Medical Device qualification: Mode of action evaluation on reconstructed human tissues

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Conclusions

In vitro **experimental protocols based on 3D reconstructed human tissues can provide:**

- **An ethical, reproducible and standardized approach to demonstrate the principal mode of action of medical devices.**
- **The possibility to apply realistic doses and exposure conditions according to the intended use of the medical device.**
- **Quantitative evidences to substantiate the physico-mechanical mechanism of action.**

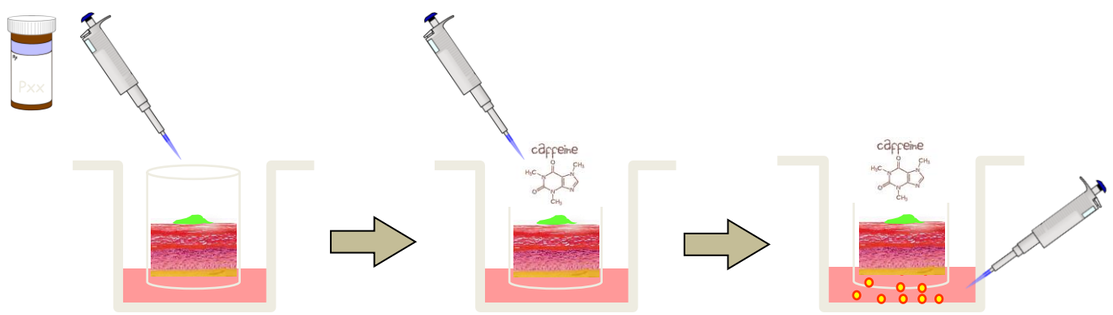
Introduction

Products used to treat or prevent a disease are classified as Medicinal Products or Medical Devices (MDs). The main difference is related to the mode of action where MDs achieve their principal intended action by a mechanical, chemical or physical means and not by pharmacological, immunological or metabolic action[a]. According to Regulation (EU) 2017/745 (MDR) manufacturers are requested to report in the technical file the rationale for the qualification of their products as devices and justify with state-of-the-art scientific data the principal mode of action of such devices. In particular, for devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body the demonstration of the principal mode of action can be crucial.

This case study is presented to provide quantitative scientific evidence for the principal mode of action, namely film forming properties, of substance-based MDs using 3D human reconstructed human epidermis (RhE) tissue.

Methods

The protocol is based on a Multiple Endpoint Analysis (MEA) approach that involves the caffeine permeability assay (**Figure 1**) to assess film forming properties on EpiSkin™ model (Episkin SA) and can include the assessment of tissue barrier permeability (Lucifer Yellow assay), function (TEER measurements) and morphology (H&E staining) to further characterize the MD interaction with the RhE tissue.



Product application: 50 mg of each product were applied on the surface of RhE tissues and left for 2 h at RT

Caffein application: 0.1mL caffeine solution in ultrapure water (1% w/v) was applied on RhE for 3h at 37°C

Receptor fluid sampling: 2mL of receptor fluid was from the recevior compartment for caffeine quantification by HPLC-UV

Figure 1: Overview of the Caffeine permeability assay protocol on the RhE Episkin™. For more details see Casiraghi et al. 2017[b]

Results and Discussion

"Film forming" properties can be described as a temporary modification of permeation through the epithelium of a specific tracker (e.g. caffeine) due to the product acting as protective physical barrier ("film"). The results for the caffeine permeability assay on Episkin™ model for five substance-based MDs (creams) are reported in **Figure 2**. A statistically significant difference was observed between the products, with P1 and P5 more performant than the others. The film forming properties can be complemented by tissue histology to better characterize the MD action on the epidermal barrier. In **Figure 3** an example of H&E staining is reported.

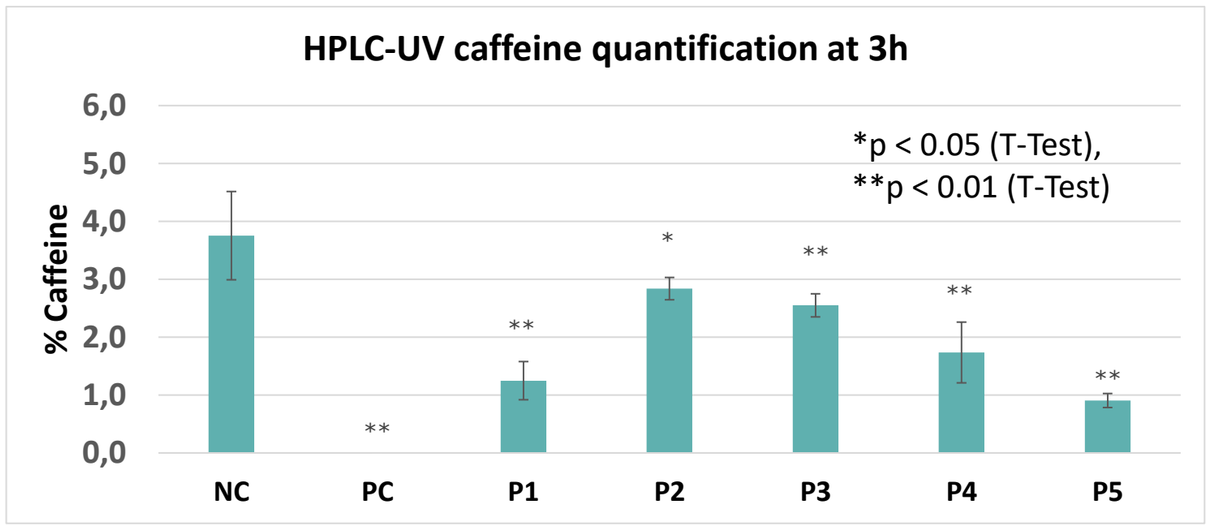


Figure 2: Percentage of caffeine permeated through Episkin™ after 3h from caffeine application. Caffeine quantification was done with HPLC-UV. NC= untreated tissue, PC= white vaselin

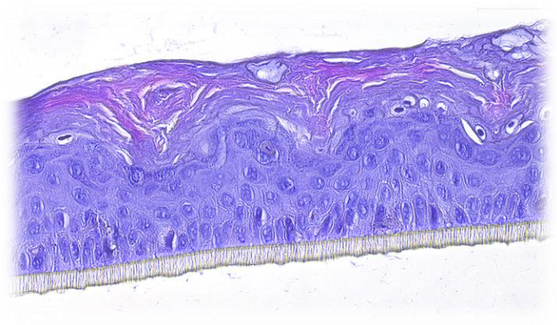


Figure 3: H&E staining of RhE. Microscope: LEICA DMi8 THUNDER imager 3D composed by camera DFC450 C.

In summary

- The demonstration of the principal mode of action of MDs can be obtained *in vitro* using 3D reconstructed human tissues in a reproducible, standardized and ethical approach[b].
- Realistic doses and exposure conditions are defined case-by-case according to the intended use of the MD on skin or other tissues covering all body barriers (e.g. oral, gingival, intestinal, vaginal, oesophageal, corneal, bladder epithelia)[c-d].
- The adopted MEA approach provides robust, relevant and quantitative evidences to to substantiate the physico-mechanical mechanism of action.

References

a) MDCG 2022 – 5 Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices, April 2022
b) Casiraghi et al. Regulatory Toxicology and Farmacology 90 (2017) 42-50
c) Pellegatta et al. Medical Devices: Evidence and Research 2020:13 57–66
d) Ceriotti et al. Medical Devices: Evidence and Research 2022:15 143–152

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