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Research paper

Liquid and semisolid SLN™ dispersions for topical application: rheological characterization

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Abstract

Aqueous dispersions of solid lipid nanoparticles (SLN™) are promising drug carrier systems for topical application. A drawback, however, is the need of incorporating the SLN dispersion in commonly used dermal carriers (creams, gels) to obtain the required semisolid consistency for dermal application. This study describes the production of SLN dispersions having the desired semisolid consistency by a one-step process. Physical characterization of these systems in terms of particle size and rheological properties revealed some interesting features. Despite the high lipid content it was possible to produce colloidal dispersions by high pressure homogenization. Continuous flow measurements revealed systems with yield point, plastic flow and thixotropy. Oscillation measurements proved the viscoelastic microstructure of the SLN dispersions. Higher concentrated SLN dispersions were found to have a prevailing elastic component in contrast to lower concentrated systems. Viscoelastic properties of a 40% SLN dispersion were found to be comparable to standard dermal preparations. Storage stability at room temperature in terms of particle size could be demonstrated over a 6-month period. The development of the gel structure of semisolid SLN dispersions is delayed comparable to commercial O/W creams with non-ionic emulsifiers. Parameters like concentration of the dispersed phase, particle size and particle shape were identified as significant factors influencing the microstructure of these complex semisolid systems.

Keywords: Solid lipid nanoparticles; SLN; High pressure homogenization; Oscillatory rheology; Viscoelastic; Topical application

1. Introduction

Solid lipid nanoparticles (SLN) [1] are promising as drug carrier for topical application. Occlusion properties which can enhance the penetration of drugs through the stratum corneum by increased hydration have been reported [2,3]. As shown for nanoemulsions, decreasing particle size can enhance drug penetration and systemic activity of drugs [4]. Similar effects of particle size reduction on penetration into the skin were found for polymeric particles [5]. Cellular viability tests proved a good local tolerability of different SLN preparations [6] and also low cytotoxicity of SLN dispersions has been observed [7]. Scaling-up of the production process to medium and large scale is easily accessible as shown for batch sizes up to 50 kg [8]. Until now, topical SLN formulations were produced by adding the SLN dispersion to a commonly used dermal carriers like hydrogels or creams to obtain a topical formulation having the desired semisolid consistency [9].

Major disadvantages of these processes are the limited SLN load in the final formulation, several time-consuming production steps and possible incompatibilities with the added ingredients (e.g. viscosity enhancer in gel or surfactants/oils in cream). It would be highly desirable to circumvent these disadvantages and to produce SLN with appropriate consistency in a one-step production process without the need of further ingredients. This goal, however, is not easy to achieve. The high lipid concentration which is needed to reach a semisolid consistency will potentially affect the homogenization efficiency, increase particle aggregation and might lead to the loss of the colloidal, particulate structure (i.e. formation of larger particles or bicoherent ointment systems).

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The present study reports on the development of highly concentrated SLN formulations with regard to topical applicability. Formulations consisting of different amounts of cetylpalmitate stabilized with sucrose palmitate were produced by high pressure homogenization (hot homogenization technique) and characterized concerning their particle size and rheological behavior. Rheological properties and in particular viscoelastic properties are important factors in different areas of pharmaceutical processes. Viscoelastic measurements are valuable tools for quality control of ingredients and final products. Viscoelasticity affects manufacturing processes like mixing, pumping, stirring, filling and sterilization. Furthermore the influence on drug release from a vehicle can be investigated by viscoelastic measurements [10]. Especially concerning the application and performance on skin, viscoelastic measurements provide important information. Consistency, spreadability, sensory properties and adherence to skin are only some examples [11]. They also permit to monitor changes during storage [12] and give valuable hints on the microstructure of complex systems [13]. This study describes the production of highly concentrated SLN dispersions having viscoelastic properties of creams but simultaneously maintain the nanoparticulate structure.

2. Materials and methods

The lipid Precifac® ATO (cetylpalmitate) was provided by Gattefossé (Weil a.R., Germany) and Cetiol®A (Lauric acid hexyl ester) by Cognis Deutschland GmbH (Düsseldorf, Germany). The surfactant sucrose stearic acid ester S1670 (Mitsubishi-Kagaku Foods Corporation) was a gift from Syntapharm (Mülheim-Ruhr, Germany). The materials were used as received.

Different SLN formulations consisting of 20–40% Precifac ATO, 5% sucrose fatty acid ester as emulsifier and bidistilled water added up to 100% (all w/w%) were produced by the hot homogenization technique with a high pressure homogenizer APV Micron Lab 40 (APV Deutschland GmbH, Lübeck, Germany). The lipid was melted at 85 °C and dispersed in the hot surfactant solution (85 °C) using an Ultra-Turrax T25 (Janke and Kunkel GmbH and Co KG, Staufen, Germany) at 9500 rpm for 1 min. This pre-emulsion was then homogenized at 85 °C by high pressure homogenization applying three homogenization cycles at 500 bar. The samples were left to equilibrate for 24 h prior to further analysis.

Particle sizes were analyzed by photon correlation spectroscopy (PCS) with a Zetasizer 4 (Malvern Instruments, UK) and laser diffraction (LD) with a Mastersizer E (Malvern Instruments, UK). Prior to particle size analysis the semisolid SLN dispersions were diluted to a lipid content of 20% with bidistilled water. PCS yields the mean particle size and the polydispersity index (PI) as a measure of the width of the distribution. The LD data were evaluated using volume distribution. A diameter 90% value of 1 μm indicates that 90% of all particles possess a diameter of 1 μm or less. All measurements were done in triplicate.

The rheological measurements were performed with a rheometer Rheo Stress RS 100 (Haake, Karlsruhe, Germany) equipped with a cone-and-plate test geometry (plate diameter 20 mm, cone angle 4°). If not indicated otherwise all measurements were carried out at a temperature of 20 ± 0.1 °C. Continuous flow measurements were performed by increasing the shear rate from 0.5 to 300 s^{-1} over 3 min followed by decreasing the shear rate from 300 to 0.5 s^{-1} over 3 min. The resulting shear stress was measured. Yield points were determined by a stress ramp with data sampling in log rate and performing two power law regression analysis. Oscillation stress sweep tests were carried out at a frequency of 1 Hz in a stress range of 0–100 Pa. Oscillation frequency sweep tests were performed over a frequency range from 0.1 to 10 Hz at a stress of 1 and 5 Pa, respectively.

3. Results and discussion

The production of SLN dispersions with lipid contents of 30, 35 and 40% cetylpalmitate led to the formation of soft to semisolid gels of different consistency. In contrast, dispersions with 10 and 20% volume fraction of the dispersed phase are still low viscous liquid dispersions with a consistency like parenteral fat emulsions. For the 30% lipid dispersion a yield point of 12.6 ± 0.3 Pa was measured which is a typical value for a topical lotion flowing under gravity [14]. Further increase of the lipid concentration to 35 and 40% resulted in much higher yield points (73.8 ± 1.7 and 88.7 ± 5.3 Pa, resp.) which are comparable to values of commonly used creme systems [15]. Thus the desired consistency can easily be adjusted by varying the lipid concentration.

Continuous shear rheometry investigations displayed plastic flow characteristics for all systems tested. The lipid particles in the dispersion tend to align with increasing shear stress which is alleviating the flow. As exemplary shown for a 30% lipid dispersion in Fig. 1, ascending and descending flow curve do not overlap and show thixotropy which is a desirable feature for semisolid drug carriers for topical application.

Particle size measurement with PCS and laser diffractometry was performed after dilution of the samples. Surprisingly it was found that the systems preserved their colloidal particle size despite their high lipid content and their semisolid gel-like character.

Table 1 presents the PCS mean diameter of the lipid dispersions with increasing lipid content. Though it can be seen that the mean diameter is increasing from 180 nm for a 20% lipid system (liquid consistency) up to 283 nm for a 40% lipid system (semisolid consistency), the particle size is still in the colloidal range and below 300 nm for all

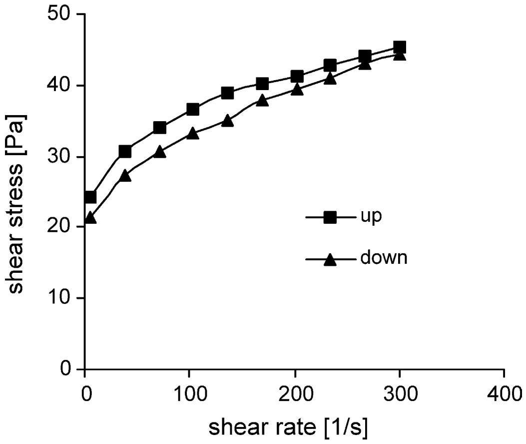

Fig. 1. Shear stress of 30% (m/m) SLN dispersion as a function of shear rate at 20 °C: up-curve, square symbols; down-curve, triangle symbols. Measurements were performed in triplicate.

investigated systems. The minor increase in particle size with increasing lipid concentration can be explained by the decrease of homogenization efficiency with increasing content of dispersed lipid phase. Laser diffraction data shown in Table 1 confirm these results. Ninety percent of the particles are below 1 μm for all tested systems. Although 35 and 40% lipid dispersions show some aggregation (indicated by the diameter 95% which is between 1 and 2 μm) long-term stability of these systems is not negatively affected by these few agglomerates. These findings are in contrast to triglyceride systems investigated by Westesen [16]. Our results indicate that individual particles are associated to a network structure by particle–particle interaction without sintering of the particles to larger agglomerates as described for tripalmitate nanodispersions [17].

In order to get comprehensive information on the rheological state of the SLN systems, oscillatory measurements yielding information about viscous and elastic properties of the investigated carrier were performed.

When conducting oscillation measurements, first the linear viscoelastic region for all tested systems has to be determined by an oscillation stress sweep test at a constant frequency. An oscillation stress sweep test is a dynamic test where the complex modulus G^* is measured as a function of stress at a constant frequency. The complex modulus is a measure of the total resistance of the system to strain. The range of stress over which G^* and phase angle δ are independent of the applied stress amplitude is called the linear viscoelastic region. Over the linear region the structure of the dispersion is intact. Thus by performing a stress sweep information concerning the stability of a system can be obtained which is also reflected in the change of the phase angle δ from the elastic region ($\delta < 45°$) to the viscous region ($\delta > 45°$) with increasing stress as exemplary shown in Fig. 2 for a 30% lipid dispersion. The viscoelastic region extends to a stress of almost 10 Pa. At this point the complex modulus decreases sharply with increasing stress. At the same time the phase angle δ increases from a value under 10° (elastic region) to a value of about 90° (viscous region) indicating a destruction of the internal structure of the sample.

Table 1
Influence of lipid content on particle size measured by PCS and laser diffraction 1 day after production

Lipid (%)	20	30	35	40
PCS-∅ (nm)	180 ± 0	208 ± 1	266 ± 3	283 ± 1
PI	0.128	0.072	0.210	0.244
D10% (μm)	0.17 ± 0	0.17 ± 0	0.17 ± 0	0.18 ± 0
D50% (μm)	0.29 ± 0.01	0.30 ± 0	0.34 ± 0	0.35 ± 0
D90% (μm)	0.53 ± 0.01	0.55 ± 0.01	0.79 ± 0.03	0.84 ± 0.02
D95% (μm)	0.62 ± 0.01	0.66 ± 0.01	1.87 ± 0.28	1.57 ± 0.14

Measurements were performed in triplicate.

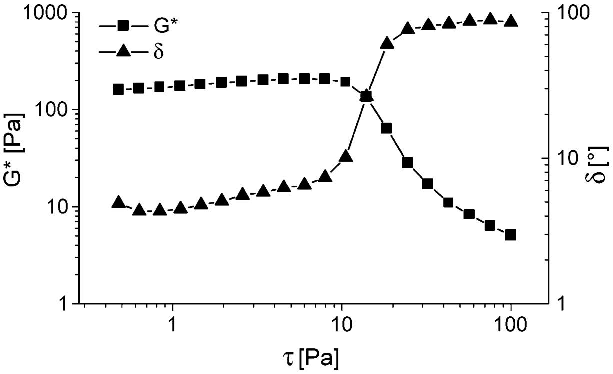

Fig. 2. Complex modulus (G^*) (squares) and phase angle (δ) (triangles) of 30% (m/m) SLN dispersion as a function of stress (τ). Measurements were performed in triplicate.

A product with high stability will have a wide linear viscoelastic region, in contrast to products with a weak and sensitive structure [18]. The stress sweep data for the SLN dispersions with different dispersed-phase concentrations are shown in Fig. 3. The complex modulus versus stress plots show a linear response (constant value of G^* independent of the stress) up to a certain critical stress which is also a measure of the yield stress of the material. Below this critical stress systems behave like elastic solids.

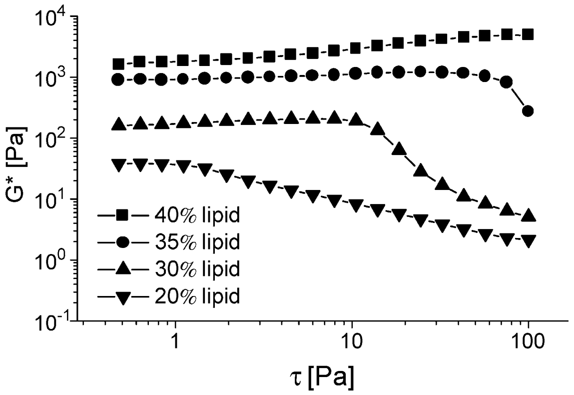

Fig. 3. Influence of volume of dispersed lipid phase on complex modulus (G^*). Measurements were performed in triplicate.

By increasing the stress over the critical stress the complex modulus drops indicating the breakdown of the network structure of the investigated SLN dispersions. The linear viscoelastic region increases with increasing volume fraction of the lipid from 20 to 40%. The increasing volume fraction of the dispersed phase leads to an increase of the particle–particle interactions, which results in a more rigid structure. Being in the viscoelastic region for all tested systems, 1 Pa was chosen as stress amplitude in all the following studies if not mentioned otherwise.

To obtain information about viscous and the elastic behavior of an investigated system and the network structure formed by particle–particle interactions an oscillation frequency sweep test has to be conducted. An oscillation frequency sweep test is a dynamic test measuring the response of a system as a function of frequency at constant stress amplitude. It reveals the storage modulus G' (elastic response) which is a measure of energy stored and the loss modulus G'' (viscous response) which reflects the energy lost. If performed within the linear viscoelastic region a frequency sweep provides a fingerprint of a viscoelastic system under non-destructive conditions. Thus the systems are examined in their rheological ground state without disrupting the structure like continuous shear techniques do [19]. The response of the dynamic measurements from systems with 20 and 30% lipid phase are shown in Fig. 4. The 20% SLN dispersion reveals an increase of G' and G'' with ascending frequency which is a typical behavior of a viscoelastic liquid [20]. At lower frequencies the loss modulus (G'') is higher than the storage modulus (G') exhibiting a more viscous than elastic response of the system. A crossover frequency at which G' and G'' become equal was noticed at about 8 rad/s. Exceeding this frequency the former plastic feature transforms into a more elastic one. The inverse of this frequency equals a characteristic time for the linear viscoelastic behavior which is called relaxation time [21]. There is no indication of gel formation for the 20% lipid dispersion. It rather shows a weak structure having a more liquid character.

Increasing the volume fraction of the dispersed phase from 20 to 30% leads to a completely different rheological behavior as a function of frequency as can be seen in Fig. 4. A strong increase of both moduli can be observed with increasing lipid concentration. The value of G', which indicates the elastic properties, increases about 30-fold from 20 to 30% dispersed lipid phase (5.9 ± 0.4 and 183.2 ± 5.5 Pa, respectively, measured at 1 Hz). In contrast to the 20% lipid dispersion both G' and G'' show only weak dependency on the applied frequency which is a typical result for a viscoelastic solid [20]. The storage modulus is about one order of magnitude higher than the loss modulus over the whole frequency range—indicating the presence of a gel-like structure. The higher values of the storage modulus show that the investigated system is more elastic than viscous in the investigated frequency range which is also demonstrated by a change in the phase angle δ. The phase angle is a good indicator of the viscoelastic nature of gel systems, being a measure of the lag in sine response after an oscillating stress has been applied to the sample [22]. Increasing the lipid concentration from 20 to 30% leads to a decrease in phase angle from 51.6 ± 1.9 to 7.6 ± 0.9 as shown in Fig. 5. For higher volume concentrations of the dispersed phase the phase angle does not alter significantly. It stays below 10° indicating elastic prevalence. The dramatic changes caused by the increase from 20 to 30% dispersed lipid phase can be attributed to the increased particle–particle interaction which comes along with the increased concentration of lipid particles in the suspension. These suspended particles link together forming a three-dimensional network structure extending through the whole system. This could be found also for other concentrated suspensions [23].

Increasing the lipid concentration of the investigated systems up to 35 and 40%, respectively, results in semisolid dispersions showing viscoelastic properties comparable to standard dermal preparations like Unguentum emulsificans aquosum. This is demonstrated exemplary for a 40% dispersion in Fig. 6. The rheological parameters storage

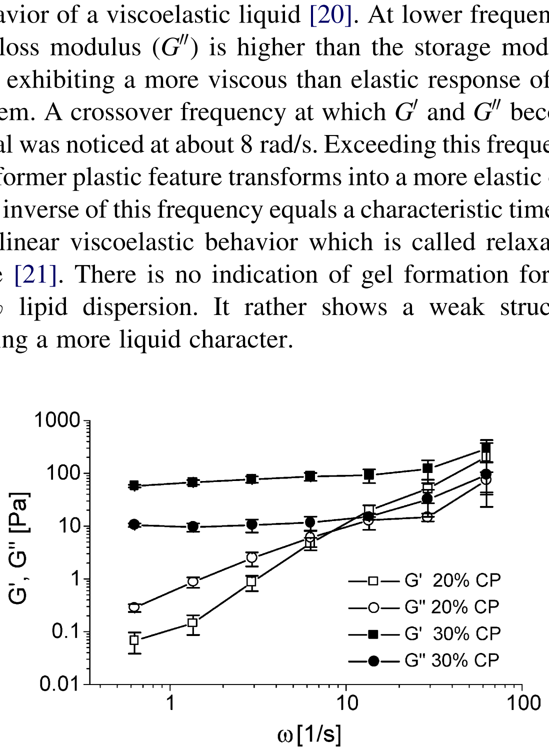

Fig. 4. Storage (G') (squares) and loss (G'') modulus (circles) of 20 and 30% lipid dispersions (empty and filled symbols, resp.) as a function of the radial frequency (ω) at a stress amplitude of 1 Pa. Measurements were performed in triplicate.

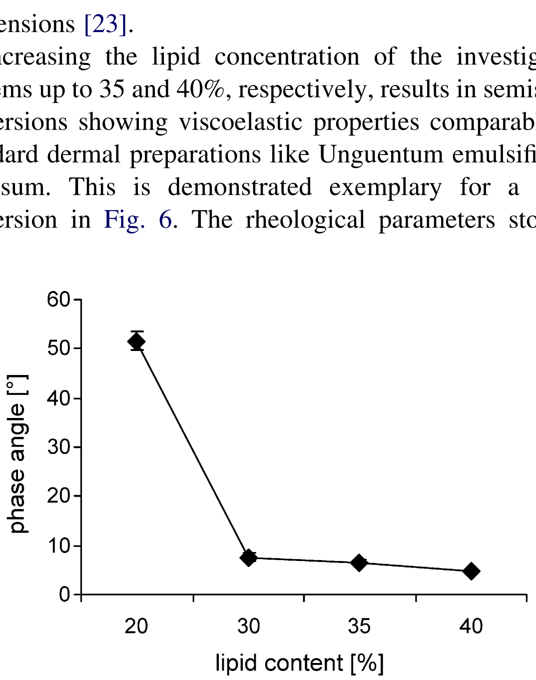

Fig. 5. Influence of the lipid content on the phase angle. Measurements were performed in triplicate.

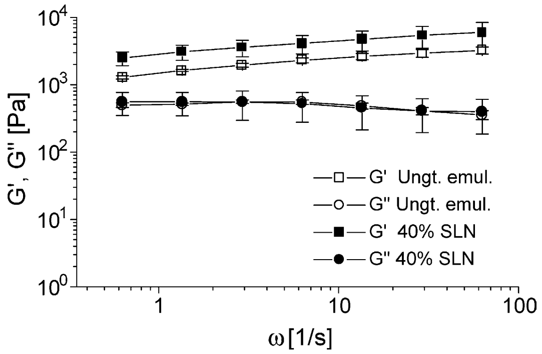

Fig. 6. Storage (G') (squares) and loss (G'') modulus (circles) of Unguentum emulsificans aquosum and 40% lipid dispersion (empty and filled symbols, respectively) as a function of the radial frequency (ω) at a stress amplitude of 5 Pa. Measurements were performed in triplicate.

and loss modulus are in the same order of magnitude as those found for Unguentum emulsificans aquosum. In addition the values of the phase angle for the 40% w/w formulation and the commercial formulation Unguentum emulsificans aquosum are in the same range (6.9 ± 1.2 and 13.4 ± 0.1, respectively) confirming the data of the frequency sweep test. Both investigated systems reveal a higher prominence of elastic over viscous behavior.

To obtain more information about the gel structure and the dependence of viscosity and elasticity on temperature, a frequency sweep measurement was carried out over a temperature range of 20–70 °C. In Fig. 7 the storage moduli of a 30% SLN dispersion (consisting of 30% cetylpalmitate, 5% sucrose ester and 65% bidistilled water) and a 30% nanoemulsion (consisting of 30% hexyllaurate, 5% sucrose ester and 65% bidistilled water) are compared. Particle sizes of both systems were comparable (mean diameter measured by PCS was 208 ± 1 and 179 ± 1 for the nanosuspension and the nanoemulsion, resp.). The shown storage moduli G' correspond to the frequency of 1 Hz. The diagram displays a huge difference in storage modulus G' of the two investigated dispersions depending on whether the carrier system consists of liquid droplets or solid particles. The value of G' at 20 °C is about 100 and 5 Pa for the nanosuspension and the nanoemulsion, respectively. Therefore, the physical state of the particles plays an important role concerning the development of a gel structure with a semisolid consistency. An important aspect that could explain these results is the different shape of the particles depending on the physical state of the matrix material (liquid or solid wax). Solid cetylpalmitate nanoparticles crystallize in a platelet like structure with a step-like surface revealing layers of defined height which was found by transmission electron microscopy (TEM) and atomic force microscopy (AFM) [24]. A similar shape was found for triglyceride nanoparticles also showing a layered crystal structure with steps after having been produced by high-pressure homogenization (hot homogenization technique) [17]. Non-spherical particles like the inorganic platelets of a Bentonit gel also show a complex gel structure termed ‘house of cards’-structure.

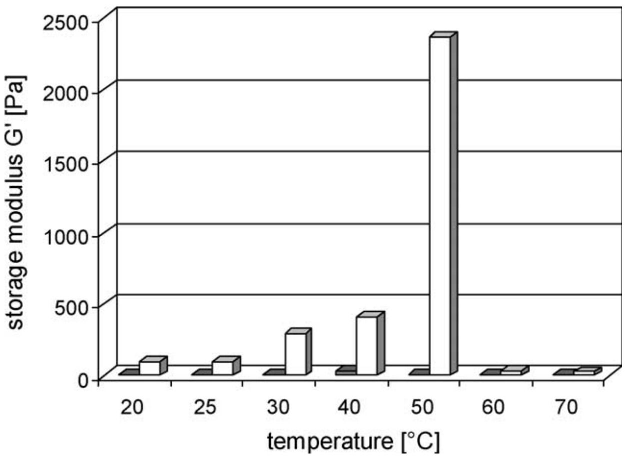

Fig. 7. Influence of temperature on storage modulus G' of 30% SLN dispersion (white columns) and 30% nanoemulsion (black columns). Measurements were performed in triplicate.

The surface area of these cetylpalmitate nanoparticles with a structured surface is much larger than for spherical liquid droplets of the reference nanoemulsion. With increasing surface area the possibility of particle–particle interactions forming a three-dimensional network structure extending through the whole system. The higher storage modulus of the nanosuspension compared to the nanoemulsion can therefore be explained by the different physical state and the following different overall particle shape of the particles. Although both systems have the same lipid content and similar particle size they show a completely different behavior concerning the storage modulus in dependence of the temperature. Considering the SLN system there is huge increase in storage modulus with temperature up to 50 °C. This increase can be attributed to the energy input by temperature increase. The particle mobility is increased by higher temperatures which leads to more particle–particle interactions (number of contact points increases) having the similar effect like increasing the volume fraction of the particles. Particles get in touch with each other more frequently and therefore the elastic response is increasing (G' is increasing, because elasticity is determined by the interaction of the particles). This effect was also found for multiple emulsions [12]. Exceeding 50 °C the storage modulus of the SLN dispersion decreases sharply. This can be attributed to the melting of the lipid nanoparticles (melting point of cetylpalmitate is about 49 °C). The particle shape alters from the platelet-like structure to round spherical droplets with less particle–particle interactions. In comparison the G' value of the 30% nanoemulsion remains fairly constant at about 5 Pa over the whole temperature range.

The effect of storage time on the particle size distribution and rheological behavior of SLN dispersions containing different amounts of lipid component was studied over a period of six months at room temperature. As shown in

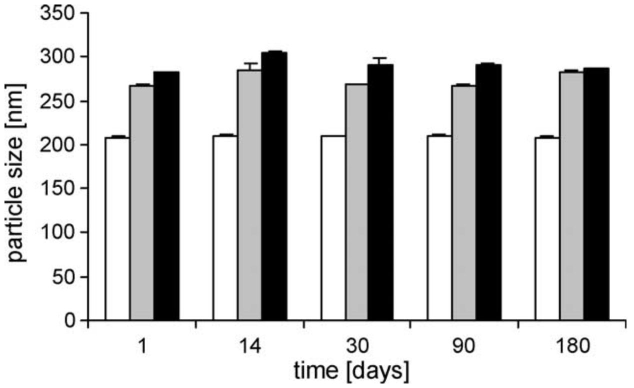

Fig. 8. Influence of storage time on particle size of 30% (white columns), 35% (gray columns) and 40% lipid dispersions (black columns) measured by photon correlation spectroscopy. Measurements were performed in triplicate.

Fig. 8 the mean PCS particle size of all investigated systems changed only slightly with storage time. This could be confirmed by the LD diameter 90% which stayed about 1 μm over the whole time range (data not shown).

Commercial O/W creams based on non-ionic emulsifiers undergo an initial period of delayed consistency development after production [25]. This fact coincides with the gel network theory saying that the consistency of a cream is due to structuring of the continuous phase via penetration and swelling of the lipid amphiphiles by the aqueous surfactant phase to form a viscoelastic gel network [26]. Concerning non-ionic surfactants this penetration is delayed and therefore consistency development is also delayed [27]. A similar process of slowly developing consistency can be noticed for semisolid SLN dispersions. Fig. 9 shows the change of the storage modulus G' and the phase angle δ with time. It can be seen that G' of a 35% lipid content SLN dispersion increases with a storage time of 180 days up to about 2000 Pa. This fact signifies that right after production the gel network of the SLN dispersion has not yet been built up completely which is comparable to the development of the lamellar crystalline gel network in O/W creams. The change of the viscoelastic properties is not caused by a change of the size of the particles but rather by their spatial arrangement. The value of the phase angle does not change significantly with time. It stays about 4–5° indicating a predominantly elastic behavior of the SLN dispersion right after production. No destabilization process which would be indicated by an increase in the phase angle could be detected. This is in contrast to creams based on non-ionic emulsifier which undergo a process of destabilization and phase separation after they have developed their consistency [25].

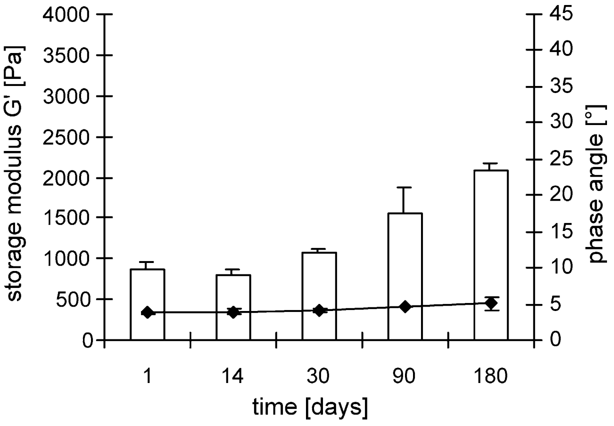

Fig. 9. Influence of storage time on storage modulus G' (white columns) and phase angle (line) of a 35% lipid dispersion (measured at a frequency of 1 Hz). Measurements were performed in triplicate.

4. Conclusions

It was possible to produce semisolid SLN dispersions in a new one-step production method by means of high-pressure homogenization. Despite the high volume concentration of the dispersed lipid phase the semisolid systems surprisingly preserved their colloidal particle size. Measurements thereof yielded particle sizes similar to liquid, low viscous SLN dispersions. These semisolid SLN dispersions turned out to have similar viscoelastic properties like standard dermal preparations. This could be proven by oscillation experiments exhibiting a predominantly elastic response over the whole frequency range. Furthermore they showed good long-term stability both concerning particle size distribution and gel structure. Compared to former processing which implied incorporating liquid SLN dispersions in semisolid drug carriers like creams or gels to get systems of semisolid consistency, the newly developed semisolid SLN dispersions combine several advantages: (1) high SLN load, (2) a simple timesaving one-step production method, (3) less ingredients, (4) no incompatibilities with other excipients and (5) easy scaling up. Physical characterization by means of continuous and oscillating rheological measurements demonstrated that drug carriers for topical application based on solid lipid nanoparticles are complex systems due to several parameters influencing the network structure of these systems. Increasing the volume concentration of the inner lipid phase of the dispersions resulted in a dramatic change of the viscoelastic properties. The former viscous solution turned into a more elastic gel just by increasing the lipid volume concentration from 20 to 30%. Furthermore it could be shown that the physical state and particle shape, respectively, of the lipid matrix plays an important role concerning the formation of a three-dimensional gel structure. It was possible to quantitatively assess the stability of semisolid SLN dispersions and to get a profound insight into the microstructure of the investigated systems. Differences and changes in microstructure of lipid dispersions which could not be detected by particle size analysis could be assessed by means of viscoelastic measurements, which turned out to be a sensitive tool in predicting the stability of solid lipid nanoparticle dispersions. The newly developed high concentrated SLN dispersions of semisolid consistency provide new opportunities for topical drug delivery using the SLN system.

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