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Betulin formulated as smartCrystals® for increasing dermal bioavailability

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Betulin, a bioactive substance extracted from the outer bark of Betula pendula, has been used as an active ingredient for the treatment/support of treatment of various skin diseases, such as eczema and psoriasis [1]. Current commercial products with betulin are Pickering emulsions. However, its poor solubility both in water and lipophilic media limits its bioavailability and absorption in the skin. To circumvent this problem, betulin was produced using the smartCrystal®-technology (nanocrystals), which can increase skin penetration by 3 different effects:
a) increased saturation solubility und thus increased concentration gradient between formulation and skin,
b) increased dissolution velocity and c) high adhesion to the skin.

The penetration was investigated in vitro by the pig ear tape strip test. Additionally, the physical stability of betulin smartCrystals® was analyzed over one year.

The production of Betulin smartCrystal® suspension was performed by two methods: a) high pressure homogenization (HPH) applying 20 cycles at a pressure of 1500 bar; b) bead milling (BM) using 0.1 mm milling beads and a milling time up to 30 minutes. Five different surfactants were investigated: Plantacare 810 UP, Plantacare 818 UP, Plantacare 1200 UP, Plantacare 2000 UP and tocopheryl polyethylene glycol succinate (TPGS). 2% drug was dispersed in 1% surfactant solution by Ultra-Turrax for 10 seconds at 8000 rpm. Subsequently, the resulting raw suspensions were applied to the two production methods. The physical stability of the nanosuspensions was evaluated by analyzing betulin samples which were stored at three different temperatures (4°C, 25°C, 40°C) for four different periods of time (0 day, 7 days, 1 month, 1 year). Mean particle size was analyzed by photon correlation spectroscopy (PCS) and zeta potential (ZP) was determined by electrophoretic light scattering. Possible larger crystals were measured by laser diffractometry (LD). Tape stripping (n=3) was performed with fresh pig ear skin and different betulin formulations were applied to the skin for 20 minutes. Drug concentrations in the strips were measured by HPLC.

Betulin smartCrystals® were successfully produced by HPH while bead milling failed. For all formulations, independent on the surfactant, the diameters of betulin smartCrystals® were below 400 nm (z-average). The four types of Plantacare were superior to TPGS in both production process and storage. When samples were stabilized with Plantacare, a diameter of around 300 nm was obtained and remained stable after one year of storage. Among these various surfactants, Plantacare 2000 UP appeared to be the most efficient stabilizer, especially in the long-term storage. The ZP in water was -56.9 mV, indicating a good stability of these betulin smartCrystals®. Furthermore, the LD and PCS diameters showed limited increase when the samples were stored at 4°C and 40°C, proving physical stability of the nanosuspensions at different temperatures. According to the pig ear study, half the concentration of betulin smartCrystals® (1.8%) incooperated into a gel (5% hydroxypropyl cellulose) showed higher skin penetration compared to a commercial product with 3.7% betulin (e.g. drug amount in the 9th strip was 16.1 µg for smartCrystals® and 11.1 µg for the commercial product).

In summary, betulin was produced successfully as smartCrystals® by HPH as superior method compared to bead milling. The well tolerated Plantacare 2000 UP was found to be the most suitable surfactant both in production process and 1 year long-term stability. The 270 nm betulin smartCrystals® showed at only half the concentration (1.8%) a higher skin penetration than a commercial reference product. The data open the perspective to produce a more efficient dermal product.

[1] Sami, A., Taru, M., Salme, K., Jari, Y. K., Eur. J. Pharm. Sci. 29(1), 1-13, 2006.