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microneedle patches

FEASIBILITY EXPERIMENTS FOR THE DEVELOPMENT OF PEPTIDE TRANSDERMAL SYSTEMS IN COMBINATION WITH MICRONEEDLES

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Introduction:

Transdermal therapeutic systems (TTS) are dosage forms developed to transport an active pharmaceutical ingredient (API) embedded in a patch through the skin across different routes (see fig. 1). However, there is a crucial limit to this type of passive diffusion. APIs with a molecular weight greater than 500 Da cannot pass the skin barrier. Several publications (e.g. Cormier et al., 2004) reported that there is a possibility to transport high molecular weight APIs through the skin. For that purpose, the skin is e.g. perforated with microneedles to form microchannels. Combining TTS with microneedles could be a promising approach to transport high molecular weight APIs across the skin (see fig. 2).

Materials and Methods:

Adhesive matrices based on either a hydrogel or silicone PSA were loaded with the model substances fluorescein isothiocyanate -dextran or desmopressin-acetate utilizing the classical solvent casting process. Several methods were used for imaging *in-vivo* and *ex-vivo* skin after perforation using high-resolution microtomography (see fig. 3). *In-vitro* skin permeation was performed using a modified permeation cell as shown in fig. 4 under sink conditions to examine whether the API passes through the perforated skin. The determination of the API was done by HPLC with UV-detection.

Results:

SKYSCAN was an excellent tool to measure (and visualize) the size and depth of the microchannels in the ex-vivo skin as outlined in fig. 5.

The microchannels were thought to represent a more hydrophilic pathway across the skin. This hypothesis could be confirmed by *ex-vivo* skin permeation experiments.

Even large hydrophilic molecules showed a high flux rate across skin when embedded in a corresponding hydrophilic patch as show in fig. 6.

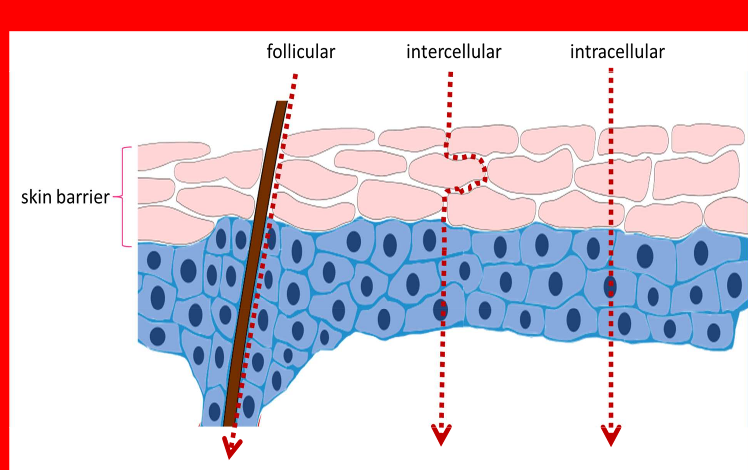

Fig. 1 Diffusion pathways across skin

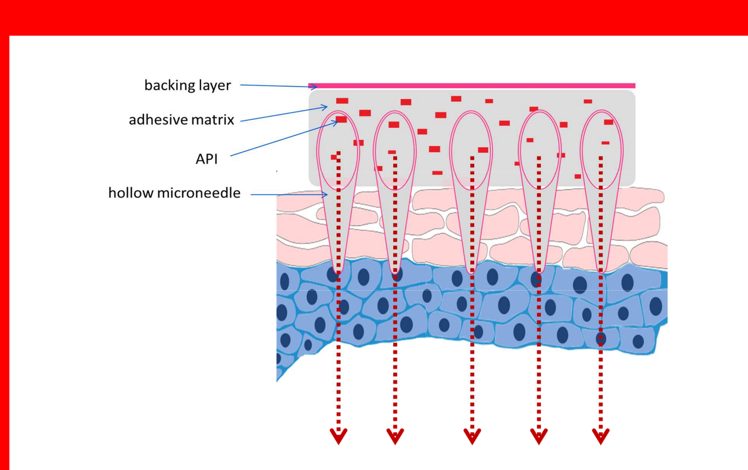

Fig. 2 Conceptual drawing of a microneedle based drug delivery system applied to the skin

Fig. 3 *Ex-vivo* human skin in the SKYSCAN 1272 high-resolution micro-CT

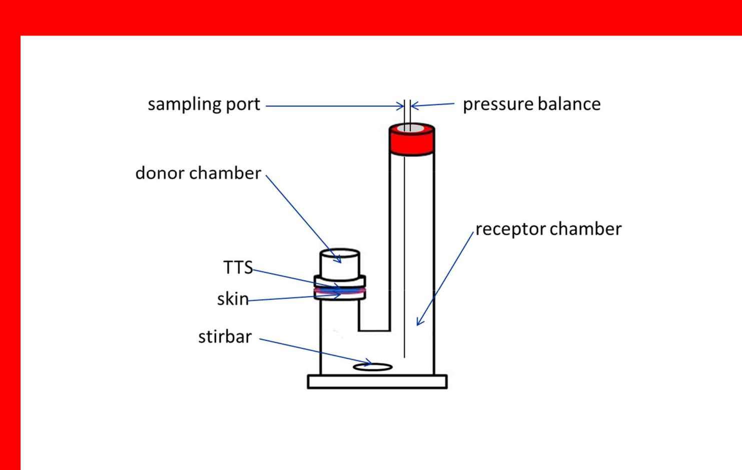

Fig. 4 Sketch of an alternative diffusion cell model (cf. Kerski et al., 2015)

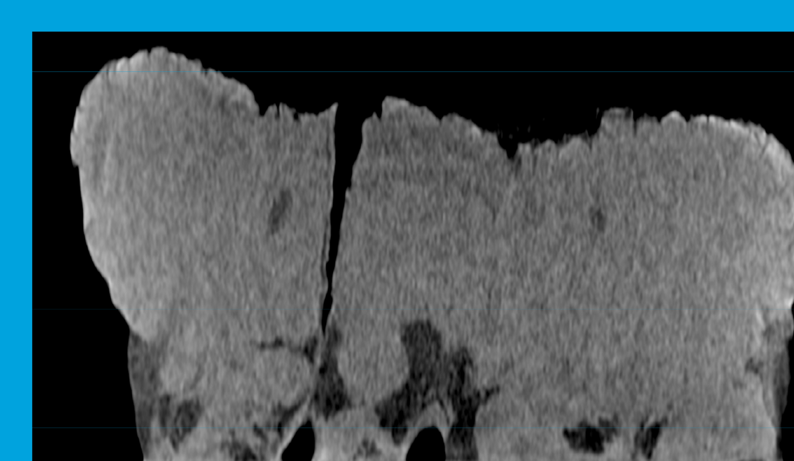

Fig. 5 *Ex-vivo* human skin after perforation with microneedles

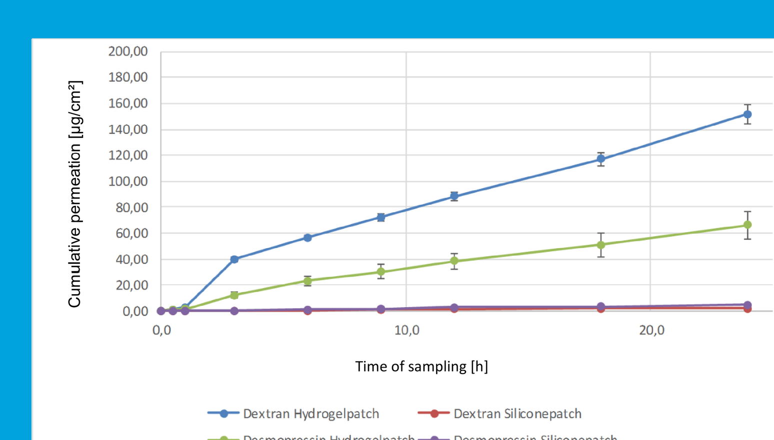

Fig. 6 Permeation of hydrophilic APIs across microporated skin from hydrogels and classical PSAs. Error bars indicate SD (n = 6)

Conclusions:

In line with expectations the results confirmed the more hydrophilic character of microchannels generated by microneedles. It was possible to deliver not only high amounts of a large model compound across the skin, but also therapeutically relevant amounts of a therapeutic peptide. A combination of a specific hydrogel patch with microneedles (fig. 3) seems to be an interesting new delivery system for peptides.

References:

M. Cormier, et al., “Transdermal delivery of desmopressin using a coated microneedle array patch system,” *Journal of controlled release*, **97**(3), 503-511 (2004).

Kerski, S., Rathsack W., & Stodt G. (2015). Germany Patent No. 20 2015 004 165.5. DPA.