Skin permeability modeling – in vitro, ex vivo and in vivo studies

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Background. The skin penetration of molecules with different physicochemical characteristics is an important focus of pharmaceutical research. Transdermal drug delivery is a promising route of drug administration and the studies on this field make possible to find the optimal drug formulations, to reduce the dose applied and to prevent or reduce the systemic side effects of the drugs. Therefore, in our laboratory we were setting up a test system including assays with different complexity for investigation drug delivery across the dermal barrier.

Methodology. Caffeine, as a hydrophilic model drug was investigated in our preliminary experiments. It was formulated as a suspension cream (2 or 4 %). As an *in vitro* approach, Franz diffusion cell systems were mounted with filter paper (d=2.7 μm), and artificial membranes (d=0.8 and 0.45 μm, respectively). Then we applied rat and mouse skin preparation between the donor and acceptor chambers as an *ex vivo* test system. Finally, the caffeine creams were tested *in vivo* in anesthetized rats and mice and the skin penetration was monitored by transdermal microdialysis. We have used tape stripping to enhance the permeability of the epidermis.

Results. The absorption of caffeine in the *in vitro* and *ex vivo* systems was dependent on the pore size of the membrane or filter paper. The rat skin showed similar permeability to the 0.45 μm membrane. However, increasing the concentration of the cream formulation from 2 to 4 %, did not result in proportional increase in the permeation.

Conclusion. In vitro penetration order detected was: filter paper >> 0.8 μm, > 0.45 μm cellulose acetate membrane ≈ rat skin. Tape stripping increased caffeine absorption into the dermis and subcutis. The penetration of caffeine was age-dependent. The *in vivo* transdermal microdialysis showed that the sensitized mouse skin is more permeable than the rat skin. The *in vitro* and *in vivo* data showed a good correlation. We have received the criticism not to have *ex vivo* data on human skin. We have applied for a permission for using human skin samples gained from plastic surgery. But we have been waiting for the ethical permission for more than one year. We would like to overcome this difficulty by using 3D printed human skin in Franz diffusion cells instead of human skin samples. For these experiments we are looking for collaboration partners. We would be glad to validate the bioprinted tissue in our systems.