Hexagonal Liquid-crystalline Nanoparticles in Aqueous Mixtures of Glyceryl Monooleyl Ether and Pluronic F127

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A liquid-crystalline nanoparticles with internal reversed hexagonal structure has been prepared by use of a single lipid system. The obtained particles are essentially monocrystalline nanoporous hexagonal prisms with the size of about 200 nm.

Self-assembled lipid liquid-crystalline phases are of great interest in science and technology because of their exceptional nanostructure, featuring mono- or bi-continuous networks of hydrophilic and hydrophobic domains.[1] It has recently been realized that owing to their ability to exist in excess water solutions reversed lipid mesophases can be dispersed in the presence of polymeric stabilizers into discrete colloidal nanoparticles with preserved internal liquid-crystalline structure.[2] Potential applications of the liquid-crystalline nanoparticles (LCNP) are in pharmaceuticals as drug delivery vehicles and in material synthesis as templating matrices.[3] Other areas of use include diagnostics, cosmetics, and carriers of nutraceuticals.

Until now, the research has been mainly focused on reversed bicontinuous cubic LCNPs, to a large extent exploiting unsaturated monoglycerides.[4] Only a few examples of hexagonal LCNPs have been presented so far.[5] An explanation for this fact is that breakup of hexagonal mesophases into particulate aggregates is more difficult. Another restriction is that hexagonal LCNPs have so far only been generated from complex multicomponent lipid mixtures.

Here, we present hexagonal LCNPs prepared utilizing a single lipid, glyceryl monooleyl ether (GME, Figure 1a) which is also significantly more stable against hydrolyses compared to the corresponding monoglyceride ester. We have recently shown that GME forms reversed hexagonal phase in excess water solution over a wide temperature range.[6] Furthermore, it has been shown that glycerol monooleate based LCNPs can be easily prepared by dispersion of the lipid in the presence of small amounts of triblock copolymeric stabilizer, Pluronic F127. Since the molecular structures of GME and glycerol monoesters are similar, we have in this work also used F127 (Figure 1b) as the polymeric stabilizer for the preparation of GME hexagonal LCNPs.

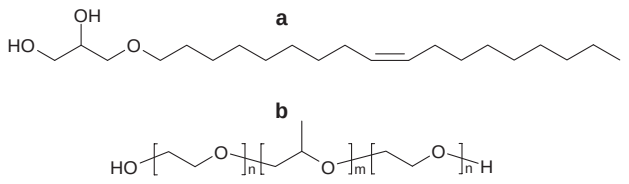

Figure 1. Molecular structures of glyceryl monooleyl ether (a) and Pluronic F127 (b), where *n* is ca. 101 and *m* is ca. 56.

The hexagonal LCNPs of GME were prepared by a recently established method.[7] Briefly, appropriate amounts of GME (Nikko Chemicals, Japan) were added into an aqueous F127 (BASF, Germany) solution. The lipid/polymer ratio was 85/15 (w/w), the water concentration was 98 wt %, and the sample volume was 50 mL. The samples were sealed, hand-shaken, mixed for 12 h on a mechanical mixing table, and homogenized by passing five times through a Microfluidizer 110S at 345 bar and 25 °C. Homogenized dispersions were then heat-treated for 20 min with a bench-type autoclave operated at 125 °C and 1.4 bar vapor pressure. The obtained samples were then allowed to cool to room temperature before analysis. This procedure resulted in homogeneous milky white dispersions. Particle size and cryogenic transmission electron microscopy (cryo-TEM) measurements are described in detail elsewhere.[7a]

Figure 2 shows the size distribution for the prepared hexagonal LCNP dispersion. As seen from the data, the overall dispersion is well defined, homogeneous, and characterized by monomodal size distribution with the mean size and polydispersity index of about 200 nm and 0.2, respectively. Neither changes in size distribution nor any visually detectable changes of the LCNP colloidal stability could be observed after at least 3 months of storage at 25 °C. It is interesting to note that the size distribution characteristics for GME/F127/water nanoparticles are very similar to other lipid LCNPs prepared according to the same heat treatment procedure.[7]

Cryo-TEM images of GME-based particles showing direct nanostructural evidence are presented in Figure 3. As judged from about a hundred of cryo-TEM images, the majority of the particles are essentially monocrystalline with the size (width) of 200–300 nm which is consistent with the particle size distribu-

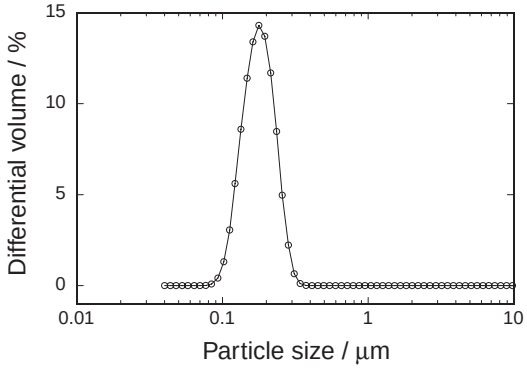

Figure 2. Particle size distribution obtained from hexagonal LCNP dispersion of GME/F127/water (1.7/0.3/98 by weight) mixture.

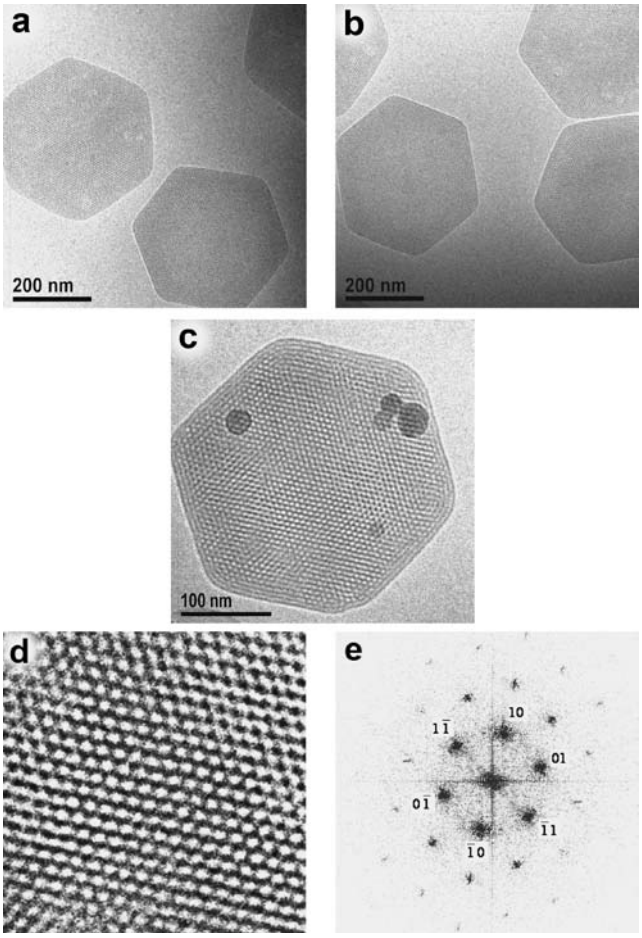

Figure 3. Representative cryo-TEM micrographs of hexagonal LCNPs at the weight ratio GME/F127/water = 1.7/0.3/98: images at lower (a and b) and higher magnification (c). The magnified area of the particle (d) together with its Fourier transform (e) show the structural periodicity of the particle interior. Fourier transformed image is inverted for better observation. It also shows indexing of the first-order reflections.

tion measurements (Figure 2). As seen from Figures 3a and 3b, the most common shape of these LCNPs is the hexagonal prism when viewed along [01] direction. In our previous studies,[5b,7b] we have shown that there is a strong correlation between the type of internal liquid-crystalline nanostructure and the shape of different nanoparticles. Thus, the most favorable shapes for bicontinuous cubic, "sponge", and hexagonal particles are cube, sphere, and "coin-like" hexagonal prism (the width being greater than the thickness), respectively. Therefore, the images in Figure 3 support the fact that particles formed in GME/F127/water system have indeed internal hexagonal structure.

Hexagonal packing of the water cylinders into "honeycomb" arrangement is clearly visible in Figures 3c and 3d where particle is projected along [01] viewing direction (parallel to water rods). The Fourier transformed image also show high degree of internal organization with long-range structural order (Figure 3e). Fourier transformation clearly reveals three reflections with average spacings of 54.2, 31.6, and 26.8 Å with relative positions in ratios $1{:}\sqrt{3}{:}\sqrt{4}$. They can be indexed as $h,k = \{1,0\}$, $\{1,1\}$, and $\{2,0\}$ reflections of two-dimensional hexagonal structure. Note that only reflections of the $\{1,0\}$ family are specified in Figure 3e.

The unit cell dimension of the hexagonal lattice can be calculated as $a = (2d_{hk}/\sqrt{3})(h^2 + k^2 + hk)^{1/2}$, where d_{hk} are the interlayer spacings obtained from Fourier transform. The calculated lattice parameter equals to 62.6 Å and is very close to that determined for the fully swollen bulk GME/water hexagonal liquid-crystalline phase.[6] This shows that the nanostructure of GME/F127/water LCNPs is essentially the same as in the fully water swollen GME phase. This also implies that the inner structure is not affected by the addition of F127. As in previous studies,[2c,5b,7b] it demonstrates that F127 is excluded from the particle core; preferentially located at the surface of the nanoparticles. Using simple geometry, the obtained lattice parameter allows an estimation of the water radius of the cylinders within the nanoparticles, $R_W = a[\sqrt{3}(1-\phi)/2\pi]^{1/2}$, where ϕ is the weight fraction of lipid in the particle. Considering the above results, we can assume that the particle core is composed of GME only. Also, from the previous study, we know that ϕ of the fully swollen hexagonal phase is about 0.27.[6] With this in mind, the calculated R_W equals to 28 Å and the size of the water channels is, therefore, about 56 Å. Very similar values can be directly obtained from Figure 3c and from an intensity profile of Figure 3d.

In conclusion, kinetically stable and structurally well-defined LCNPs of the reversed hexagonal phase can be easily prepared in a simple system consisting of one lipid and one polymeric stabilizer. This opens up yet other possibilities for the use of soft nanoporous liquid-crystalline aggregates in cosmetics, drug delivery, and material sciences.

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