Investigation of the phase behavior of monoolein/poloxamer dispersions

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Colloidally dispersed cubic phases of glyceryl monooleate (MO, C18:1) in water have been proposed as potential carriers for the intravenous administration of peptide and protein drugs. For the preparation of such dispersions, e.g., high pressure homogenization of a coarse dispersion consisting of MO, Poloxamer 407 (P407) and water has been described. After homogenization, however, particles without cubic structure have been observed besides the desired particles with cubic structure [1]. The aim of this study was to get additional information on the influence of MO grade, P407 concentration and temperature on the phase behavior and structural parameters of the dispersed particles to complete previous studies [2].

All of the samples investigated in this study were prepared according to the following procedure: The MO and the required amount of P407 (6%, 8%, or 12% (w/w), respectively, based on the sum of MO and P407) were melted together at 60°C and mixed. The liquid mixture (approx. 40-50°C) was added dropwise to water at room temperature under stirring. The resulting MO/P407-dispersions of 5% (w/w) were stored for at least 1 day under stirring at room temperature for equilibration. High pressure homogenization was performed using a Microfluidizer M-110 (Microfluidics Inc., USA) at 350 bar and 40°C for 15 minutes. The used MO grades were Rylo MG 19, Dimodan DGMO (both from Danisco Cultor, Denmark), GMOrphic-80, or Myverol 18-99 (both from Eastman Chemical Company, USA), respectively.

Small angle X-ray diffraction data of different dispersions were collected at selected temperatures in the range from 25°C to 95°C. The samples were equilibrated at the corresponding temperature for at least 5 to 10 minutes prior to the measurement (exposure time 10 minutes). Liquid crystalline phases were assigned by comparison of the diffraction patterns with the characteristic spacing ratios (table 1) of the expected phases. The lattice parameters below are given as the mean value calculated from the first three peaks of the diffraction pattern.

Table 1: Characteristic spacing ratios of liquid crystalline phases

phase	characteristic spacing ratios
H_{II}	1 : √3 : √4 : √7 : √12 : √13 : √16 : ...
cubic G (Ia3d)	√6 : √8 : √14 : √16 : √20 : √22 : ...
cubic D (Pn3m)	√2 : √3 : √4 : √6 : √8 : √9 : √10 : √11 : ...
cubic P (Im3m)	√2 : √4 : √6 : √8 : √10 : √12 : √14 : √16 : ...

To study the influence of P407-concentration on the phase behaviour of the systems, dispersions containing Rylo as MO and 6%, 8% and 12% P407 were prepared and the diffraction patterns were collected at 25°C, 40°C and 60°C. At 25°C, the dispersions containing 6% and 8% P407 display Im3m-reflections (cubic P) with similar lattice parameters (14.5 nm in the case of 6%, and 14.8 nm in the case of 8%). In contrast to this, the dispersion containing 12% P407 does not display any reflections. At 40°C and 60°C, the reflections of the 8%-dispersion are still of the Im3m-type without any other detectable reflections. In the case of the 6%-dispersion, some weak reflections (probably due to Pn3m, indicating a cubic D phase besides the cubic P phase) occur additionally to the Im3m-reflections at 60°C. An observable broadening of the second and the third Im3m-peak at 40°C is probably due to the presence of very weak Pn3m-peaks even at this temperature (fig. 1).

To test the influence of different MO grades, dispersions containing 12% P407 were prepared by using Dimodan, GMOrphic and Myverol and the diffraction patterns were collected at 25°C. None of these dispersions displays any reflections. In contrast to the usual result for Rylo-dispersions containing 12% P407, this time an additionally prepared Rylo-dispersion displayed reflections of the Im3m-type with a lattice parameter of 14.9 nm which may be due to an inhomogenous composition of the raw material.

Additionally, dispersions containing 8% P407 were prepared using Rylo and GMOrphic. At 25°C, these dispersions display reflections of the Im3m-type (cubic P) with similar lattice parameters (Rylo: 14.4 nm, GMOrphic 14.2 nm). These reflections are the only ones observed at temperatures up to 60°C, as already reported previously. By applying an additional heating programme from 70°C to 95°C in steps of 5°C, additional reflections of the Pn3m-type (cubic D) occur at 70°C. The intensity of these Pn3m-reflections increases when increasing the temperature to 75°C and that of the Im3m-reflections decreases. At 80°C, no more Im3m-reflections are detectable, all reflections can be explained solely by the presence of a cubic D phase (in the case of Rylo, an additional small reflection occurs which may be due to a small amount of a H_{II} phase). At 90°C and 95°C (GMOrphic) or at 95°C (Rylo), respectively, no reflections can be detected any more (fig. 2).

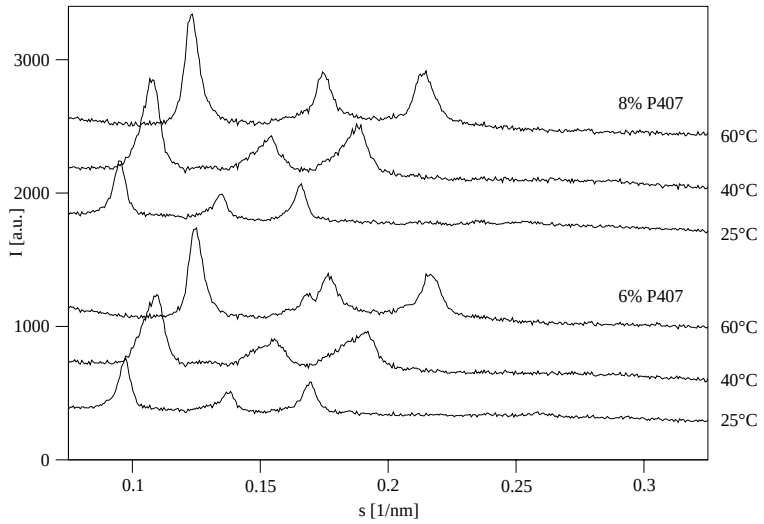

Figure 1: Small angle X-ray diffractograms of Rylo dispersions with 6% and 8% P407 at different temperatures (curves are displaced along the ordinate)

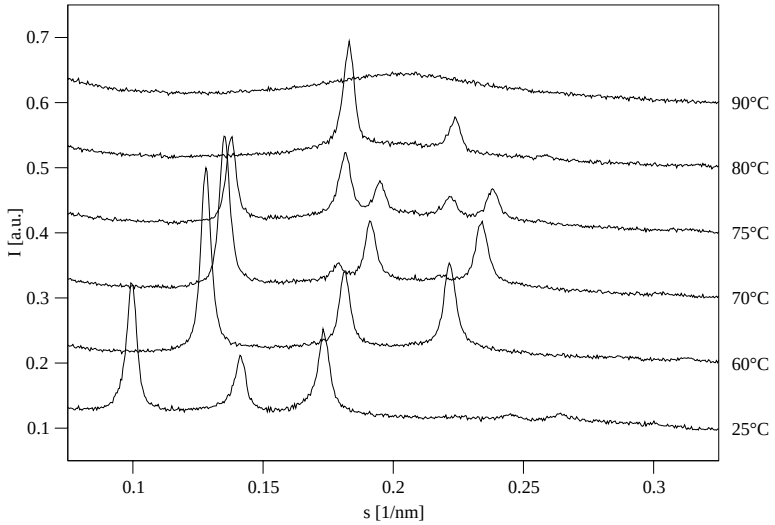

Figure 2: Small angle X-ray diffractograms of a GMOrphic dispersion with 8% P407 at different temperatures (curves are displaced along the ordinate)

References

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