Session 3: Aspects of formulation

How to develop and characterise innovative formulations

Prof. Dr. Monika Schäfer-Korting
Institut für Pharmazie,
Freie Universität Berlin
Königin-Luise-Str. 2-4
D-14195 Berlin

While topical therapy of diseases reduces the risk of systemic adverse drug reactions due to the primary local action of the agent, the horny layer barrier severely inhibits the access of the agent to the site of disease as penetration of the skin is limited to a few percent only. Drug candidates for topical use have to meet the needs for skin penetration, which means rather low molecular weight and log P of about 1-3. This can mean prodrug formation and is often realised with topical glucocorticoids which are of highest importance in inflammatory skin disease. Whereas the intrinsic skin permeability can be estimated by calculation taking these parameters into account, this fails with drug formulations. Drug release and (per-) cutaneous absorption are studied in vitro using the Franz cell approach.

Comparing three glucocorticoids in clinical use and related marker agents, the relevance of the physicochemical parameters and formulation effects are outlined. Innovative nanoparticulate formulations, lipid nanoparticles and core-multi shell (CMS) nanotransporters as example are compared to conventional formulations. In general, drug release from conventional vehicles (e.g. cream, ointment) is relevant for skin penetration – yet the relation can fail with agents (e.g. prodrugs) biotransformed in the skin, if vehicle constituents induce local toxicity.

Intact nanoparticles do not surmount the horny layer barrier. With nanocarriers drug release and skin penetration are not always related. As lipid particles can directly interact with skin surface lipids particle size is of minor relevance only, if at all, for skin penetration. In fact, lipid nanoparticles can enhance skin penetration about 4fold, CMS nanotransporters even up to 13-fold.

Besides enhancing skin penetration formulations need to be well tolerated. This can be studied in vitro, too, using standardised procedures. Cytotoxicity is derived from dye reduction in normal human keratinocytes and fibroblasts and can be also studied in reconstructed human epidermis. The latter matrix is also used to investigate the irritant potential, although the current ECVAM-adopted procedure is set-up for the testing of chemicals and needs modification to detect agents of low irritancy, too. The same holds true with the HET-CAM test for eye irritation. Using these test systems, solid lipid nanoparticles and CMS nanotransporters appeared well tolerated. This is well in accordance with the GRAS (generally recommended as safe) status of the lipids used for nanoparticle production. The final prove of carrier safety, however, asks for detailed toxicological testing with CMS nanotransporters as these are chemically new entities.