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Dermal open flow microperfusion: Sampling of interstitial fluid directly from the dermis for pharmacokinetic and pharmacodynamic evaluations

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Introduction

Dermal open flow microperfusion (dOFM) is a minimally invasive sampling method that enables sampling of interstitial fluid (ISF) directly from the dermis and thus allows evaluation of dermal pharmacokinetic (PK) and pharmacodynamic (PD) parameters of topically or systemically applied drug products.
The exchange are of the dOFM probe is designed as an open mesh and allows sampling of high molecular weight substances and even whole cells from the dermal ISF (Figure 1). dOFM and its CE-certified devices are highly valuable tools in preclinical and clinical pharmaceutical research studies and in clinical trials.

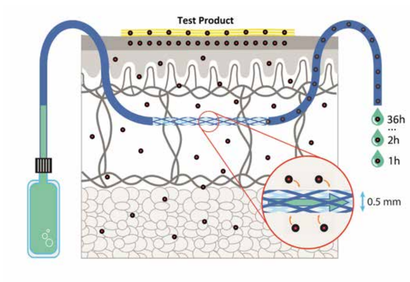

Figure 1: Schematic representation of dOFM sampling. dOFM probe is nserted into the dermis and is perfused at very low flow rates (1-10 µL/min) to gain diluted but otherwise unchanged ISF for subsequent analysis.

Successful Studies

In the, past dOFM has been applied in a large number of clinical trials (Figure 2) and preclinical studies as well in ex-vivo studies using excised human skin samples:

- Clinical trials
  - Determination of the cutaneous bioavailability of subcutaneously injected antibody (secukinumab) in healthy and psoriasis subjects (Dragatin et al. 2016).
  - Pharmacokinetic and pharmacodynamic (PD) evaluations of a topically applied anti-psoriatic drug (BCT194, Novartis Pharma AG; Switzerland) in 12 psoriasis patients (Bodenlenz et al. 2012a).
  - PK and PD evaluations after treatment with clobetasol-17-propionate (Dermovate cream, GSK, Austria) in non-lesional and lesional skin of psoriasis patients and healthy subjects (Bodenlenz 2016a).
  - Bioequivalence study of topically applied acyclovir by comparing the bioavailability of different cream products based on the measured cutaneous PK parameter (AUC, CMAX) (Bodenlenz 2016b).
- Preclinical studies in pig models and rat models
  - PK and PD studies in pig skin after topical application of dermatological products (unpublished data)
  - Investigation of the immune cell response of an induced psoriasis-like skin inflammation in Sprague-Dawley rats by analyzing the ISF samples by flow cytometry (FACS) (Birngruber et al. 2017).
- Studies in excised human skin
  - PK study of topically applied fentanyl solutions (Holmgaard et al. 2012).
  - PK study of topically applied clobetasol-17-propionate (Schwingenschuh et al. 2017).
  - Bioequivalence study of topically applied acyclovir creams (Tiffner et al. 2018).
  - PD studies in burned skin (cytokines, immune cells) (unpublished data).

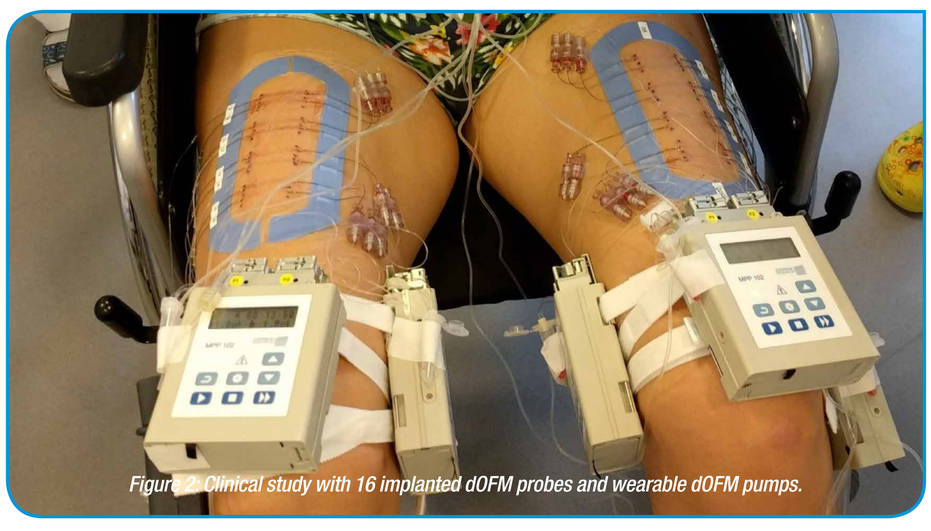

Figure 2: Clinical study with 16 implanted dOFM probes and wearable dOFM pumps.

Study Results

- dOFM was reliable used to assess the absolute concentration of the subcutaneous administered therapeutic antibody secukinumab (Dragatin et al. 2016). Dermal secukinumab concentrations were measured 8 and 15 days after administration in healthy and psoriasis subjects (Figure 3).
- dOFM had the ability to verify the PD response after repeated treatment of topically applied clobetasol-17-propionate (Bodenlenz et al. 2012b). The treatment with clobetasol-17-propionate significantly decreases IL 6, IL8 and IP 10 levels on all treated areas (Figure 4).
- These and other studies highlight the applicability of dOFM to reliably assess PK and PD response after administration of different drug products. Furthermore, it was proven that dOFM is a sensitive and reproducible method to evaluate bioequivalence of acy-clovir creams.

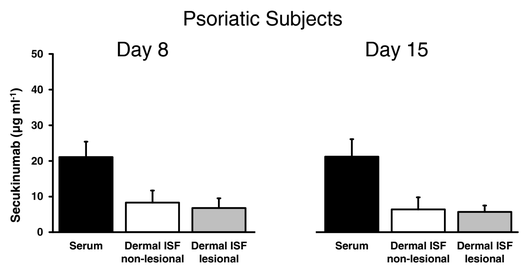

Figure 3: Secukinumab concentration (mean ± SD) in serum and in ISF of lesional and non-lesional skin of eight psoriasis patients 8 and 15 days after subcutaneous administration (Dragatin et al. 2016).

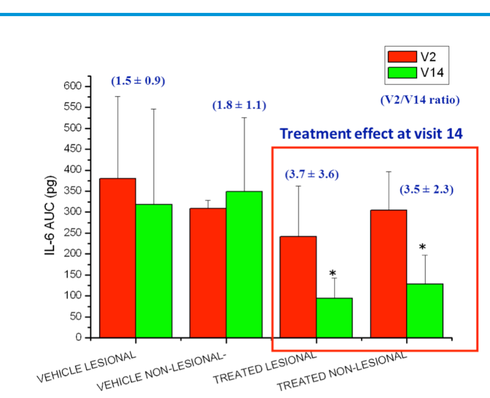

Figure 4: IL 6 response (AUC; mean+SD) on day 1 and 14 of repeated treatment with CP-17 or vehicle in lesional and non-sesional skin (Bodenlenz et al. 2012b).

Conclusion

dOFM can reliably sample a wide range of substances from small, lipophilic topical drugs to large antibodies and whole cells enabling the local evaluation of dermal PK and PD. As dOFM is well applicable in clinical trials, ex-vivo studies (excised human skin and pig skin) and preclinical animal models (rat, pig), dOFM is a valuable tool in phar-maceutical basic research studies as well as in drug approval and bioequivalence studies.

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