Prolonged transdermal peptide delivery utilizing physically induced microchannels

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INTRODUCTION

Classical transdermal therapeutic systems (TTS) are dosage forms used to passively transport an active pharmaceutical ingredient (API) across the skin via different routes (see fig. 1). This is done by applying an API containing patch to the skin. However, there is a crucial limit to this TTS technology. APIs with a molecular weight exceeding ca. 500 g/mol cannot pass through the skin barrier. Yet, such delivery can be enabled by reducing the barrier function of the epidermis. This can be achieved by minimally invasive and pain free microporation [1, 2, 3, 4]. The skin is treated with an ablative laser or microneedles to temporarily create microchannels. The combination of this approach with classical TTS patch technology was investigated with regard to its possibilities to enable delivery of macromolecules e.g. peptides or vaccines. This approach is considered a way to overcome the biological barrier that so far has been a natural limitation to TTS technology.

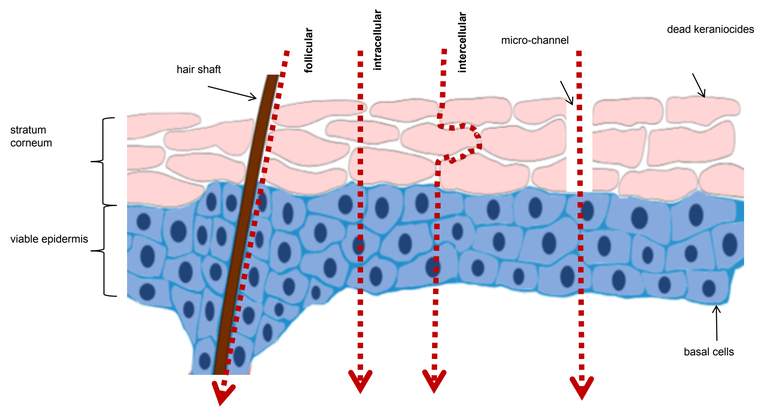

Fig. 1: Diagrammic illustration of the diffusion through the human skin. Shows the different routes throgh the skin barrier

MATERIALS AND METHODS

Different hydrophilic polymer films containing 5% of desmopressin-acetate were cast utilizing the classical solvent casting process on an occlusive backing with a thickness of 500 µm using a Film Applicator (Hemer, Germany).

Ex-vivo and *in-vivo* human skin was treated with a P.L.E.A.S.E.® (Precise Lasers Epidermal System) Laser (Pantec Biosolutions) (Fig. 2 & Fig 6) resulting in ca. 100 microchannels per 0.82 cm². The penetration depth of the laser was set to 59 µm.

For imaging *ex-vivo* skin after perforation SKYSCAN micro-computed tomography was used.

In-vivo transepidermal water loss (TEWL) was measured using a Tewameter® TM 300 w (Courage + Khazaka electronic GmbH).

Ex-vivo Franz-cell skin permeation was performed under sink conditions to examine whether the API passes through the perforated skin. The Kerski permeation cell (ProSense B.V.) (Fig. 3) was used [4, 5].

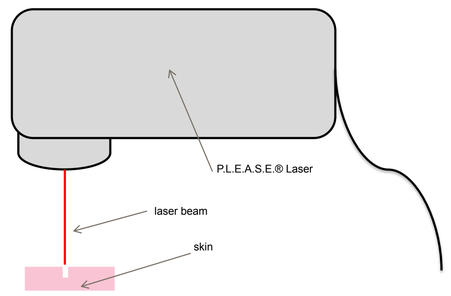

Fig. 2: Sketch of the used P.L.E.A.S.E.® Laser

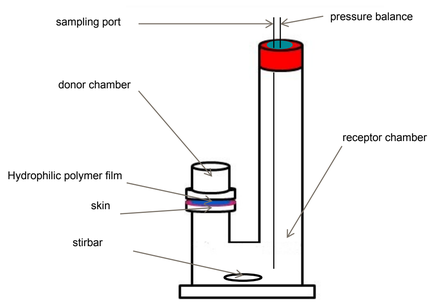

Fig. 3: Sketch of the used Kerski permeation cell

RESULTS AND DISCUSSION

The microchannels created with the laser were not only evenly distributed but also extremely homogenous and reproducible. The standard deviation of the TEWL measurements confirm that the laser treatment is very uniform. First in-vivo TEWL measurements show a fast skin regeneration even under occlusive conditions (fig. 4). Different desmopressin-acetate films were placed on untreated and microporated ex-vivo human skin and the flux of the API across skin was investigated over a time period of 48 hours (fig. 5). In line with expectations, no permeation of the ca. 1000 g/mol peptide was found through intact skin. Over the investigated time period of 24 hours up to 110 µg/cm2 of desmopressin permeated through the microporated skin (which is more than 25 times of the recommended daily dose).

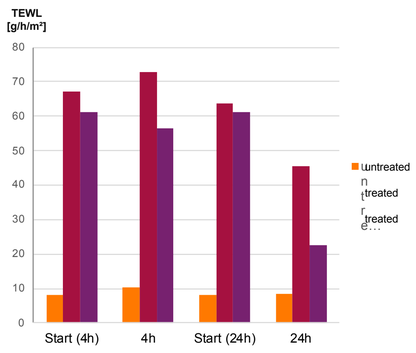

Fig. 4: TEWL in g/h/m² *in-vivo* skin, after treated with a P.L.E.A.S.E.® Laser 100 microchannels per 0.82 cm², penetration depth 59 µm.
In-vivo measurements show a regeneration under occlusion.

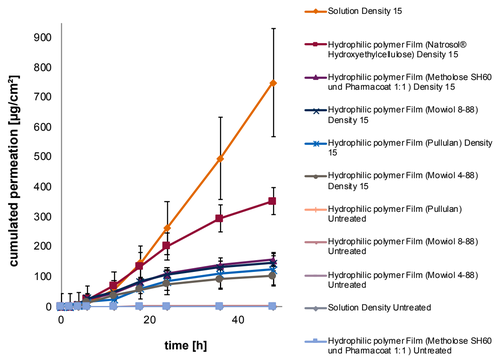

Fig. 5: *Ex-vivo* skin permeation kinetics. Error bats indicate SD (n=4)
Different PVA-patches containing 5% (w/w) of this peptide were placed on untreated and microporated *ex-vivo* human skin and the flux of the API across skin was investigated over a time period of 48 hours.

CONCLUSION AND OUTLOOK

In-vivo TEWL measurements showed that skin regenerates even after occlusion following laser treatment. A modified formulation might slow the healing process. The experiments demonstrated a significant permeation of macromolecules across microporated skin. The results confirmed that is it possible to deliver peptides (and other large molecules) from classical patches via the transdermal route utilizing a pain-free and minimally invasive microporation technology. Due to the more hydrophilic nature of the induced microchannels [2] (and the API), the use of hydrophilic polymer Films as patch matrix is recommended. In contrast to drug coated microneedles causing a short "burst-like" drug release only, this technology allows for a controlled sustained release of peptide drugs for several days [3].

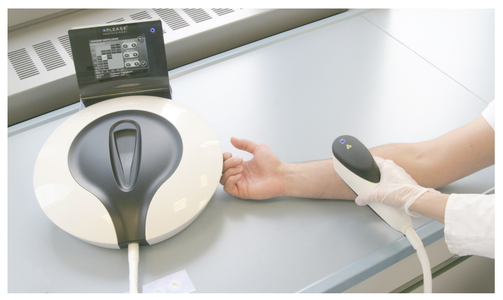

Fig. 6: Picture of the Laser during treatment

Fig. 7: Picture of a TTS Prototype

ACKNOWLEDGEMENTS

We thank Tobias Bächle (Pantec Biosolutions AG), Christiane Uhl (Courage+Khazaka electronic GmbH), Sebastian Schmidt-Lehr (tesa SE, Micro-CT), Gabriele Stodt (tesa Labtec GmbH) and Eva Kerski (University of Wuppertal).

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