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Do nanoparticles prepared from lipids solid at room temperature always possess a solid lipid matrix?

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Abstract

Nanoparticles prepared by melt-emulsification from lipids solid at room temperature do not always represent suspension particles. Dispersed trilaurin forms metastable supercooled melts at room and refrigerator temperature. Such systems can be considered as o/w emulsions but not as dispersions of solid lipid nanoparticles.

Keywords: Solid lipid nanoparticle; Supercooled melt; Trigylceride; Trilaurin; Emulsion

Solid nanoparticles prepared by melt-homogenization of solid lipids have recently been suggested as a new kind of drug carrier system inter alia for intravenous administration (Lucks et al., 1992; Siekmann and Westesen, 1992). By the use of particles with a solid lipid matrix, stability problems, e.g., drug leakage or coalescence, often observed for drug-loaded lipid dispersions such as emulsions or liposomes may be overcome. Moreover, drug release from the solid matrix is supposed to be degradation controlled and thus slower than diffusion-controlled release from emulsions.

Compositions of lipid nanoparticles that are exclusively based on physiological compounds avoid the toxological problems often described for polymeric nanoparticles. Lipids such as tristearin, tripalmitin, trilaurin, hard fat or cetyl palmitate (Siekmann and Westesen, 1992; Maaβen et al., 1993; Müller et al, 1993; Westesen et al. 1993; Schwarz et al. 1994) have been used for the production of lipid nanoparticles.

Physicochemical characterization of nanoparticulate tripalmitin and hard fat dispersions revealed a solid, crystalline state of the particles (Siekmann and Westesen, 1992,1994; Westesen et al. 1993). The recrystallization of the colloidally dispersed materials occurred, however, at lower temperatures than that of the bulk material (Westesen et al. 1993; Siekmann and Westesen, 1994). The increased supercooling of the nanoparticles and their lower melting point was attributed inter alia to the colloidal size of the lipid particles.

As the advantages discussed for these novel drug carrier systems are essentially based on the solid state of the particles, the solidification of the particles after the homogenization process

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has to be ensured. Therefore, supercooling must be considered when preparing lipid nanoparticles by melt-homogenization.

In the present study, the formation and recrystallization tendency of nanoparticles prepared from molten triglycerides was investigated. Trilaurin, trimyristin, tripalmitin and tristearin (Dynasan, Hüls AG) dispersions were prepared by high-pressure melt-homogenization (Micron Lab 40, APV Gaulin; 5 cycles at 800 bar) (Table 1).

All triglycerides yield lipid particles in the nanometer size range as determined by photon correlation spectroscopy (PCS, Zetasizer 3, Malvern Instruments) (Table 1). The physical state of the particles was investigated by differential scanning calorimetry (DSC, Perkin Elmer DSC 2-C). Nanoparticles of tristearin and tripalmitin are crystalline when stored at room temperature. Under the same conditions, colloidally dispersed trimyristin and trilaurin particles remain in the liquid state for at least several months of storage. The existence of the particles in a solid amorphous state appears hypothetical from theory as well as from practice, since the presence of such particles should lead to a DSC-detectable glass transition. According to DSC, recrystallization of the trimyristin particles starts at about 10°C while the trilaurin dispersions retain the state of emulsions even at refrigerator temperatures over several months.

As a result of their small particle size lipid nanocrystals melt about 3–5°C lower than the corresponding bulk material. Crystallization of the molten lipids is retarded by about 20°C in the colloidal dispersions compared to the bulk lipids. Supercooling increases from about 38°C for tripalmitin and tristearin dispersions over 44°C for trimyristin particles to 51°C for the trilaurin dispersions and thus increases with decreasing triglyceride chain length (Table 1). The nucleation tendency appears to be greater in triglycerides with longer chains.

Obviously, nanoparticles prepared from triglycerides solid at room temperature do not necessarily recrystallize on cooling to common storage temperatures. If recrystallization of the particles is not enforced by cooling the dispersion below a critical recrystallization temperature, the particles can remain in the supercooled state for a long period of time.

According to the present results, it must be assumed that the data on so-called solid lipid nanoparticle dispersions prepared from trilaurin melts (Maaβen et al., 1993; Müller et al., 1993; Schwarz et al., 1994) were not obtained on dispersions of solid particles but on emulsions of

Table 1
Preparation parameters and characteristics of triglyceride dispersions

Lipid (10%)	Emulsifier composition	Temperature of preparation (°C)	Approximated PCS mean particle size by number (nm)	Melting temperature (°C) (β-form)		Recrystallization temperature (°C) (α-form)		Supercooling (°C)	
				SLP	bulk	SLP	bulk	SLP	bulk
D112	a	70	108	43 [a]	47	−8	11	51	36
D112	b	70	61	43 [a]	47	−8	11	51	36
D114	a	75	116	53	56	9	28	44	28
D114	b	80	93	53	56	8	28	45	28
D116	a	80	144	59	64	21	42	38	22
D116	b	80	87	60	64	21	42	39	22
D118	a	90	136	68	73	30	51	38	22
D118	b	80	139	68	73	30	51	38	22

SLP, solid lipid nanoparticles; D112, D114, D116, D118, Dynasan 112 (trilaurin), 114 (trimyristin), 116 (tripalmitin), 118 (tristearin). Emulsifier composition: a, 1.6% phospholipid Lipoid S100, 0.4% sodium glycocholate; b, 2% phospholipid Lipoid S100, 2% Tyloxapol. The aqueous phase contains 2.25% glycerol and 0.01% thiomersal. DSC: heating/cooling rate, 5°C/min. The values given correspond to the maxima in the heating/cooling curves. All samples had been stored at refrigerator temperature.

[a] The melting temperatures were determined after enforced recrystallization of the particles.

supercooled melts. Therefore, it should be considered that any experimental results such as size distribution, long-term stability, lyophilizability, cell toxicity, etc., obtained on liquid trilaurin nanoparticles might not be valid for solid lipid particles.

The physical state of the particles is very important from the technological as well as from the biopharmaceutical point of view. Stability problems that are related to the recrystallization process of the particles, e.g., the formation of gel-like systems (Westesen and Siekmann, 1994) or significant particle growth due to system inadequate stabilizer properties, do not occur in dispersions of supercooled melts which behave essentially as emulsions. The drug incorporation capacity of amorphous, liquid droplets might be higher than that of the crystal lattice of solidified particles. Moreover, the supercooled state of the droplets is not thermodynamically stable. Although a considerable kinetic stability was observed for the dispersions of supercooled melts, gradual recrystallization upon long-term storage cannot be excluded. This may result in products changing significantly in properties upon storage. In contrast to supercooled trilaurin nanoparticles which cannot be forced to recrystallize above 0°C, supercooled trimyristate particles will crystallize immediately when stored below their critical recrystallization temperature of around 10°C. Recrystallization processes may, however, lead to stability problems such as gelling or expulsion of incorporated drug. As these phenomena are random processes, the pharmaceutical quality of such kind of carrier system would be difficult to ensure, especially if the dispersions are intended for parenteral administration.

The results of this study emphasize the necessity of a comprehensive physicochemical characterization of colloidal drug carrier systems. The properties of colloidally dispersed substances, such as recrystallization and melting temperatures or the kinetics of polymorphic transitions, can differ significantly from that of their bulk material. Only investigations on the native dispersions can give reliable information on the characteristics of the dispersed material that have to be determined for each single composition (lipid, emulsifiers). Reports lacking declaration of the lipid composition used for the dispersions (e.g., Lucks et al., 1992) can only be interpreted with caution, and any results published for trilaurin nanoparticle dispersions (Maaβen et al., 1993; Müller et al., 1993; Schwarz et al. 1994) probably give no information on the properties of solid lipid nanoparticles.

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