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Research paper

Characterization of solidified reverse micellar solutions (SRMS) and production development of SRMS-based nanosuspensions

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Abstract

Solidified reverse micellar solutions (SRMS), i.e. binary mixtures of 30–60% (w/w) lecithin and two different hard fats, were investigated regarding their physicochemical properties and the influence of lecithin on solid lipids. For this purpose, the systems were characterized with X-ray and thermal analysis, transmission electron microscopy (TEM) and photon correlation spectroscopy. The melting point (m.p.) of the solid lipids, which is a crucial parameter of the solid state, was not altered up to a lecithin concentration of 50% whereas reverse micelles were likely to be frozen still in the solid state. In addition, solubilities of 17β-oestradiol-hemihydrate, pilocarpine base and hydrochloride in the SRMS melt were studied for evaluation of the drug carrier potency. Drug solubilization in the SRMS melt increased linearly with rising amount of lecithin.

SRMS-based nanosuspensions were developed with a given lecithin/hard fat ratio of 1:1 (w/w). High-pressure homogenization was applied on cold to avoid lecithin loss. Optimization of the systems in terms of a variation of the homogenizing parameters such as pressure, number of cycles and temperature resulted in nanoparticulate systems with a polysorbate 80/SRMS ratio of 1:5 (w/w), and a total amount of 5 and 15% (w/w) SRMS, respectively. Production temperatures near the lipid m.p. proved best to be maintained by varying the pressure, yielding small nanoparticles with a narrow particle size distribution. The solid lipid nanoparticles were characterized with X-ray and thermal analysis as well as TEM. The crystalline particles (β modification) are of anisometrical shape and have transition temperatures far below the bulk m.p. due to the colloidal character of the systems.

Keywords: Reverse micellar solution; Lecithin; Hard fat; Nanosuspension; Solid lipid nanoparticles; High pressure homogenization; Physicochemical characterization; 17β-oestradiol-hemihydrate; Pilocarpine base; Pilocarpine hydrochloride

1. Introduction

Reverse micellar solutions (RMS) consisting of lecithin (30% w/w) dissolved in an oily vehicle, e.g. isopropylmyristate or middle-chain triglycerides, transform into a lamellar mesophase on contact with water [1,2]. This application-induced transformation into a semisolid system of liquid crystals enables controlled release of solubilized drugs [3,4]. A solid analogue consisting of lecithin and solid triglycerides which are used as suppository bases shows the same transformation on contact with water after melting at the site of application [5]. The first aim of the present contribution is to further characterize such solidified reverse micellar solutions (SRMS), especially those with higher contents of lecithin. Therefore, binary mixtures of two different hard fats with lecithin were investigated with respect to the influence of lecithin on solid lipid properties.

Due to low acceptance of oily systems for ophthalmic use, a system with improved applicability had to be developed. We decided for the manufacturing of aqueous nanosuspensions based on SRMS. A second aim of this study is the characterization of these SRMS-based nanosuspensions.

Solid lipid nanoparticles are biodegradable particles of lipids with a particle size up to 1000 nm and in a solid state at room temperature. These particles are dispersed in an aqueous solution which usually contains one or more surfactants [6]. Solid lipid nanoparticles have been proposed

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for controlled release of solubilized or dispersed drugs [7–9]. However, the aspect of drug loading capacity is discussed very controversially [7,9,10]. Factors determining drug loading capacity are the solubility of the drug in the molten lipid, the chemical and physical structure of the solid lipid matrix and the polymorphic state of the lipid [9].

For the manufacturing of solid lipid nanoparticles, different techniques may be applied. By using hot homogenization technique, the molten lipid (with or without drug) is dispersed in a hot aqueous surfactant solution. The resulting primary emulsion is then homogenized with a high pressure homogenizer at temperatures far beyond the melting point (m.p.) of the lipid and afterwards cooled down for solidification of the particles [6]. Another method for SLN manufacturing is the precipitation in o/w emulsions [11,12]. By using this technique, triglycerides are first dissolved in an organic solvent and then emulsified within an aqueous phase by high-pressure homogenization. Subsequent evaporation of the organic solvent results in the precipitation of triglyceride nanoparticles.

In contrast to the most common manufacturing procedure for solid lipid nanoparticles, which is hot high-pressure homogenization of molten lipids, cold high-pressure homogenization [6] is applied in order to prevent phospholipid transformation or loss and leakage of solubilized drugs. Furthermore, the nanosuspensions are characterized with regard to their physicochemical properties.

2. Materials and methods

2.1. Materials

Softisan® 100 (S100) and Softisan® 142 (S142), solid triglyceride mixtures with a m.p. of 309 and 316 K, were supplied by Condea (Witten, Germany). Phospholipon® 90 G (P90G), a purified soybean lecithin with at least 90% (w/w) phosphatidylcholine, was provided by Nattermann Phospholipid GmbH (Köln, Germany), polysorbate 80 (PS80) and sorbitol were purchased from Caesar and Loretz (Hilden, Germany), thimerosal was purchased from Merck KGaA (Darmstadt, Germany), pilocarpine base (PB) and hydrochloride (PHCl) were supplied by Dr Winzer Pharma (Olching, Germany), 17β-oestradiol-hemihydrate (EST) was provided by Jenapharm (Jena, Germany). Water was used in bidistilled quality.

2.2. Manufacturing of solidified reverse micellar solutions

A binary mixture of 30–60% (w/w) P90G and S100 or S142, respectively, was stirred with a Teflon coated magnet at a temperature of 333 K until a transparent yellow melt was obtained. Then, the homogeneous mixture was stirred at room temperature until solidification.

After characterization of the different SRMS, a 1:1 (w/w) mixture of P90G and S100 or S142, respectively, was chosen for preparation and further characterization of nanosuspensions. Solid 1:1 (w/w) mixtures are abbreviated to SRMS100 and SRMS142, respectively, depending on the type of solid lipid.

2.3. Manufacturing of nanosuspensions

SRMS100 or SRMS142 were ground in melting nitrogen for 15–20 min (seven grinding processes). The frozen SRMS powder was dispersed in an aqueous solution of PS80 under stirring for 20 min with a Teflon coated magnet (during screening of emulsifier concentration) or for 90 s at 13000 rpm with an Ultra-Turrax T25 basic (Ika, Staufen, Germany) to yield a content of 5 or 15% (w/w) of SRMS in the dispersion.

After screening of the emulsifier concentration, the suspensions were manufactured with an emulsifier/SRMS ratio of 1:5 (w/w) and the systems were preserved with 0.005% (w/w) thimerosal except for those which were cooled in an ice bath.

An EmulsiFlex-C5 (Avestin, Ottawa, Canada) was used for high-pressure homogenization. The coarse suspension was passed through the apparatus first without pressure for two cycles in order to disrupt greater agglomerates and was then homogenized discontinuously at a pressure of 1000 or 1500 bar, respectively, for up to 30 cycles. The following conditions were used for temperature equilibration of the homogenization procedure:

1. No temperature equilibration was applied (room temperature, RT).
2. Just a cooling coil behind the outlet tubing was immersed into ice water (CC).
3. The whole homogenizer including the cooling coil (see condition 2) was placed into an ice bath (ICE).

For screening of emulsifier concentration, condition 3 was used. After manufacturing, the suspensions were stored at a temperature of 278–281 K overnight. Systems, which were produced for thermal and X-ray analysis, were isotonized with 4.75% (w/w) sorbitol related to the aqueous phase and homogenized continuously for 20 cycles at 1000 (SRMS100 systems) or 1500 bar (SRMS142 systems).

2.4. Wide angle X-ray diffractometry

Wide angle X-ray diffractometry (WAXD) measurements of the SRMS were performed in an aluminium sample holder with a PW 1050/25 X-ray goniometer connected to a PW 1710 generator including a PW 2213/20 X-ray tube with a copper anode (Philips, Kassel, Germany). A nickel foil served as K_β filter. The tube voltage was 40 kV and the anode current 25 mA. A PW 1711/10 xenon counter was linked to the analyzing software

PC-APD (Philips, Kassel, Germany) for interference detection.

WAXD studies of liquid systems were carried out for 12 h in a rotating glass capillary with a Debye–Scherrer X-ray camera PW 1024/10 (Philips, Kassel, Germany) connected to a PW 1830 generator including a PW 2253/11 X-ray tube with a copper anode (Philips, Kassel, Germany). A nickel foil served as K_β filter. The tube voltage was 40 kV and the anode current 40 mA. Interference detection was achieved with Structurix D7 FW X-ray films (Agfa–Gevaert, Mortsel, Belgium).

2.5. Differential scanning calorimetry

For thermal analysis, a differential scanning calorimeter DSC 220 C with disk station SSC 5200 H (Seiko, Tokyo,

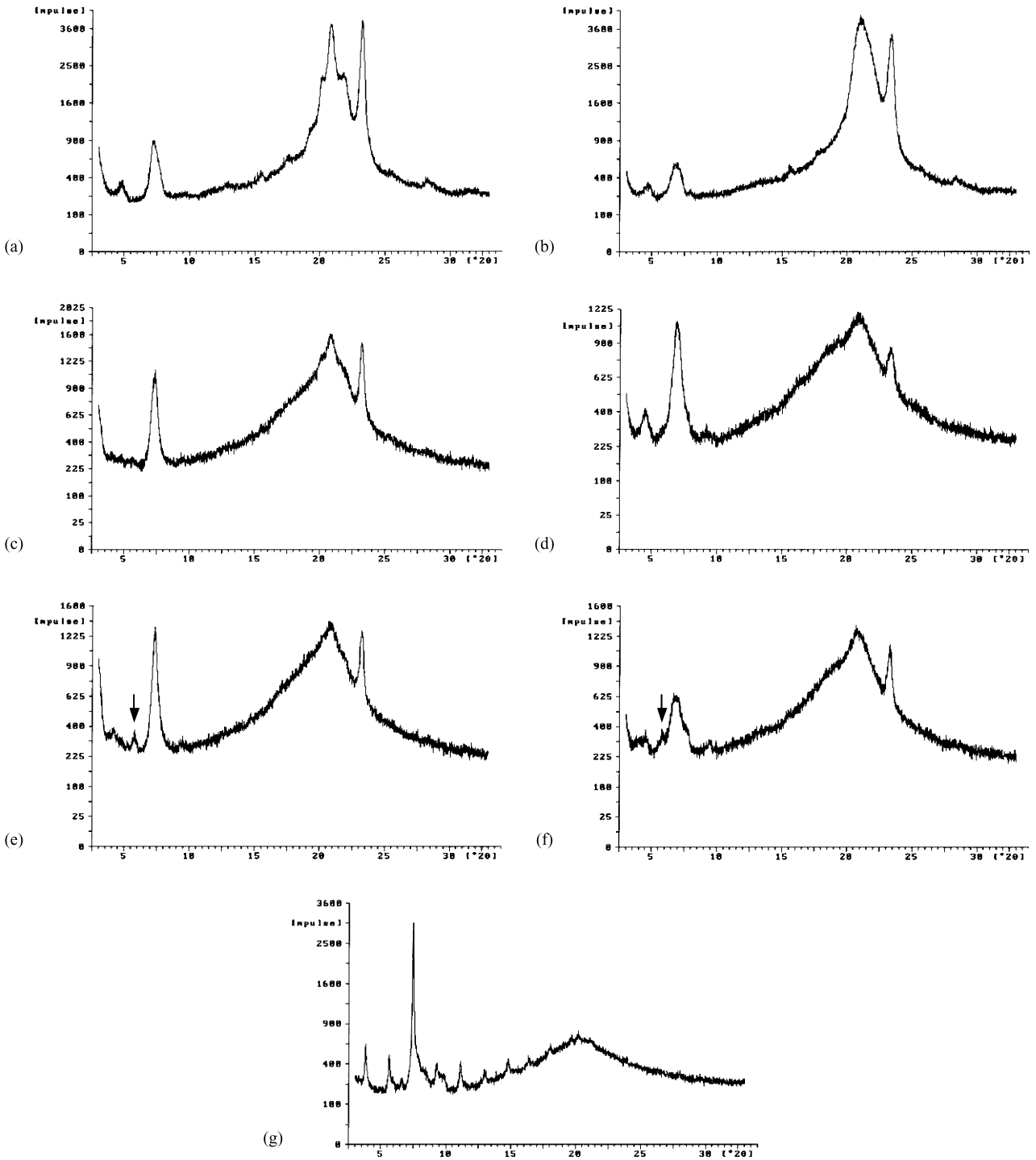

Fig. 1. Wide angle X-ray diffraction patterns of (a) S100, (b) S142, (c) S100 with 50% P90G, (d) S142 with 50% P90G, (e) S100 with 60% P90G, (f) S142 with 60% P90G and (g) P90G.

Japan) was used. Samples were measured in aluminium pans (C3-Analysentechnik, Baldham, Germany) and the sample weight was around 5 mg for both SRMS systems and nanosuspensions. Samples were investigated within a temperature range of 2–60 or 2–75 °C with a heating rate of 5 K min^{-1}.

2.6. Transmission electron microscopy of freeze-fractured specimen

Samples were shock-frozen in melting nitrogen at 63 K between two flat gold holders. The frozen systems were fractured at 173 K in a BAF 400 instrument (Balzers, Wiesbaden, Germany). Specimens were shadowed with platinum/carbon (2 nm) at 45° and with pure carbon (20 nm) at 90° for replica preparation. After cleaning in concentrated sulphuric acid and water, the replicas were viewed on uncoated grids with a transmission electron microscope EM 300 (Philips, Kassel, Germany) at a voltage of 80 kV.

In contrast to nanosuspensions which were shock-frozen immediately after placing between the gold holders, melts of pure hard fats and SRMS were first solidified between the gold holders. Freezing and fracturing of these systems were performed after 1 day of storage to allow recrystallization.

2.7. Photon correlation spectroscopy

Photon correlation spectroscopy (PCS) measurements were performed with a Zetasizer 3 (Malvern, Herrenberg, Germany) modified with a He/Ne laser model 127 (Spectra Physics, Mt. View, CA, USA). After dilution with filtered bidistilled water to avoid multiscattering events, the different suspensions were investigated at an angle of 90° in a measuring cell AZ 10 equilibrated at 293 K. Lecithin hard fat mixtures were investigated undiluted at a temperature of 323 K.

2.8. Determination of drug solubility in the SRMS

For investigations on drug solubilization in the SRMS, PB or EST were added to the melt of the SRMS and then solubilized under stirring at a temperature of 333 K whereas PHCl had to be added in various amounts of an aqueous solution of the drug (33.3% w/w). The hereby incorporated water, which intermediately transformed the melt into a lamellar mesophase, was evaporated while stirring the melt. The solubility limit of the drugs in the SRMS melt was determined macroscopically at a temperature of 333 K in steps of 0.5% (w/w) and it corresponds to the highest drug concentration at which a transparent melt could be obtained.

3. Results and discussion

3.1. Characterization of lecithin hard fat mixtures

To study crystallinity of the triglycerides and SRMS, i.e. lecithin hard fat mixtures, wide angle X-ray studies were performed. Both, S100 (Fig. 1a) and S142 (Fig. 1b) crystallize in a metastable β′ modification according to [13,14] as may be recognized from typical interferences which belong to interlayer spacing of 0.38 ($2\theta = 23.4°$) and 0.42 nm ($2\theta = 21.1°$). No additional interferences appear with increasing P90G concentrations up to 50% (Fig. 1c and d) indicating a dissolution of the lecithin whereas addition of 60% P90G results in a typical interference of phospholipid (Fig. 1g) at 1.52–1.57 nm ($2\theta = 5.6–5.8°$) which points at lecithin association and orientation in distinct units (Fig. 1e and f, arrows). In terms of the long range order at low angles, both, lecithin and triglycerides exhibit an interference of 1.21–1.34 nm ($2\theta = 6.6–7.3°$). However, the intensities of this interference differ. With increasing phospholipid content, the intensity of this

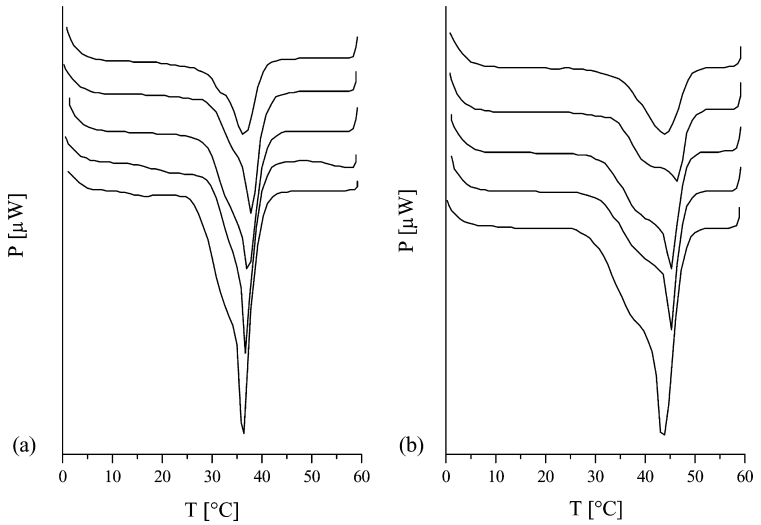

Fig. 2. DSC thermograms of (a) lecithin S100 mixtures, (b) lecithin S142 mixtures with varying P90G contents of 0, 30, 40, 50, 60% (w/w), (bottom to top), respectively.

interference increases in relation to the other triglyceride interferences. High intensities in this range could also be obtained with pure P90G (Fig. 1g).

Thermal analysis of lecithin hard fat mixtures shows no significant influence of the phospholipid on the melting behaviour of the triglycerides in terms of peak minimum and onset temperature (Fig. 2). S100 as well as S142 and their mixtures with lecithin exhibit a considerable shoulder derived from a wide fatty acid distribution within the triglycerides. With an increasing amount of P90G the melting enthalpy decreases linearly in consequence of non-crystallized phospholipid (Table 1). Extrapolation to a zero enthalpy gives a hard fat concentration of about 10 (S100) or 11% (S142). To this extent, the incorporation of lecithin seems to disturb the recrystallization of the triglycerides.

Freeze-fractured samples of S100 and S142 as well as their mixtures with 50% (w/w) P90G were investigated by transmission electron microscopy (TEM). Typical features of the triglyceride lattice such as planar layers were observed with all systems. Fig. 3a shows a characteristic micrograph of S100. In contrast, only the systems containing lecithin exhibit in addition spherical associates of about 10–20 nm size which are located between layered areas (Fig. 3b). This finding suggests the existence of reverse micelles even in the solid state of the system, i.e. the conservation of this type of lecithin associates during solidification of the melt. PCS measurements at a temperature of 323 K demonstrate a size of associates in the SRMS100 and SRMS142 melt of 12.2 ± 3.1 and 11.1 ± 3.5 nm ($n = 6$), respectively. At a lecithin concentration of 50%, one would expect an equal amount of spherical associates in the freeze-fractured sample. However, regions with spherical particles occupy a smaller area. Therefore, other types of lecithin association in the solid state such as lamellas or the localization between triglyceride molecules are very likely.

For examination of the solubilization potential of the SRMS, the macroscopically soluble drug concentration at 333 K was determined (Table 2). The solubility of EST, PB and PHCl in the melt of the SRMS with S100 increases linearly with rising amount of lecithin demonstrating drug interactions with lecithin associates.

Table 1
Melting enthalpy ±SD [mJ/mg] of lecithin S100 mixtures and lecithin S142 mixtures vs. P90G concentration ($n = 4$)

P90G [% w/w]	Lecithin S100 mixtures	Lecithin S142 mixtures
0	186.5 ± 3.7	193.5 ± 3.2
30	119.9 ± 1.1	122.6 ± 4.4
40	100.8 ± 3.1	102.0 ± 6.0
50	84.5 ± 3.7	84.9 ± 5.5
60	62.1 ± 3.2	64.2 ± 1.3
Linear fit	$y = -2.06x + 184.7$	$y = -2.15x + 191.0$
R	0.999	0.998

Table 2
Macroscopically soluble concentration of EST, PB and PHCl in lecithin S100 mixtures vs. P90G concentration

P90G [% w/w]	EST [% w/w]	PB [% w/w]	PHCl [% w/w]
0	0.6	3.5	0
30	6.5	5.5	2.5
40	9.0	6.5	3.5
50	10.0	7.0	4.5
60	12.0	8.0	6.5
Linear fit	$y = 0.19x + 0.77$	$y = 0.07x + 3.43$	$y = 0.10x - 0.3$
R	0.997	0.997	0.983

3.2. Screening of emulsifier concentration

A 1:1 (w/w) mixture of P90G and S100 (SRMS100) or S142 (SRMS142), respectively, was chosen for the manufacture of nanosuspensions. These systems with 50% lecithin exhibit a high solubilization capacity for drugs without being as sticky and soft as systems with 60% lecithin.

Nanosuspensions with 5% (w/w) SRMS were prepared by cold high-pressure homogenization at 1000 bar with different amounts of PS80. A sufficient amount of emulsifier has to be added for stabilizing the nanosuspensions, because the high phospholipid content in the particles is intended for drug solubilization in later studies and is only partially present at the particle surface. After pre-emulsification with a magnetic stirrer and subsequent homogenization on cold, the particle sizes and particle size distributions were not sufficiently small and narrow. An emulsifier/SRMS ratio of 1:5 (w/w) proved to be the best compromise in terms of a distinct particle size reduction with an emulsifier concentration as low as possible to minimize irritation potential after administration. No further distinct reduction in size could be obtained with higher concentrations of PS80 whereas a ratio of 1:10 leads to systems with even larger particles (Table 3). Furthermore, the latter systems transform into a semisolid state within 4 weeks of storage at room temperature. This kind of gel formation has been described by Westesen and Siekmann [15] as an incomplete emulsifier adsorption on crystal interfaces.

Table 3
Mean particle size ±SD [nm] in dependence of the PS80/SRMS ratio after homogenization at 1000 bar for 10 cycles ($n = 3$)

Ratio	5% SRMS100	5% SRMS142
1:10	371.9 ± 9.9	413.5 ± 14.8
1:5	331.6 ± 13.1	312.2 ± 2.7
1:3.3	290.2 ± 7.0	336.8 ± 8.2
1:2.5	416.2 ± 12.0	323.6 ± 6.6
1:2	299.6 ± 10.1	309.5 ± 5.7

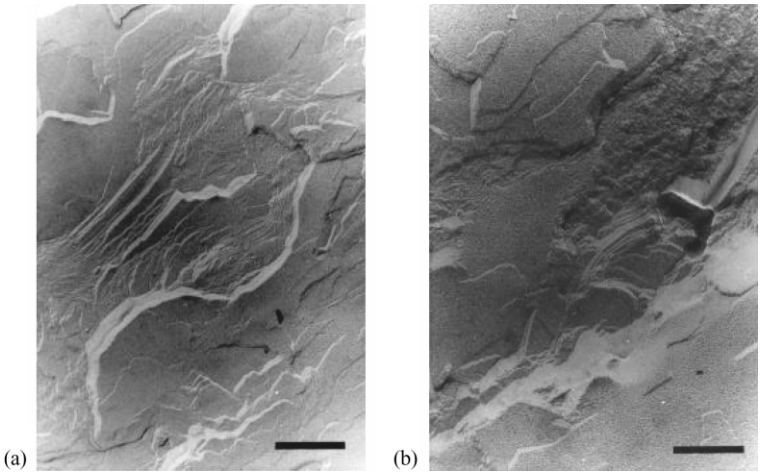

Fig. 3. TEM micrographs of (a) S100 (bar = 303 nm), (b) S100 with 50% P90G (bar = 182 nm).

3.3. Optimization of homogenizer adjustments

For optimization of the homogenization process, systems with a PS80/SRMS ratio of 1:5 were investigated further. Prior to the high-pressure homogenization, the systems underwent a pre-emulsification with an ultra-turrax instead of a magnetic stirrer as in Section 3.2.

In a first step, the influence of the homogenization temperature on particle size was studied. The use of an ice bath, which cools the product down to 279–283 K during homogenization, results in particle sizes of 400–800 nm with a broad distribution. The polydispersity indices of these systems vary considerably. In contrast, nanosuspensions homogenized at room temperature without cooling display significantly smaller particles with smaller polydispersity indices (Table 4).

Homogenization at room temperature was performed on SRMS100 suspensions at pressures of 1000 (product temperature 306–310 K) and 1500 bar (313–317 K), respectively (Fig. 4). Particle diameters after 20 cycles are below 80 nm and polydispersity indices are smaller than 0.3 indicating a narrow particle size distribution. Increasing pressure, temperature and numbers of cycles lead to smaller particles, although nanosuspensions of sufficiently small particle sizes and distributions could be manufactured with 1000 bar and 20 cycles.

Results from SRMS142 dispersions with higher melting points, exhibit similar particle sizes at 1500 bar, but significantly larger particles with broader distribution after homogenization at 1000 bar compared to SRMS100 systems (Fig. 5). Furthermore, using a cooling coil with a resulting product temperature of 285–291 K in combination with the lower melting SRMS100 leads to poor distributions (Fig. 4).

3.4. Characterization of nanosuspensions

PCS results are in accordance with TEM investigations of freeze-fractured suspensions. Fig. 6 shows a typical micrograph of a SRMS100 nanosuspension with diameters from 30 to 130 nm. The obtained nanoparticles exhibit an anisometrical, often platelet-like shape as also shown by Siekmann and Westesen [16,17]. Layered structures like terraces, steps and kinks could be observed within the particles demonstrating a crystalline character even after homogenization. Although the systems contain a high amount of lecithin, spherical particles with (uni)lamellar interfaces indicating liposome formation due to lecithin leakage during the homogenization process could not be found.

Thermal analysis of isotonized systems with 15% SRMS displays transition temperatures of the nanosuspensions which are 8–9 K lower than those of the SRMS bulk (Table 5). This finding is related to the colloidal dimensions of the particles and their large surface to volume ratio and is not related to a recrystallization of an α modification with a lower m.p. [18]. Furthermore, X-ray analysis shows that the nanoparticles exist in a stable β modification [13,14]

Table 4
Mean particle size (*z*-average) and polydispersity index (PI) after homogenization in an ice bath (ICE, $n = 3$) or at room temperature (RT, $n = 6$) at 1000 bar

Cycles	10		15	
System	*z*-average ± SD [nm]	PI ± SD	*z*-average ± SD [nm]	PI ± SD
5% SRMS100-ICE	587.2 ± 53.5	0.871 ± 0.123	654.8 ± 91.6	0.970 ± 0.051
5% SRMS142-ICE	461.5 ± 34.8	0.619 ± 0.087	411.3 ± 7.7	0.512 ± 0.036
5% SRMS100-RT	136.3 ± 9.7	0.457 ± 0.039	127.6 ± 8.1	0.443 ± 0.040

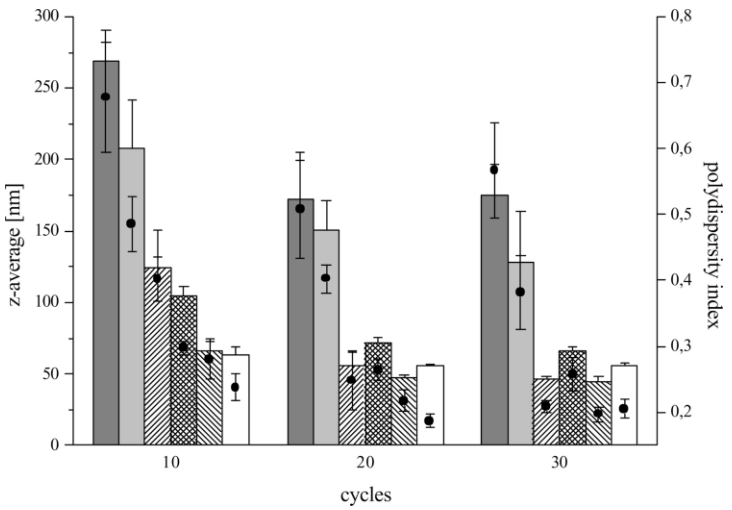

Fig. 4. Mean particle size (z-average, columns) + SD and polydispersity index (dots) ± SD vs. number of cycles. Influence of SRMS content and pressure on SRMS100 systems homogenized either at RT or with a cooling coil (CC) ($n = 6$). CC: 5%, 1000 bar ■, 15%, 1000 bar □; RT: 5%, 1000 bar ▨, 15%, 1000 bar ▩, 5%, 1500 bar ▧, 15%, 1500 bar □.

Table 5
Transition temperatures ± SD [°C] of nanosuspension (15% SRMS) and bulk material 1 day after production or recrystallization ($n = 2$)

System	Bulk ($n = 2$)	Nanosuspension ($n = 4$)
SRMS100	34.8 ± 0.2	26.2 ± 0.1
SRMS142	42.6 ± 0.2	33.7 ± 0.3

whereas the bulk materials crystallize in a metastable β' modification (see Section 3.1).

During the first 9 days of storage at room temperature, the m.p. of the nanosuspensions increases by 1–2 K (Fig. 7). This increase in m.p. goes along with an increase in particle size. After 3 weeks of storage, the particle size remains nearly constant at about 120–130 nm for SRMS100 systems and 100–110 nm for SRMS142 systems, respectively, in contrast to a particle size of 70–80 nm directly after production (Fig. 8). However, the polydispersity indices of the nanosuspensions remain constant at 0.232 ± 0.027 (SRMS100) and 0.174 ± 0.021 (SRMS142).

4. Conclusions

Liquid RMS enable controlled release of solubilized drugs after their transformation into a lamellar mesophase [3]. Moreover, they offer a high solubilization rate for substances. Drug solubility is also high in the melt of SRMS, hence, SRMS represent a potent carrier for different types of drugs. Physicochemical characteristics of the solid lipids like melting point and crystal modification are not

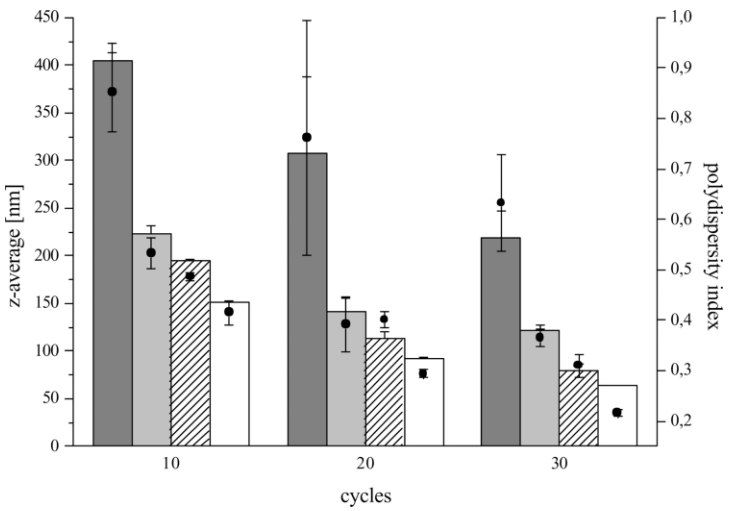

Fig. 5. Mean particle size (z-average, columns) + SD and polydispersity index (dots) ± SD vs. number of cycles. Influence of SRMS content and pressure on SRMS142 systems homogenized at RT ($n = 6$). 5%, 1000 bar ■, 15%, 1000 bar □, 5%, 1500 bar ▨, 15%, 1500 bar □.

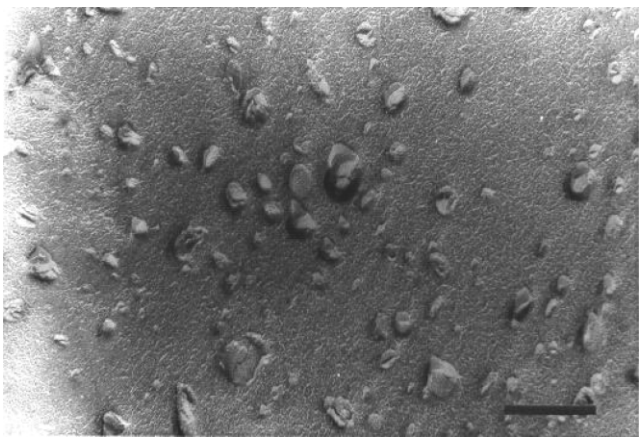

Fig. 6. TEM micrograph of SRMS100 (5%) homogenized at 1000 bar for 30 cycles at RT (bar = 238 nm).

influenced by a lecithin concentration of up to 50% and reverse micelles seem to be conserved in the solid state.

For production of SRMS-based nanosuspensions, a PS80/SRMS ratio of 1:5 is sufficient for particle size reduction. Homogenization on cold with resulting product temperatures far below the m.p. of the systems causes broad particle size distributions. However, to achieve small nanoparticles with a narrow particle size distribution, homogenization on hot is not required. Instead, the suspension temperature has to be just near the m.p. for more flexibility of the solid lipids or for a partial melting. This could be controlled by varying the homogenization pressure at room temperature. A pressure of 1000 bar results in a temperature near the m.p. of SRMS100, that of 1500 bar in a temperature near the SRMS142 m.p.

The nanosuspensions contain crystalline particles (β modification) of anisometrical shape which have a transition temperature far below the bulk m.p. due to the colloidal character of the systems. An increase in transition temperature after production coincides with an increase in particle size because of particle agglomeration or growth.

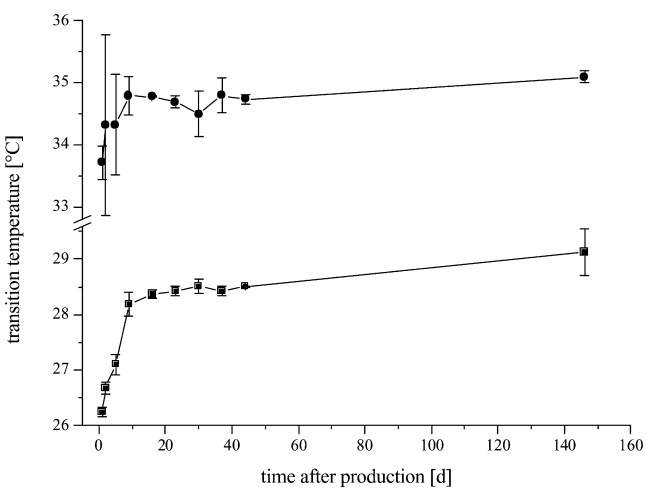

Fig. 7. Transition temperatures (± SD) of the nanosuspensions vs. time after production ($n = 4$). 15% SRMS100 (■), 15% SRMS142 (●).

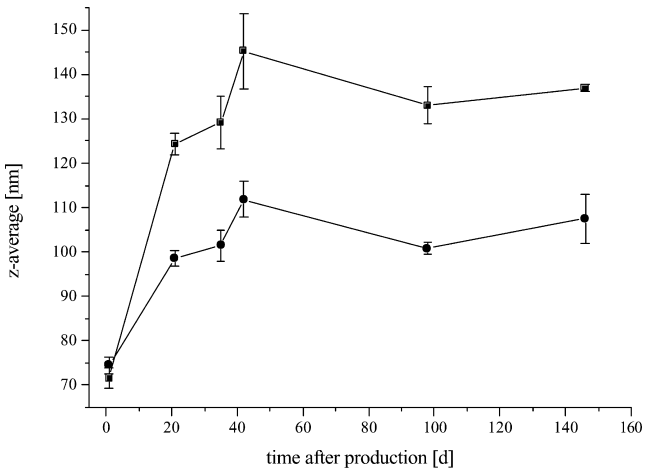

Fig. 8. Mean particle size (± SD) of the nanosuspensions vs. time after production ($n = 6$). 15% SRMS100 (■), 15% SRMS142 (●).

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