

Lecture: computer assisted procedures

## One step further towards computer assisted simulation of percutaneous absorption to avoid animal experiments – the combination of experiment and simulation effectively helps to identify new important parameters

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In the prospect of the EU-chemicals policy REACH and the 7th cosmetics amendment from March 2009 mathematical modeling to predict skin permeability of chemicals, drugs and cosmetics becomes more and more a focus. In contrast experiments with human skin are expensive and time consuming. They are also limited by a lack of sufficient skin resources. Therefore a number of equations have been established to predict skin permeability based on physicochemical molecular characteristics. Usually molecular weight and the octanol-water partition coefficient are used to estimate quantitative structure activity relationships (QSAR) assuming that skin permeability is conclusively determined by a compound's affinity to lipids and its size (Potts and Guy, 1992; Magnusson et al., 2004). Meanwhile, QSAR-software is readily available on the internet for free use.

However, these predictive models have several major drawbacks that are often not sufficiently respected. These are: (i) since additional datasets are scarce they mostly rely on the heterogeneous Flynn database comprising the skin permeability data of 97 compounds; (ii) they only apply to aqueous dispersion media; and (iii) they repeatedly failed to predict experimentally measured permeabilities (Schaefer-Korting et al., 2007).

Therefore, we are using an alternative strategy. Heisig et al. developed a diffusion model of human stratum corneum to predict non-steady state stratum corneum-depth profiles and to estimate permeability parameters like apparent permeability coefficient and lag-time (Heisig et al., 1996). This model has now been adapted to an experimental database (Naegel et al., 2008). We have developed experimental methods to provide the model with all relevant input parameters and validated the predictions with experimental data (Hansen et al. 2008). In the context of this work the corneocytes were found to influence both the skin penetration of a hydrophilic and of a lipophilic, however ionizable, test compound significantly. We could now specify the mechanisms of interactions dependent on the physicochemical characteristics of the compound. Hydrophilic water soluble compounds will be taken up into corneocytes by dissolution in water that is present due to physiological hydration or artificial occlusion. Lipophilic compounds with the potential to protein binding may adsorb to stratum corneum proteins such as intra-corneocyte keratin or proteins of the cornified envelope or inter-cellular desmosomes. These findings may have significant consequences for the risk assessment of compounds as protein adsorption may lead to depot formation within the stratum corneum and sustained release of bound substance long after removal of the topical hazard (Vieth and Sladek, 1965). Additionally, for hydrophilic compounds their skin penetration may strongly be increased by swelling of the skin. This may readily occur during occupations where the skin of especially the hands is in prolonged or repeated contact with water or under occlusive conditions.

### References

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