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Influence of stabilizer systems on the properties and phase behavior of supercooled smectic nanoparticles

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ABSTRACT

Colloidal dispersions of cholesterol esters in the supercooled smectic state (supercooled smectic nanoparticles) are potential novel carrier systems for poorly water soluble drugs. As the supercooled smectic state is metastable, evaluation of its stability and of parameters influencing it is essential. In the present study, the effect of different emulsifiers on the stability of the supercooled smectic state of cholesteryl myristate (CM) nanoparticles and their crystallization was investigated. Nanoparticles were prepared by high-pressure melt homogenization and characterized by dynamic light scattering (DLS), laser diffraction combined with polarization intensity differential scattering (LD–PIDS), synchrotron radiation small-angle X-ray scattering (SAXS), differential scanning calorimetry (DSC) and transmission electron microscopy (TEM, negative staining and cryo-preparation). The various stabilizers resulted in clear differences in the crystallization behavior of the nanoparticles: stabilizers containing a fatty acid chain in their molecule (e.g. phospholipids, sodium oleate and sucrose monolaurate) induced a multiple crystallization event accompanied by a comparatively high recrystallization tendency. In contrast, the recrystallization tendency of nanoparticles stabilized with polymers (e.g. gelatin polysuccinate, poloxamer, poloxamine, polyvinyl alcohol) and sodium glycocholate was much lower and a single crystallization event was observed. The high stability against recrystallization during storage of smectic nanoparticles stabilized with polysorbate 80 in spite of the presence of a fatty acyl group in the molecule suggests that the polar head group (e.g. polyethylene glycol chains) of the emulsifier may also play a significant role.

1. Introduction

Dispersions of supercooled smectic cholesterol ester nanoparticles have been introduced as potential novel carrier system for poorly water soluble, lipophilic drugs [1–4]. Cholesterol esters are non-polar lipids and are the physiological storage and transport form of cholesterol occurring in lipoproteins, mainly low density lipoproteins (LDL [5]). Cholesterol esters are crystalline solids at room temperature and form liquid crystalline phases upon heating (thermotropic mesophases [1,6]). Substances with very anisometric, rod-like molecule shape like cholesterol esters can form two major types of thermotropic mesophases: the smectic and the nematic (or cholesteric) phase, where the smectic phase (if present) always occurs at lower temperature. The smectic phase has a layered structure with an almost parallel arrangement of the molecules along their long axes. In the nematic phase, the molecules are also aligned side by side, but not ordered in specific layers. Cholesterol esters typically form a variant of the nematic phase, the cholesteric mesophase which presents a twisted nematic structure [1,6]. Upon cooling, the smectic phase may persist at temperatures at which the crystalline form is the thermodynamically stable one (i.e. be supercooled) already in the bulk phase [1,4]. Due to the absence of crystallization promoting impurities in the individual nanoparticles, supercooling is even more pronounced in the colloidal state [1,2]. The effect of extended supercooling in the colloidal state is well known and an important consideration in the case of solid lipid nanoparticles, another type of lipid-based drug carrier systems [7]. Monoacid triglyc-

Abbreviations: CM, cholesteryl myristate; DLS, dynamic light scattering; LD–PIDS, laser diffraction with polarization intensity differential scattering; SAXS, small-angle X-ray scattering; DSC, differential scanning calorimetry; TEM, transmission electron microscopy; WAXS, wide-angle X-ray scattering; S100, soybean lecithin Lipoid S100; E80, egg yolk lecithin Lipoid E80; SML, sucrose monolaurate; SGC, sodium glycocholate; SO, sodium oleate; PS, polysorbate 80; PVA, polyvinyl alcohol; GPS, gelatin polysuccinate; POL, poloxamer 188; TET, poloxamine (Tetronic 908); Ph.Eur., European Pharmacopoeia (Pharmacopée Européenne); PDI, polydispersity index; PCS, photon correlation spectroscopy; EMBL, European Molecular Biology Laboratory; DESY, Deutsches Elektronen Synchrotron.

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eride nanoparticles, for example, may remain in the supercooled molten state for considerable times after high-pressure melt homogenization (emulsions of supercooled melts [8]) and nanoparticle crystallization may, therefore, require special measures [9]. While supercooling of the lipid phase is a rather undesirable effect during the preparation of solid lipid nanoparticle dispersions, this phenomenon can be exploited for the development of smectic cholesterol ester nanoparticles. Due to its high viscosity combined with mobility at the molecular level [1] the smectic state of the nanoparticles is expected to provide some advantages over other types of lipid nanoparticles like colloidal fat emulsions and solid lipid nanoparticles in terms of physicochemical stability and drug loading capacity. Lipid nanoparticles like colloidal fat emulsions, smectic or solid lipid nanoparticles are thermodynamically unstable and require adequate stabilization which is achieved by admixture of emulsifiers. In addition to lowering the interfacial tension, emulsifiers increase the nanoparticle stability by providing electrostatic and/or steric repulsion due to surface modification. The stabilizer system may, however, affect the phase behavior – in particular crystallization and polymorphism – of dispersed lipidic material as shown, e.g. for alkane [10,11] and triglyceride [12–15] dispersions.

Cholesteryl myristate (CM, Fig. 1) was chosen as model for the evaluation of dispersions of supercooled smectic nanoparticles due to its favorable physicochemical properties (enantiotropic phase behavior and nanoparticle crystallization around 0 °C). The phase behavior of CM nanoparticles has been extensively studied in comparison to that of the bulk lipid by DSC, and small- (SAXS) and wide-angle X-ray scattering (WAXS) to clarify its general properties in the colloidal state [1,2]. Interestingly, a characteristic, very complex crystallization pattern was observed when the nanoparticles were stabilized on the basis of phospholipids [1,2]. Although CM does not exhibit polymorphism in the crystalline state [6], a

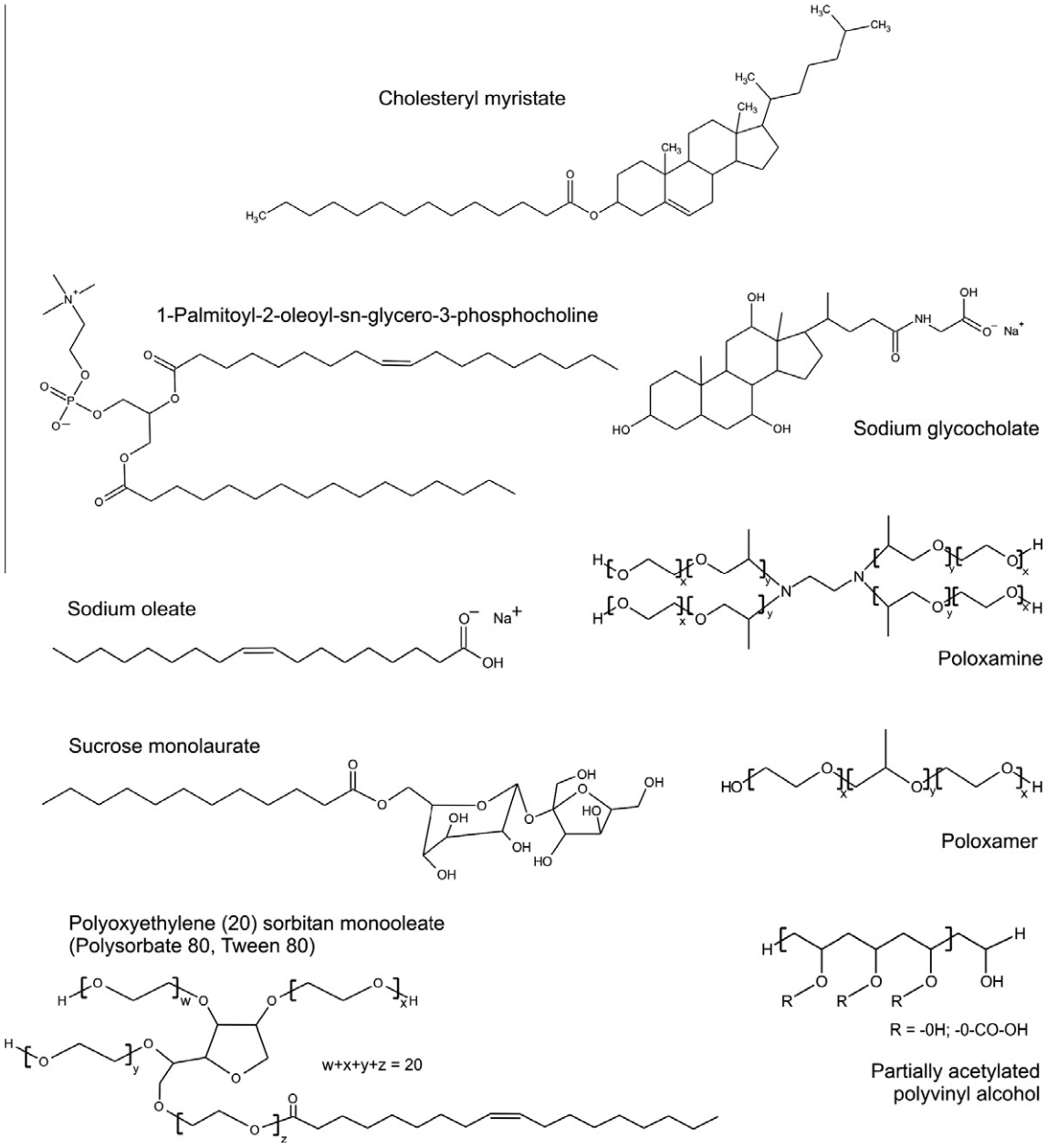

Fig. 1. Chemical structure of cholesteryl myristate and the emulsifiers used in this study (except gelatin polysuccinate). For lecithin – a mixture of phosphatidylcholines with different fatty acid residues – the structure of the most common palmitoyl-oleoyl-phosphatidylcholine (POPC) is given.