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Dermal smartCrystals® – new model for better understanding of nanocrystal penetration mechanism

Gregori Bahu Romero (1), Lucie Vidlářová (2), František Štěpánek (2), Cornelia M. Keck (1, 3), Rainer H. Müller (1)

(1) Freie Universität Berlin - Institut für Pharmazie; Pharmaceutics, Pharmaceutical Nanotechnology & NutriCosmetics; Kelchstr. 31, 12169 Berlin, Germany
(2) Department of Chemical Engineering, University of Chemistry and Technology Prague, Technická 3, 166 28 Prague 6, Czech Republic
(3) PharmaSol GmbH, Stubenrauchstr. 66, 12161 Berlin, Germany

smartCrystals® are nanocrystals, which consist of pure active, being in size in the nanodimension (< 1,000 nm = < 1 µm). Due to their small size they have nanoproperties such as increased saturation solubility (Cs), and thus increased penetration into the skin. They are an ideal formulation to increase skin penetration of poorly soluble actives (e.g. flavonoids), but also medium soluble compounds such as caffeine. Curcumin is a very interesting active for dermal delivery, e.g. anti-inflammatory, anti-oxidant and anti-cancer properties. In addition, it is fluorescent, easy to detect, and thus it was used as model molecule. Curcumin has low water solubility, low penetration into the skin, and yellowish color of limited consumer acceptance. Thus the aim was to develop a formulation with distinctly increased bioavailability compared to existing commercial products, and curcumin concentration as low as possible to minimize color effects. For this, penetration was investigated as function of nanocrystal concentration in the dermal formulation. From the findings, a new model of penetration enhancement was derived. By now, the sufficient concentration of nanocrystals in dermal formulations was roughly estimated. The new model allowed for the first time to give a scientifically well-based concentration recommendation for nanocrystal formulations.

smartCrystals® were produced by bead milling (PML 2, Bühler, Switzerland) and subsequent high pressure homogenization (Micron LAB 40, APV Deutschland). The suspension consisted of 5% curcumin, 1% Plantacare 2000 UP (all w/w %) and distilled water. Characterization was performed by photon correlation spectroscopy (PCS), laser diffraction, light microscopy and electron microscopy. For penetration studies, aqueous nanosuspensions and nanocrystals in hydroxypropyl cellulose (HPC) gels were applied to pig ear skin in a Franz cell, and after certain times (1-20 hours) skin slices were taken with a microtom, and analyzed by confocal laser scanning microscopy (CLSM). Nanocrystal concentrations investigated were 2%, 0.2%, 0.02% and 0.002%. As comparison, a commercial dermal curcumin product with 0.0001% dissolved curcumin (= saturation solubility) was used.

From the nanocrystal theory by now, only the saturation solubility of nanocrystals was considered as the dominating factor, leading to a distinct penetration driving concentration

gradient (Cs-Cskin). Based on this, the penetration should be the same for 2% to 0.002% nanocrystal formulations (all have identical Cs). However, similar good penetration was found for 2%, 0.2% and 0.02%, but very little penetration for 0,002%. Obviously the density of nanocrystals on the skin surface plays also an important role. The density needs to be so high, that the "diffusional coronas" of dissolved active around the nanocrystals on the skin surface overlap. This provides a continuous, skin surface covering layer of highly concentrated dissolved active. As a rule of thumb, a concentration as low as 0.02% can now be recommended for dermal nanocrystal formulations. This reduces costs for the nanocrystals, and at the same time reduces color effects of colored actives such as curcumin.

The commercial product with dissolved curcumin (= solution) showed practically no detectable fluorescence in the skin, in contrast to nice fluorescence of the 0.02% nanocrystal formulation. This confirms the "old galenic rule" of better penetration from "suspensions", and the superiority of the nanocrystal technology.