Abstracts

Symposium

„Development and Regulatory Aspects of Topical Dermatics Today“

BfArM

Session 3 and 4

3: Characterization of active pharmaceutical ingredients

4: Aspects of formulation

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Session 3: Characterization of active pharmaceutical ingredients

Toxicological characterization of new active pharmaceutical ingredients for dermatics

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When designing the preclinical toxicological program for the development of dermatologically active drugs, the specific characteristics and the particular requirements of dermatologically active substances have to be taken into consideration. Usually dermatics are designed to act locally and to avoid systemic exposure. Depending to their application they are potentially exposed to environmental factors, especially to the sun, and may first and/or only be metabolized in the skin. Therefore the toxicological characterization may include the investigation of local toxic effects and systemic toxicity caused by absorption of the pharmaceutical ingredient or its metabolites into the organism. The toxicological profile gained by the multiple toxicological tests has to be combined with the therapeutic profile to get an adequate risk-benefit assessment for the application of the drug to humans.

First, introductory experiments should address the potential phototoxicity, including the photoallergenicity and photogenotoxicity of the substance as well as the systemic exposure. As systemic exposure may highly depend on the formulation, it has to be considered as an important component of the compound to be tested in the toxicological program. If it can be demonstrated that the active ingredient in the formulation used is not systemically available the toxicological program might be limited to the evaluation of the local tolerance which includes potential sensitization reactions and eye irritation but also potential genotoxic activities.

In the case that the systemic availability has to be considered, the complete safety testing program for systemically effective substances has to be applied. This includes for programs leading into phase I clinical trials single dose and repeated dose toxicity studies in two adequate species (one of them rodent, one of them non-rodent) and the safety pharmacology core battery. For later stages, studies about reproduction toxicity and carcinogenicity also have to be considered. The application routes to be tested have to be decided on a case by case basis. Depending on the pharmacological, metabolic and kinetic properties of the substance, a test program using only one dermal application route might be sufficient. In other cases, a combination of the dermal application route with the intravenous or subcutaneous application route might be appropriate or the dermal application route might be replaced by a combination of subcutaneous testing of systemic toxicity and dermal local tolerance testing. Metabolism of the active ingredient and resorption of the drug must be taken also into consideration when choosing the appropriate non-

rodent species for the preclinical testing.

Local and international authorities support all aspects of preclinical testing of dermatics by appropriate guidelines which are published on their web sites.

Session 3: Characterization of active pharmaceutical ingredients

Pharmacological Characterization of New Active Pharmaceutical Ingredients

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Development of new active dermatics today is rather challenging. The new compound will hit a market with a plethora of active compounds which have been successfully used partially over decades with quite success. This is especially the case for glucocorticosteroids which are broadly used in many patients and different indications and systemic side effects as observed earlier are rather uncommon, at least with low – medium potent compounds. Market needs has to be understood early on in project work and preclinical research has to address these needs. Preclinical research is obliged to implement an improved disease and compound understanding, develop screening and disease models that reflect these novel developments and are especially suited for chronic diseases and therapeutic settings and finally address potential side effects early on.

In dermatological research, the understanding of cytokine networks in acute vs. chronic skin diseases led to the in house development of several models of chronic T cell mediated skin diseases (e.g. Schneider C et al. J Invest Dermatol 2009; Röse L et al., submitted). The aim to further reduce attrition rates due to lack of efficiency fuelled the implementation of humanized xenotransplantation models as late-stage, confirmatory models (e.g. Igney F. et al. Trends Pharmacol Sci 2006). To further profile novel compounds against competitors, optimized models for relevant side effects are essential at latest for development candidates. These models should address the needs of the patients, e.g. for compounds interacting with the glucocorticoid receptor the typical potential systemic (e.g. growth retardation, interference with the HPA axis, hyperglycemia) and topical (e.g. skin atrophy) undesired effects.

Taken together, characterization of novel pharmaceutical ingredients starts with a continuous improvement of our understanding of diseases and pharmacological concepts, the understanding of our patients' needs and will finally translate this into projects for desired new drug discovery projects, with the need of thorough characterization of potential development candidates and their competitors in a plethora of state of the art efficacy and side effects models.

Session 4: Aspects of Formulation

Regulatory aspects of pharmaceutical quality with dermatics

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The regulatory framework for the quality assessment of marketing authorization procedures of drug products is outlined. An overview of the quality dossier is presented.

The pharmaceutical development of topical dermatological products should include characterization of the properties of the active substance with focus on those attributes which may influence performance, efficacy and safety of the drug product. Compatibility between active substance and excipients should be ensured. The choice and function of excipients should be explained. The need for antioxidants and preservatives should be justified concerning the quality and stability of the finished product as well as regarding the patient groups (e. g. paediatric use). For novel excipients, detailed information concerning manufacture, characterization of structure, physical properties, chemical properties, purity, specifications, validated analytical procedures as well as data to support the safety of the novel excipient need to be provided. Formulation development should be described. Overages need to be justified. Physicochemical and biological properties should be characterized, and parameters critical to the quality of the drug product should be identified. The development of the manufacturing process should be described. Critical manufacturing steps and process conditions should be outlined.
The suitability of the container closure system for storage of the drug product should be shown. The possibility for leachables of primary packaging components into the drug product as well as the possibility of sorption phenomena should be addressed.
The microbial requirements for topical dermatological products and demonstration of antimicrobial efficacy are discussed.
Tests of the final drug product and stability tests are outlined.

Issues of the quality documentation which can be optimised are summarized.

Session 3: Aspects of formulation

Optimal conventional galenics: microemulsion as a paradigm

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Microemulsions are complex systems of oil, water and emulsifiers (surfactant and cosurfactant). Excellent solubility potential for lipophilic and hydrophilic substances, thermodynamic stability and ease of manufacture cause the great attraction of microemulsions as dermal drug delivery system. Yet, the large amount of surfactant/cosurfactant may result/yield in skin irritation. Therefore, optimization of the composition of the microemulsion is often required. Since microemulsions are usually only formed in narrow specific concentration ranges of the ingredients, investigation of the suitable composition is a demanding process. So far, compositions of microemulsions are determined by the time- and cost-consuming titration method (drop method) and represented in pseudoternary diagrams.

This presentation will introduce a new, time and material-saving method called “Phase Diagram by Micro Plate Dilution” (PDMPD) for creating pseudoternary phase diagrams for microemulsions. The novel PDMPD method is based on the preparation of dilution series of the individual components in microplates and the examination thereof with a computer assisted technique to create the pseudoternary diagram. Consequently, the concentration of the components can be chosen more accurate in order to reduce the surfactant amounts and by this local dermal irritation.

Session 3: Aspects of formulation

How to develop and characterise innovative formulations

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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.