Thermal analysis of nanosuspensions based on solidified reverse micellar solutions (SRMS)

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Introduction
Solidified reverse micellar solutions (SRMS) consisting of a 5:1 (w/w) mixture of lecithin and Softisan® 100 (SRMS100) or 142 (SRMS142), respectively, offer a high solidification rate for different types of drugs [1]. The solidification at temperatures near the melting points (m.p.) of the lipids is applied for the manufacturing of nanosuspensions based on these SRMS, i.e. solid lipid nanoparticles (SLN). The homogenization temperature is hereby controlled by the homogenization pressure according to [2].

Aim of the present contribution is the manufacturing of SRMS-based nanosuspensions with a liquid concentration of 15 % (w/w) and the investigation of their thermal behavior.

Experimental methods
Preparation of SRMS
The SRMS were ground in melting nitrogen for 15-20 min (7 grinding processes). The frozen fat powder (15 % w/w) was dispersed in an aqueous solution of polysorbate 80 (Caelo, D-Düsseldorf) modified with a He/Ne laser (7 grinding processes). The frozen fat powder (15 % w/w) was dispersed in a 1:1 (w/w) mixture of lecithin and Softisan® 40 kV and the anode current 40 mA. Interference detection was achieved with Structurix D7 FW X-ray films (Agfa-Gevaert, B-Wiesbaden). Specimens were shadowed with platinum/carbon (2 mm) at 45° and with pure carbon (20 nm) at 90° for replica preparation. After cleaning to 10-100 nm, sulphuric acid and water the replicas were viewed on uncoated grids with a transmission electron microscope EM 300 (Philips, D-Kassel) at 80 kV.

Results and discussion
The nanosuspensions contain particles with a mean particle size of about 70 nm and a narrow particle size distribution after manufacture. These solid lipid nanoparticles (SLN) exhibit an amorphous, often plate-like shape (Figure 1). Layered structures like terraces, steps and kinks could be observed within the particles demonstrating a crystalline character even after homogenization.

Thermal analysis of the nanoparticulate systems displays a melting enthalpy of about 10 mJ/mg (equal about 67 mJ/g for solid lipids) in comparison with 62-65 mJ/g of the SRMS bulk representing equivalent crystallinity of the nanoparticles. In contrast, the transition temperatures of the nanosuspensions are 8-9 K lower than those of the SRMS bulk (Figure 2). This finding is related to the colloidal dimensions of the particles and their large surface to volume ratio and is not related to a recrystallization of an modification with a lower m.p. [3]. Furthermore, X-ray analysis shows that the nanoparticles exist in a stable modification according to [4], whereas the bulk materials crystallize in a metastable β modification.

During the first nine days of storage at room temperature the m.p. of the nanosuspensions increases by 1-2 K (Figure 3). This increase in m.p. goes along with an increase in particle size. After three weeks of storage the particles reach a constant diameter at about 120-130 nm for SRMS100 systems and 100-110 nm for SRMS142 systems, respectively, in contrast to a particle size of 70-80 nm directly after production (Figure 4). However, the polydispersity indices of the nanosuspensions remain constant at 0.232 ± 0.027 (SRMS100) and 0.174 ± 0.021 (SRMS142).

Conclusions
The nanosuspensions contain crystalline particles (β modification) of anisometrical shape which have transition temperatures far below the bulk m.p. due to the colloidal character of the systems but not due to a crystallization of a modification with a lower melting point. The large surface to volume ratio causes numerous molecules to exist in a state of higher energy at the surface of the particles. Hence a lower temperature is required for melting of these particles.

An increase in transition temperature after production coincides with an increase in particle size because of particle agglomeration or growth. With this increase in size the surface to volume ratio decreases.

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References