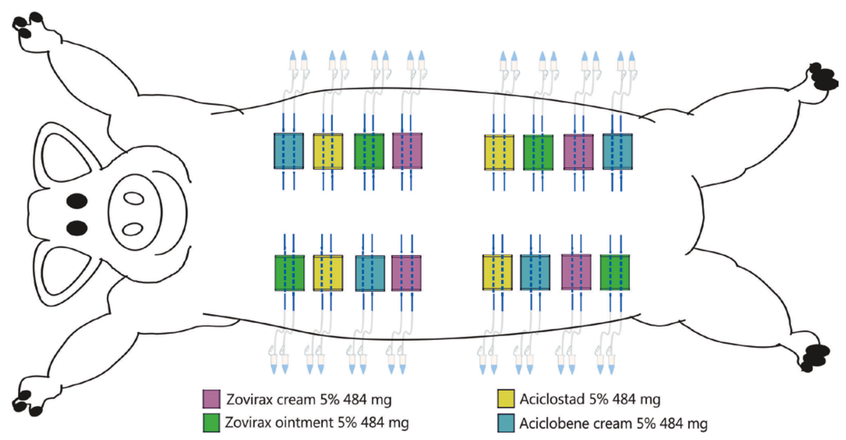
- 32 dOFM probes (perfusate: Elomel+ 1% HSA)
- 12 portable OFM pumps (flow rate: 1 µL/min)

Study protocol

- Danish Landrace pig (n=1)
- Infinite dosing: 5 mg/cm²
- 16 test sites tape stripped (2 dOFM probes per site)
- Sampling period: 12 hours (hourly sampling)
- TEWL measurement (skin integrity)
- Ultrasound measurement (probe depth)

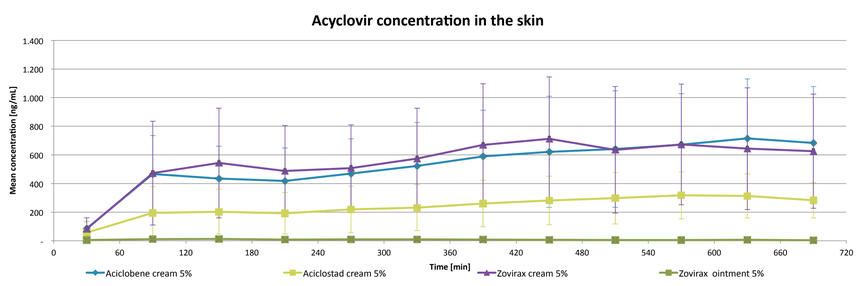
Analysis of Samples

- UHPLC-MS (LLOQ: 0.1 ng/mL)



Experiment set-up: *Four different acyclovir test products were applied on one pig with 16 test sites, two dOFM probes at each test site. dOFM sampling was performed for 12 hours with hourly sampling intervals. Skin was tape stripped 11 times and skin integrity was measured with TEWL. At the end of the experiment probe depth was measured by using ultrasound.*

Results



Results: *The concentration-time profile for acyclovir for each test product is plotted over a period of 12 hours.*

Zovirax cream 5% and Aciclobene cream 5% have very similar concentration-time profiles. Aciclostad cream 5% and Zovirax ointment 5% profiles indicate a lower penetration rate compared to the other two products. Especially the concentration-time profile for Zovirax ointment 5% is very low, barely above the LLOQ.

Conclusion

In this first preclinical trial we were able to show that dOFM is a promising method for bioequivalence testing in the skin. To investigate the PK profile of acyclovir in the dermis of humans a clinical trial will be conducted for bioequivalence and non-bioequivalence testing. This trial will evaluate PK parameters such as AUC and Cmax according to the FDA guidance for Industry: “Statistical approaches to establishing bioequivalence.”