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Preparation Method for Ultra Small Gelantin Nanoparticles for Dermal Delivery of Peptides & Enzymes

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Cosmetic industry is increasingly interested to use peptides or enzymes in cosmetic products. Examples are the peptides by the Spanish company lipotec (e.g. the very successful Argireline) or enzymes like superoxide dismutase by American company Estee Lauder. As water soluble molecules they can be simply dissolved in the water phase of a cream/gel or of liposomes. However, to chemically stabilize these molecules and/or to achieve a controlled prolonged release, incorporation in a solid matrix particle is desirable. As preferable over hydrophobic matrices of polymeric nanoparticles appear nanoparticles from hydrophilic gelatin. Of special interest are ultra small gelatin nanoparticles (GNPs), that means < 100 nm, and especially < 50 nm. The smaller the particles, the more adhesive they are to the skin. In addition it was shown that core-multishell (CMS) nanoparticles by Haag et al of a size of about 40 nm were able to deliver more efficiently fluorescent marker into epidermis (1). However, most of the GNPs production methods yield nanoparticles above 250 nm. Very important is that incorporated enzymes are again released and retain their enzymatic activity! Therefore the aim was to produce GNPs below 100 nm, and to prove remaining enzymatic activity by using lysozyme as model.

A two-step desolvation method for the preparation of GNPs was developed by modification of a method described by Coester (2). Briefly the gelatin was dissolved in water and first desolvated by acetone to separate high molecular weight fractions. Glutaraldehyde was added as crosslinker after a second time desolvation and formation of particles. GNPs possessing a mean PCS size of about 60 nm were obtained with optimized production parameters, like a starting gelatin concentration of 2.5%, a pH of 2.5 and a precipitation time of 5 minutes. In the next step, GNPs were loaded with lysozyme, which changed the size only slightly to 78 nm. A drug loading efficiency of 89% was obtained. The activity of the released lysozyme was checked by HPLC, and proved to be 93%. Storage studies were performed over 6 months at 3 temperatures, apart from 40°C the GNPs remained physically stable.

Conclusion: GNPs distinctly below 100 nm could be produced, activity of the model enzyme remained. Further modification of the method should allow to produce GNPs ≤ 40 nm, having similar skin delivery potential to CMS nanoparticles. However, the GNPs have the

advantage that – in contrast to the dendrimer CMS – gelatin is a regulatorily accepted excipient and can be used in dermal formulations.

[1] Küchler S, Radowski MR, Blaschke T, et al. Eur. J. Pharm. Biopharm. 2009, 71(2):243-50.
[2] Coester CJ, Langer K, Von Briesen H, et al. J. Microencapsul. 2000, 17(2):187-93.