ESRF	**Experiment title:** Thickness dependent melting of triglyceride nanocrystals in aqueous suspension	**Experiment number:** LS–1558
Beamline: ID02A	**Date of experiment:** from: 31.3.2000 to: 02.04.2000	**Date of report:** 20.2.2000
Shifts: 8	**Local contact(s):** Peter Boesecke	*Received at ESRF:*

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Report:

The melting behaviour of suspended monoacid triglyceride nanoparticles, which are under investigation as drug delivery systems [1], is strongly influenced by the thickness distribution of the platelet–shaped crystals as shown in previous X–ray investigations for trilaurin and trimyristin dispersions [2, 3]. The multiple endotherms in slow DSC–heating runs of these systems are due to the stepwise melting of the nanocrystals with particle thicknesses of $2, 3, 4, \ldots$ molecular triglyceride layers only.

The project was mainly focused on the investigation of tripalmitin nanosuspensions, which besides the melting effect exhibit a strong tendency to form stack–like arrangements of the flat particles (superstructure) [4, 5]. The investigated nanosuspensions were prepared by high–pressure melt homogenization at 85°C. The aqueous suspensions contained 10 mass–% tripalmitin and as stabilizers 3.2% phospholipids (S100, Lipoid) and 0.8% sodium glycocholate. The aqueous phase contained 2.25% glycerol.

SAXS–patterns of a native sample ("TP") and the diluted "TP" sample (1:2 with the aqueous phase) were recorded at 25°C, 30°C, 35°C, 40°C, 42°C, 44°C and in the temperature range from 45°C to 63°C in steps of 0.1°C using a sample – detector distance of 10 m. The measurement was repeated using a sample – detetector distance of 2 m for the diluted sample, in order to detect the (001)–reflection of the tripalmitin crystal structure. The mean "thickness" of the particles (perpendicular to the (001)–plane) melting in the range of two successive temperatures was determined using a single line Fourier peak shape evaluation method of corresponding difference diffraction patterns collected in the s–range of the (001)–reflection (cf. Fig. 1) [3].

In agreement to previous results from trilaurin and trimyristin suspensions, an increase of the particle thickness with increasing temperature and even the step–like shape of the D vs. T curve is observed for the diluted tripalmitin sample.The peak shape analysis gives reliable results only for diluted samples because the shape of the (001)–reflection of native dispersions is often distorted due to particle interactions (see below). The most intense endothermal DSC peaks can be ascribed to discrete crystal thicknesses that melt at corresponding temperatures.

The native "TP" sample exhibit a strongly distorted (001)–reflection due to the formation of a lamellar superstructure. The first three diffraction orders of this structure can be observed in the SAXS–patterns displayed in Fig. 2.

The interference of higher diffraction orders with the scattering due to the particles' internal structure leads to the mentioned distortions of the broad (001)–reflection. The first order reflection of the superstructure is significantly more intense than the higher diffraction orders. Therefore, the occurence of this reflection should be a sensitive indicator for the formation of lamellar arrangements. Computer simulations indicated that this should be true, even for strongly distorted self–assemblies.
The superstructure vanishes when the particles melt (cf. Fig. 2). The majority of the lamellar structures, however, are destroyed at temperatures below the onset of the melting process. It could be demonstrated that the superstructure of trimyristin and tripalmitin, respectively, also vanishes when diluting the dispersion 1:2 with the aqueous phase. This observation indicates but does not ensure the pharmaceutical safeness of such nanosuspensions for intravenous application with respect to the formation of particle aggregates.

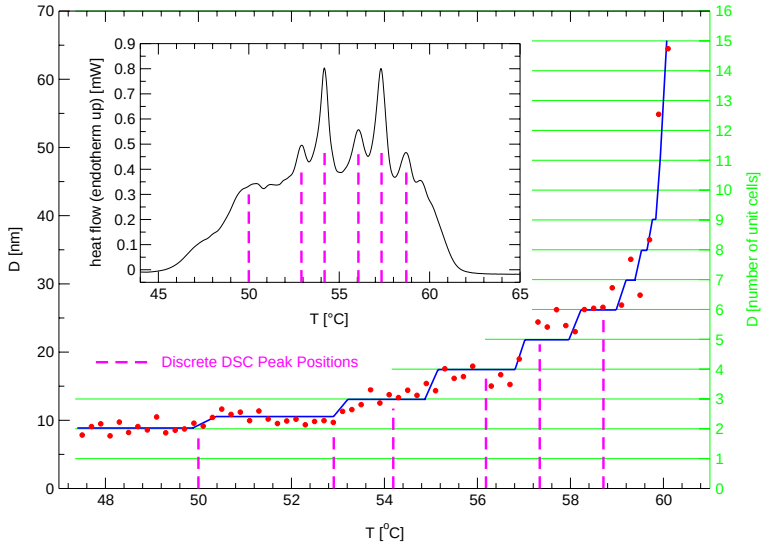

Fig. 1: Particle thickness D versus melting temperature T. D was estimated from temperature resolved SAXS–measurements on sample "TP" diluted 1:2 with water using a single line Fourier peak width evaluation method of difference diffraction patterns of the tripalmitin (001)–reflection. The solid line symbolizes the stepwise melting process of the nanoparticles. The dashed lines represent the most intense peaks of the DSC–curve of sample "TP" displayed in the insert (heating rate: 0.1 °C/min).

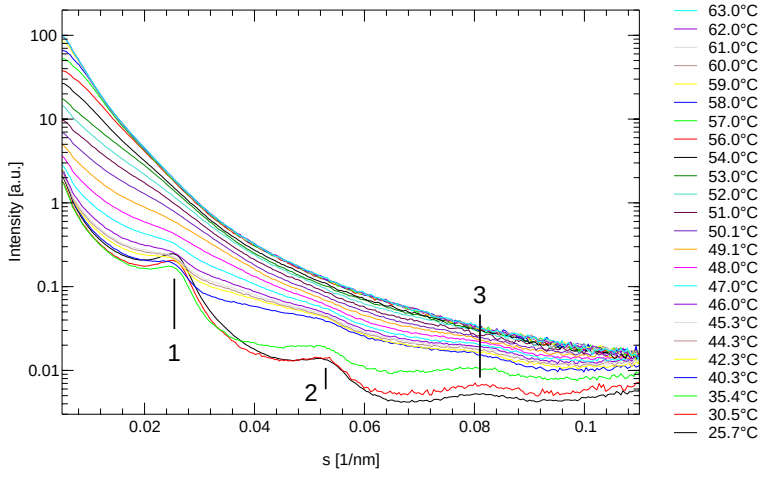

Fig. 2: Temperature resolved SAXS–measurements on sample "TP". The peaks of the curves at low temperatures indicate a lamellar order (superstructure) of the flat nanocrystals. The labels represent the orders of the lamellar reflections.

References

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