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Caffeine Nanocrystals -Novel Concept for Improved Dermal Delivery & Production Method

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Since 2000 nanocrystals are pharmaceutically applied to increase the oral bioavailability (BA) of poorly soluble drugs of the Biopharmaceutical Classification System (BCS) class II (e.g. product Rapamune®/sirolimus). The rate limiting step of absorption of class II drugs is the low solubility and related low dissolution velocity. Transfer to the nanodimension changes the physico-chemical properties of materials, in case of poorly soluble drugs it increases the saturation solubility Cs, and related dissolution velocity dc/dt. The increased concentration gradient leads to increased membrane permeation and consequently BA.

However, completely forgotten was to apply this successful principle to improve dermal BA of cosmetic ingredients and of drugs. In 2007 we introduced the first cosmetic product on the market based on the poorly soluble antioxidant rutin (Juvena), in 2009 hesperidin nanocrystals (La Prairie). In a human study rutin nanocrystals showed a 1,000 fold higher antioxidant activity in the skin [1]. A novel approach is to apply this principle to well soluble actives such as caffeine (e.g. used in cellulite products). At the first glance, nanocrystals from soluble actives seem to make no sense, because the active is soluble anyway!

However, it was found that the penetration of caffeine increases with its concentration in the product, thus cellulite products compete with increasing caffeine concentrations. To avoid reduction of the caffeine concentration in the applied dermal formulation due to skin penetration, it makes sense to add additionally caffeine crystals as depot. Favourably are nanocrystals compared to µm-sized crystals, because they increase Cs and consequently the concentration gradient and related flux into the skin. In addition, crystals of optimal size (around 700 nm) can accumulate in the hair follicles and penetrate from there into the surrounding cutaneous tissue. Massage during application – performed anyway with some consumer care products – can further enhance follicular uptake.

However, when producing nanocrystals in a traditional high energy wet milling process of e.g. high pressure homogenization, supersaturation effects lead to pronounced crystal growth (Ostwald ripening effects), even larger than the starting material (fibre formation). A special process was developed based on low energy milling (bead mill) in combination

with dispersion media with low dielectric constant D (e.g. water-ethanol, water-glycerol mixtures) to yield nanocrystals of varying sizes, e.g. 900 nm to 660 nm, 250 nm, and by controlled separation 90 nm. In the next step, the nanocrystals will be tested in human to verify if their performance is superior to a caffeine solution. If yes, this principle could be applied to other soluble actives and introduced as novel dermal delivery concept.

[1] Petersen, Rolf, patent application 20100047297 DE (2005)