Wissenschaftliche Posterausstellung: Poster 11

Follicular penetration of a novel template of solid lipid microparticle dispersion for retinoids

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Introduction: Retinoids are highly teratogenic active pharmaceutical ingredients and cause severe congenital defects to the unborn child or spontaneous abortion. Thus, a novel formulation promoting the penetration of retinoids such as adapalene into the orifices of hair follicles as the drug target and enabling the circumvention of any systemic adverse effects meets an unmet medical need. Galenical target parameters are a mean particle size (MPS) of approximately 5 µm, a narrow particle size distribution, lipophilic material, and solidness of the particulate carrier system [1, 2].

The innovative pharmaceutical solid lipid microparticle dispersion (SLM) consisting of hydrogenated palm oil, purified phosphatidylcholine, poloxamer 407 (P407), polyethylene glycol 12000, potassium sorbate, anhydrous citric acid, and water in double distilled quality was optimized with a Box Behnken design for MPS and span in dependence on introduced lipid matrix (LM) content, P407 content, applied dispersion rate, and dispersion time. Potential for follicular penetration was evaluated via differential tape stripping on porcine ear skin compared to the commercial product Differin® cream [3].

Methods: LM and P407 phases were dispersed with different dispersion rates for varying dispersion times set within the design of experiments. MPS and span were determined with a laser diffractometer including polarization intensity differential scattering (Beckman Coulter, D-Krefeld). Approximately 30 mg SLM comprising 0.1%(w/w) adapalene and Differin® cream were spread on 6 cm^2 of the marked areas of the dorsal side of porcine ears for 3 minutes. 10 tapes (Beiersdorf, D-Hamburg) for tape stripping and 2 subsequent tapes for differential tape stripping with cyanoacrylate glue (Uhu, D-Bühl) were removed and extracted in the mobile phase of 45%(v/v) acetonitrile, 35%(v/v) tetrahydrofuran, and 20%(v/v) purified water for drug quantification via high performance liquid chromatography with a LiChroCART® 250-4 Purospher® STAR RP-18 endcapped (5 µm) column (Merck, D-Darmstadt), the mobile phase additionally containing 0.1%(v/v) acetic acid, a flow rate of 1.2 ml/min, and at a detection wavelength of 270 nm. Tapes were also analyzed via fluorescence microscopy (Olympus, D-Hamburg).

Results: The response surface designs of the constructed Box Behnken model reveal that the MPS decreased from about 4.6 to 3.5 µm with a lower content of LM,

a higher amount of P407, and a high dispersion rate no matter what dispersion time is applied. The narrowest span below 1.4 or 1.2 µm, respectively, was obtained with a LM content up to 20%(w/w) with 12%(w/w) P407 as the phase parameters while using a dispersion rate of 16000 rpm and dispersion time of 3 minutes as the centrally set process parameters.

Both the optimized SLM loaded with 0.1%(w/w) adapalene and the Differin® cream exhibited a high density of single fluorescent signals on the first 2 tapes being indicative of the presence of lipid particles containing adapalene or adapalene crystals, respectively, on the surface. Isolated hair follicles on the 2 cyanoacrylate tapes featured the particular signals as well, demonstrating a penetration into the orifices of hair follicles of both formulations.

2.031 µg adapalene/cm² from the first 10 tapes for the applied SLM and 1.509 µg adapalene/cm² from the tapes for the Differin® cream were detected which may be assigned to the stratum corneum [4]. Regarding the follicular content, 0.257 µg adapalene/cm² from the SLM and 0.117 µg adapalene/cm² from Differin® were recovered from the cyanoacrylate tapes. No statistically significant difference between both contents was determined. However, the absolute amount of penetrated adapalene was higher for the SLM.

In conclusion, the novel optimized pharmaceutical formulation provides a similar penetration behaviour like a commercial dermal product and does actually show a follicular penetration.

Disclosure: The authors filed a patent application for the novel pharmaceutical formulation claiming a broad range of the composition.

References:

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