Description of the award-winning project:

Nanotechnology / QbD / Clinical Pharmaceutics

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The active ingredient imiquimod (IMQ) is approved for the treatment of actinic keratosis (AK), basal cell carcinoma (BCC) and genital warts. IMQ is commercially available in the form of the finished drug product Aldara™, an oil-in-water cream in which the active ingredient is dissolved in isostearic acid. Although the use of Aldara™ in humans has shown safety and effectiveness, side effects in the form of severe erythema are common during the treatment of AK due to the poorly tolerated excipient isostearic acid and the high skin permeation of dissolved IMQ.

With the aim of improving the tolerability of IMQ, a novel IMQ formulation "IMI-Gel" without isostearic acid was developed. The concept of Quality by Design was utilized aiming for the provision of a quality-optimized product.

In a first step, a formulation concept was designed that was intended to delay the skin permeation of IMQ. For this purpose, IMQ in the form of nanoparticles was incorporated into the formulation with an additional disperse phase made of jojoba wax. A delay in permeation was expected on the one hand due to the migration of the drug nanoparticles into hair follicles. Nanoparticles can stay there for up to 10 days, which makes targeting the hair follicles as a long-term reservoir attractive. The size of the nanoparticles is crucial for their migration into the hair follicles. Optimal hair follicle penetration occurs with a particle size of around 300-600 nm. After migrating into the hair follicles, the nanocrystals can slowly dissolve there and penetrate into the skin. Furthermore, the delayed entry of IMQ into the skin is caused by its poor solubility: only a very small amount of the active ingredient is present within the formulation in a dissolved state, which can then enter the skin via passive diffusion according to Fick's first law. The addition of the oil component served as a further permeation retardant.

A quality target product profile (QTPP) was created, which defined the relevant quality attributes of the nanocrystalline IMQ formulation. Based on this profile, a manufacturing process was designed which ensures the defined and reproducible production of crystalline IMQ nanoparticles using a wet ball milling process. The disperse jojoba wax phase was incorporated into the aqueous IMQ suspension using a high-pressure homogenization process. After adding the hydrogel consisting of hydrated polyacrylic acid, a spreadable cream preparation was obtained.

Using an Ishikawa fishbone diagram and a risk assessment matrix, potential critical process parameters (CPPs) and potentially critical material attributes (CMAs) were identified and their influence on the critical quality attributes (CQAs) of the novel IMQ formulation was assessed. The process parameters of the duration of the milling process and the milling speed turned out to be critical, as these parameters largely determine the resulting IMQ particle size. With the aim of achieving the desired particle size while keeping the particle size distribution as narrow as possible, these process parameters were optimized using the concept of Design of Experiments, DoE by applying a central composite design.

It was shown that the optimal process conditions of milling duration and milling speed were 650 rpm for 140 minutes to produce IMQ nanocrystals with a target size in the range of 300-400 nm with minimal particle size distribution. Furthermore, in-process controls (IPCs) and quality control tests (QC) were installed before, during and after production for the process parameters (CPPs) and material attributes (CMAs) that were assessed as critical in order to ensure consistently high quality of the manufactured product batches. The data from IPC and QC controls of the manufactured batches (according to Good Manufacturing Practice (GMP)) demonstrated a high quality of the manufactured IMI-Gel batches with low batch variability.

Despite these measures, the quality of a tube of the IMI-Gel product was criticized by a patient in the phase I study. The complaint concerned the physical stability of the product. As part of a root cause analysis, the pH value, the primary packaging, investigations into the physical stability of the formulation inside and outside the primary packaging and rheological analyzes were carried out. The pH value, as an indicator of the structural stability of the gel-forming polyacrylic acid, showed no deviation from the acceptance criterion. An inspection of the primary packaging revealed no visible damage. Tests on the physical stability of the formulation at 40 °C and 80 °C within its primary packaging showed no changes. Storage of the formulation inside the primary packaging with the cap opened and outside the primary packaging led to rapid separation of the disperse jojoba wax phase. In a long-term stability test for formulations stored at 25 °C/65% rH for 12 months and at 40 °C/75% rH for 6 months, rheological rotation and oscillation analyzes were used to show the physical stability of the formulation. As long as it is stored tightly closed in its primary packaging only minimal structural changes could be observed. The most likely cause of the quality deficiency was incorrect handling after the test medication was handed to the patient.

To check the effectiveness and safety of the new formulation IMI-Gel, the patient data from the phase I /II study were evaluated. It was shown that the IMI-Gel formulation had the same effectiveness as the comparison preparation Aldara™. This assessment is based on a comparable elimination rate of AK lesions (no significant difference) and a non-significantly different (effective) reduction in AK lesion areas for both treatment groups. The assessment of tolerability turned out to be significantly better for the IMI-Gel. For this purpose, the cosmetic assessment of the skin condition after treatment was analyzed, which was assessed by both the respective patient and the treating doctor. In addition, patients treated with IMI-Gel demonstrated lower rates of ulceration and exudates, although the differences from patients in the Aldara™ treatment group were not statistically significant.

In summary, it can be stated that the safety, effectiveness, and tolerability of the IMI-Gel was demonstrated and the goal of improving tolerability compared to the comparator preparation was achieved while maintaining the same effectiveness.