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Research paper

Sucrose ester nanodispersions: Microviscosity and viscoelastic properties

Sebastian Ullrich, Hendrik Metz, Karsten Mäder *

Institute of Pharmaceutics and Biopharmaceutics, Martin-Luther-University of Halle, Halle (Saale), Germany

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ABSTRACT

Sucrose esters have the potential to enhance both drug solubility and drug absorption. They are therefore alternatives to the widely used glycerides in the formulation of lipid-based drug delivery systems. A simple production of aqueous nanosized drug carrier systems consisting of amphiphilic sucrose fatty acid esters using exclusively nontoxic materials has been achieved. By only using 2 wt% of the emulsifier a high viscosity of the sample could be reached. Diverse history of fabrication led to the differences in the macroviscosity of SE dispersions with equal chemical composition.

Combining the well-established oscillating rheology with the electron paramagnetic resonance technique, three orders of magnitude difference in macroviscosity between the dispersions containing 2 wt% of the amphiphilic SE were obtained, whereas the viscosities at the molecular level were all close to the viscosity of water. Viscoelastic behaviour could also be shown for these systems. TEM experiments visualized coexisting irregular micelles and lamellar structures in the SE dispersions.

The results are important to understand the complex LDDS based on amphiphilic SE

1. Introduction

Lipid-based drug delivery systems (LDDS) play a key role in pharmaceutics [1]. They are widely used to improve drug solubility and absorption [2–4], but also for controlled release applications [5]. Lipidic ingredients used for formulations include a wide range of several materials which differ in their hydrophilicity and dispersibility. A classification system, which was suggested by Pouton, is now generally accepted [6].

In many cases the majority of lipidic ingredients are based on glycerids or phospholipids. The input of high energy and shear forces are involved to produce nanoscaled systems. That is why chemical and physical stability and drug incorporation rate of LDDS are still critical points [7]. Therefore, there is a need to search for alternative LDDS. Sucrose esters (SE) have a great potential as new and alternative matrices for LDDS. This study was focussed on the SE S1170F from Mitsubishi-Kagaku Foods Corporation, which has a hydrophilic lipophilic balance (HLB) value of 11 and contains mainly mono- and di-esters of sucrose and mainly stearic acid 7 (Fig. 1). HLB value of 11 means that the hydrophilic and lipophilic properties are well balanced. Owing to the lack of own charges, SE are tolerable surfactants of low toxicity [8,9]. SE are already permitted as food additives E473 [10] and they are available in pharmaceutical quality on the market. SE are widely in use in the food and cosmetic industry [11]. Awareness of the pharmaceutical industry towards SE increased during the last years. Besides their function as stabilizers in cough syrup, SE can be found as controlled release agents in tablets. In modern drug application techniques like the dose sipping technology (DST® [12]) SE are included. Academic researchers used SE in microemulsions [13,14]. Work on a transdermal patch containing SE was recently published [15].

Few papers report on sucrose ester based aqueous systems in the submicron range [16,17]. Nanoscaled drug delivery systems, which are solely composed systems based on sucrose esters and do not form microemulsions, have not yet been described to the best of our knowledge. Until now SE were used as a minor part in the blend of ingredients either for solid oral formulations or topical application [18,19]. No work has been done to exclusively use SE as excipients. The aim of this study was to explore the potential of the sucrose esters as alternative matrices for LDDS. A detailed physicochemical characterization of LDDS is a prerequisite to understand and to optimize their properties. Therefore, a combination of various methods was applied.

Having the main focus on viscosity phenomena, we investigated the rheological behaviour. In addition to the oscillating rheology, electron paramagnetic resonance (EPR) was used to characterize the viscosity at the molecular level noninvasively [20]. An introduction to the technique and an overview of its applications are described in detail in the following articles: [20–22]. Light microscopy, PCS, DSC and TEM were applied to obtain detailed structure information.

* Corresponding author. Martin-Luther-University of Halle, Institute of Pharmaceutics and Biopharmaceutics, Wolfgang-Langenbeck-Strasse 4, 06120 Halle (Saale), Germany. Tel.: +49 345 55 25167; fax: +49 345 55 27029.
E-mail address: karsten.maeder@pharmazie.uni-halle.de (K. Mäder).

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2. Materials and methods

Ryoto® Sugar Ester S1170F was kindly provided by Mitsubishi-Kagaku Foods Corporation, Japan. Sorbitol was kindly provided by Merck, Germany. Tempol (4-hydroxy-2,2,6,6-tetramethyl-1-oxo-piperidinium) was purchased from Sigma, Germany. Glycerol (99.5%) was obtained from Carl Roth, Germany.

2.1. Sample preparation

Double distilled water was isotonized using 5.25 wt% (weight/weight) sorbitol.

S1170F (20 wt%) was hot dispersed (hd) in the isotonic solvent at 60 °C and stirred with a magnetic stirrer. This sample was named 20% hd. A part of the 20% hd sample was diluted to 2 wt% with the isotonic solvent, and cold dispersed (cd) at room temperature. This sample was named 2% cd. Another part of the 20% hd sample was also diluted to 2 wt% with the isotonic solvent but hot dispersed at 60 °C. This sample was named 2% hd.

All the samples were centrifuged at 12,000*g*, tempered at 20 °C, with a Centrifuge 5804R (Eppendorf, Germany) to remove the remaining air bubbles.

2.2. Light microscopy

A microscope (Axiolab re, Zeiss, Germany) with polarized light and an optical zoom of 50 × 0.70 was used. All the experiments were performed at 20 °C and done in triplicate.

2.3. Rheometry

A Rheometrics Fluids Spectrometer RFS II (Rheometrics Scientific, Piscataway, NJ) was used. Low viscous samples were measured with a couette geometry (cup diameter 34.0 mm, bob diameter 32.0 mm and bob length 33.3 mm). A cone plate configuration of diameter 25 mm (cone angle: 0.0995 radian; gap: 0.482 mm) was used for samples of higher viscosity. A device to avoid evaporation was installed.

Strain amplitude sweep measurements were executed at a radian frequency of 10 rad/s beginning with high strains. Strain frequency sweep measurements were carried out at a strain of 10% for working in the linear viscoelastic region and started with high frequencies. All the measurements were performed at 20 and 37 °C, and were done in triplicate. Data were evaluated using Rheometrics software (RSI Orchestrator V. 6.5.8, Rheometrics Scientific, Piscataway, NJ).

2.4. Electron paramagnetic resonance spectroscopy (EPR)

An EPR spectrometer working at a microwave frequency of about 9.5 GHz (X-Band; Miniscope MS 200 with temperature controller MO1) from Magnettech (Berlin, Germany) was used. The measurements were conducted with the following typical parameters: temperature: 20 °C; modulation frequency: 100 kHz; microwave power: 10 mW; B_0-field: 335.0 mT; scan range: 5 or 6 mT; scan time: 80 s or 96 s; modulation amplitude: 0.025 mT; accumulations: 3. A concentration of 0.1 mM of the spin probe Tempol was incorporated into each sample.

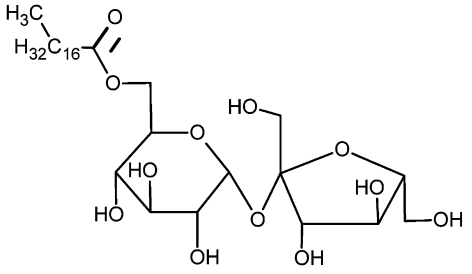

Fig. 1. Molecular structure of sucrose monostearate: the main ingredient (approx. 57%) in Ryoto Sugar Ester S1170F.

Simulation of the EPR spectra was first performed by means of Public EPR Software Tools (P.E.S.T.) V. 0.96 from National Institutes of Health (National Institute of Environmental Health Sciences, Research Triangle Park, USA) [23]. The applied optimization method was LMB1. The parameter given by the software as simple line width was the peak width at half height of the absorption line. The second applied software was EPRSIM V. 4.99 from Biophysical laboratory EPR centre (Josef Stefan Institute of Solid State Physics Ljubljana, Slovenia). For default values, the simplex optimization was used first and at last the genetic optimization was used. The method according to Katzhendler was used to calculate the viscosity in the environment of the spin probe from the ratio of the line widths [24]. The rotational correlation time τ_c as a measure of mobility was calculated from parameters obtained from the simulated spectra [25].

2.5. Differential scanning calorimetry (DSC)

For DSC measurements, samples of a definite weight were put into balanced aluminium pans with pierced lids. All samples were measured against an empty, sealed pan with the calorimeter DSC 200/1/F (Netzsch Thermal Analysis, Germany). The heating and cooling rates were 10 K/min. In the first applied protocol, two heating and cooling cycles with a temperature range from 5 to 80 °C were scanned. In another protocol, two cycles were scanned with an extended temperature range starting from room temperature to −30 °C, then to 80 °C. Other settings were kept.

2.6. Photon correlation spectroscopy (PCS)

PCS measurements were performed at a scattering angle of 173° (Malvern HPPS, Malvern Instruments, UK). The mean particle diameter, which is expressed as *z*-average, and the polydispersity of the nanosized systems were determined at 25 °C. Measurements were done in triplicate. Data treatment was performed using the Malvern software.

2.7. Transmission electron microscopy (TEM)

For transmission electron microscopy, samples were freeze-fixed using a propane jet-freeze device JFD 030 (BAL-TEC, Balzers, Liechtenstein). Afterwards, the samples were freeze-fractured and freeze-etched with a freeze-etching system BAF 060 (BAL-TEC, Balzers, Liechtenstein). The surfaces were shadowed with platinum and subsequently with carbon. The replicas were floated in sodium chloride, rinsed in distilled water, washed in acetone and rinsed again in distilled water. Thereafter, the replicas were mounted on grids and observed with a transmission electron microscope (TEM 900, Carl Zeiss SMT, Germany) operating at 80 kV. Pictures were taken with a Variospeed SSCCD camera SM-1k-120 (TRS, Germany).

3. Results and discussion

The hot dispersion of 20 wt% of the amphiphilic sucrose ester led to a highly viscous paste (20% hd sample). Further dilution in heat (hot dispersed samples) or at room temperature (cold dispersed samples) led to samples with equal chemical content but diverse viscosity. The cold dispersed (cd) sample 2% hd appeared macroscopically to be gel like, whereas the hot dispersed (hd) sample 2% was fluid like (Fig. 2). Furthermore, the application of heat

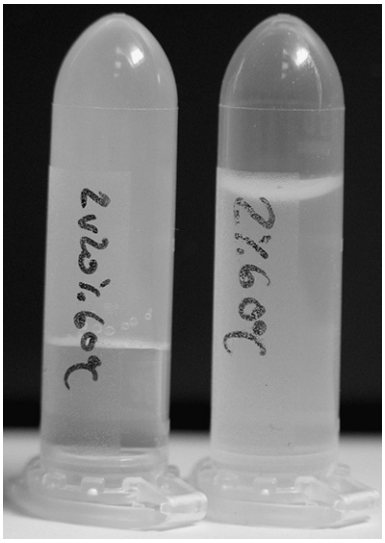

Fig. 2. Aqueous dispersions of equal sucrose ester content are shown. Left: The high viscous, cold dispersed 2% system. Right: The fluid 2% hot dispersed sample.

led the cold dispersed sample turn into a low viscous sample. However, this step was not reversible. All the formulations remained macroscopically stable for several months.

3.1. Light microscopy

Polarized light microscopy, as a simple method, was used to get first impressions on possible structures, which might have created the differences in viscosity.

No surfactant particles could be observed under the light microscope. When polarized light shone through both the 2% samples, it was partially reflected. The Tyndall effect was observed and weak textures lead one to suspect lamellar structures, which were, however, not large enough to create clearly visible evidence.

In conclusion, both the samples gave similar micrographs. No microscopic visible structure could be identified to be responsible for the differences. These findings point to particle sizes below 2 μm, if present.

3.2. Rheometry

3.2.1. Macroviscosity

In order to asses the rheological behaviour quantities like the elastic module G', the viscous module G'' and the complex viscosity η^* were of interest. The rheological measurements supported the macroscopic observations. The complex viscosity values η^* of both the samples differed up to three orders of magnitude over the whole measured range (Fig. 3). That differences in the way of production can lead to such a great difference, although both the 2% samples had equal chemical content, is remarkable. Also the induction of such an uncommonly high strength by only 2 wt% of the emulsifier is seldom found for lipidic systems and should be emphasized. Besides the described sucrose ester-based nanodispersions, bolaamphiphiles are known to show the formation of gels at low amphiphile concentration [26].

The great difference in macroviscosity at 20 °C (Fig. 3a) was found at 37 °C as well (Fig. 3b). A similar temperature independent behaviour of SE matrices below melting point was described by Fanun et al., when they examined changes in microemulsions under thermal treatment [13].

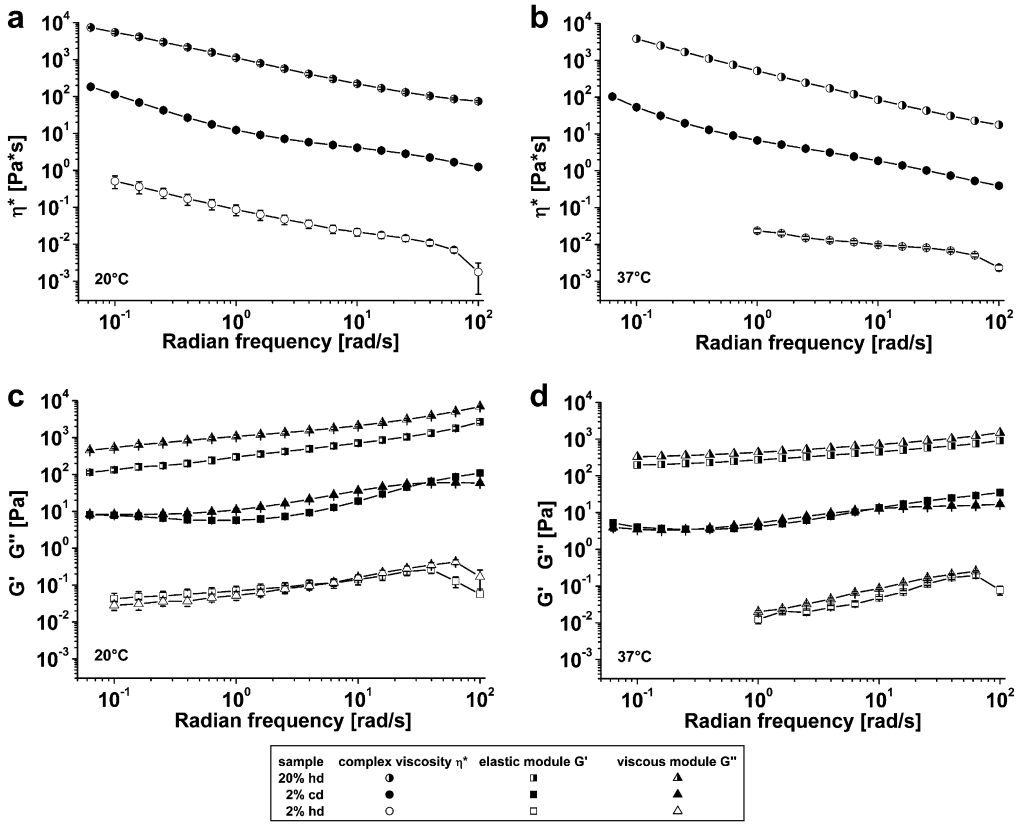

Fig. 3. Dynamic frequency measurements of aqueous sucrose ester dispersions were carried out at a strain of 10% and at 20 and 37 °C, respectively. The measured values of the complex viscosity η^*, the elastic module G' and the viscous module G'' were plotted against the radian frequency.

3.2.2. Viscoelasticity

Another effect of the SE-based nanodispersions is their viscoelastic behaviour. Data from oscillatory measurements could prove the viscoelastic properties at room and body temperature (Fig. 3c and d).

Although absolute viscosity values differed up to three magnitudes between the cold dispersed and the hot dispersed 2% samples, the elastic module (G') was about as large as the viscous module (G'') was (Fig. 3c and d). This means that changes in viscosity are not linked to significant changes in the G'/G'' ratio. The increase in elastic behaviour with the increasing frequencies is a common phenomenon for viscoelastic substances [27].

3.3. Microviscosity by EPR measurements

The microviscosity can differ from the macroviscosity. Nevertheless the mobility at the molecular level is crucial for the understanding of nanoscaled lipid-based drug delivery systems.

EPR is based on the interaction of unpaired electron spins with an applied magnetic field. The hydrophilic paramagnetic molecule Tempol (Fig. 4a) belongs to the group of stable nitroxyl radicals and was used as a drug model substance in our studies. Spectral information such as the distances between the peaks state to the polarities, are a prerequisite for comparison of spectra. The analyses of the spectral shape (line width, amplitude) allow the determination of polarity and molecular mobility. Environments of low viscosity result in isotropic EPR spectra with small lines. A typical example is Tempol in water (Fig. 4b, top). Line broadening effects can be observed in media of moderate viscosity (Fig. 4b, bottom).

For microviscosity calculations the following approach was used: if water is mixed with glycerol, no structures of a higher order influencing the viscosity are built. Therefore it can be assumed that the obtained macroviscosity complies with the viscosity at the molecular level.

The small, uncharged, hydrophilic spin probe Tempol (0.1 mM) was used as a reporter molecule. Water was mixed with different glycerol ratios and the spectra of the water glycerol solutions were recorded at 20 °C. The macroviscosities of those solutions at 20 °C were obtained from the tables [28].

The rotational correlation times (τ_c) of the water glycerol solutions were calculated as described in Section 2. The plot of τ_c as a function of viscosity [mPa s] is shown in Fig. 5.

X-Band EPR is sensitive to isotropic motions in a time range between 8 ps and 3 ns [29]. For correlation times at the margins of this range the uncertainty increases [30].

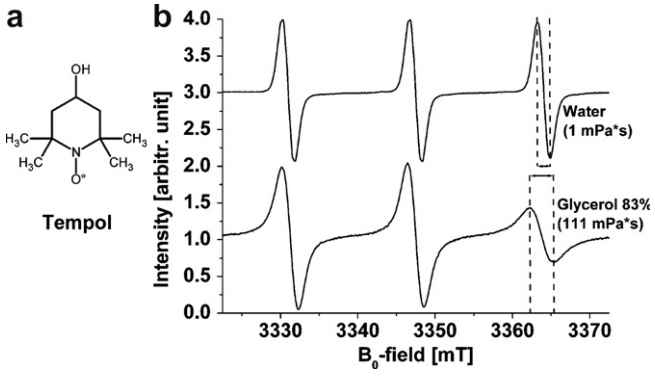

Fig. 4. (a) The molecular structure of the hydrophilic spin probe Tempol is displayed. (b) Top: Tempol dissolved in water gave a highly mobile spectrum with narrow lines. Bottom: Tempol dissolved in a water glycerol mixture (17/83) gave a spectrum of reduced mobility, which led to line broadening.

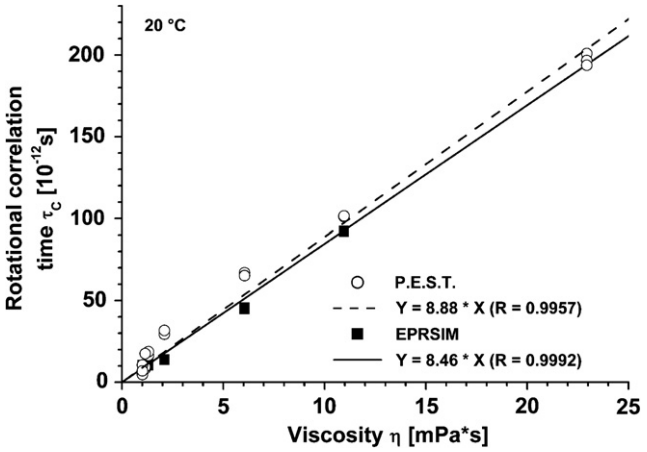

Fig. 5. Water was mixed with different glycerol ratios. The correlation times at 20 °C either simulated with P.E.S.T. or processed with EPRSIM were plotted versus the viscosities obtained from the Merck Index. The linear fits for both the methods are also shown.

In order to validate the data yielded from P.E.S.T. software-based calculations, a second simulation software EPRSIM was used, where τ_c could directly be yielded from the data of the simulated spectra. The detailed procedure of the EPRSIM software to calculate τ_c is not known to the authors, but the results of both the methods were in a good agreement (Fig. 5).

The obtained spectra of all the SE dispersions were comparable in their polarity and their shape to those of low viscous glycerol water mixtures (statistical significance of 95%, data not shown). Consequently, the yielded data from the calibration curves could be used for the determination of the microviscosities of the sucrose ester matrices (see Table 1).

Taking the uncertainty into account, the determined ranges of τ_c of the samples were comparable. This resulted in microviscosities comparable to water, not only for the isotonic solvent, but also for all the measured SE dispersions. Such a high mobility of small molecules in all the dispersions stands in contrast to the rheology results. There we found large differences in macroviscosities. We suppose that network-like structures are responsible for the high macroviscosity, whereas within such a network enough space is left for small molecules to remain highly mobile. Differences between the macroviscosity and the microviscosity have also been reported for polymer-based systems by Kempe et al. [31].

3.4. Differential scanning calorimetry (DSC)

For detailed information about the temperature dependent behaviour of the SE dispersions DSC was applied.

The S1170F is a blend of mono-, di- and poly-esters of sucrose and fatty acids. Therefore, SE-based systems showed not a sharp peak but a melting range around 50 °C (Fig. 6). Heating the SE dispersions up to 60 °C during production caused the melting of the lipid chains, and therefore the rearrangement of the systems.

Besides the macroscopic differences in viscosity, the melting enthalpy of the 2% hd sample was reduced to approximately 40% of the 2% cd sample.

The DSC results indicated that sucrose esters did only partially recrystallize. Especially monoesters are highly hydrophilic and could remain dissolved. In order to force complete crystallization the SE-based systems were cooled down to minus 30 °C. But that did neither alter the ratio of the enthalpies significantly, nor did it alter the melting properties. Further heating and cooling cycles did not have any effect on the enthalpy values. The results support macroscopic findings that the hot dispersed samples and the heat

Table 1
The microviscosities η calculated from rotational correlation times τ_c (a) were compared to the macroviscosities η^* obtained by rheometry

Sample	Public EPR software tools		EPRSIM		Rheometry
	τ_c[a] [ps]	Viscosity η [mPa*s]	τ_c[a] [ps]	Viscosity η [mPa*s]	Viscosity η^* (at 1 rad/s) [mPa*s]
Solvent	9.14 ± 1.97	1.03 ± 0.22	10.53 ± 0.23	1.24 ± 0.03	1.0 ± 1.0
2% hd	14.00 ± 0.67	1.58 ± 0.08	9.63 ± 0.22	1.14 ± 0.03	575 ± 192
2% cd	17.50 ± 1.35	1.97 ± 0.15	10.17 ± 1.48	1.20 ± 0.18	133,400 ± 15,740
20% hd	18.68 ± 0.68	2.10 ± 0.08	13.47 ± 0.72	1.59 ± 0.08	5,482,700 ± 412,500

Values are displayed as mean ± SEM (n = 3).

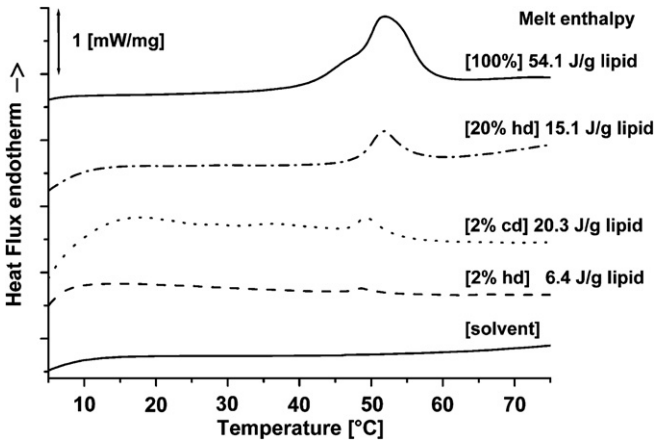

Fig. 6. DSC curves of sucrose ester dispersions at a heating rate of 10 K/min and the resulting melt enthalpies are displayed. The heating curves were normalized and the heat fluxes were plotted in arbitrary values.

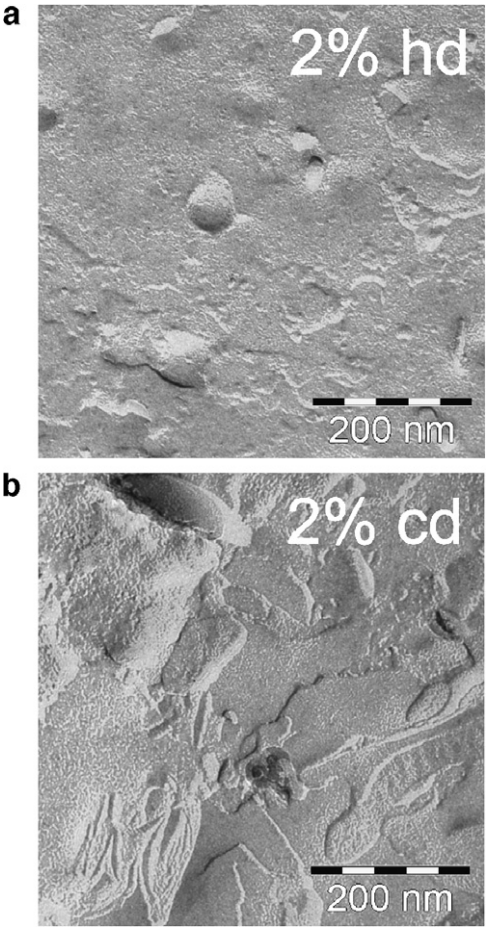

Fig. 7. TEM photomicrographs of sucrose ester dispersions. Samples shown were treated by freeze fracture and etching. (a) The low viscous 2% hd formulation. (b) The viscous 2% cd sample.

treated cold dispersed samples were equal. In conclusion, the macroviscosity was connected with the melt events.

3.5. Photon correlation spectroscopy (PCS)

In order to continue with the investigation of particles or other structures below the visible level, PCS was applied. Preliminary to the experiment the refraction index of the isotonic solvent was determined. The value 1.332 did not differ from that of water found in the literature. The viscosity of 1.155 mPa s was obtained by Ubbelohde capillary viscosimeter at 25 °C. Dynamic light scattering measurements were only possible with the 2% hd sample, because the other samples were too viscous. Average particle diameters of 447 nm indicated to structures in the submicron range. The high polydispersity 69% ± 15% (mean ± SEM, n = 5) showed that particle sizes of a wide range were observed. Hence hot dispersion of SE in water induced formation of micelles of irregular shape. The formation of wormlike micelles is possible, because it was reported for related systems (mixtures of hydrophilic sucrose palmitates and cosurfactants) [32].

3.6. Transmission electron microscopy (TEM)

TEM as imaging technique was applied to reveal the structures in the submicron range. Micrographs of the high viscous 2% cd SE formulation showed single lamellas, which were horizontally fractured (Fig. 7a). Few micelles with no defined shape could also be observed.

In the low viscous 2% hd sample also coherent layers, but apparently less in numbers, were found (Fig. 7b). Here the Micelles had no defined size or shape as well. Micrographs made by the negative staining technique led to the conclusion that besides the coexistence of lamellar and micellar phases the higher number of ordered lamellas in the 2% cd sample might be the reason for the increased viscosity. However, this has to be proven by additional experiments.

4. Conclusions

Sucrose esters (SE) are a very interesting class of pharmaceutical excipients. In contrast to other systems, LDDS based on SE have not yet been intensively characterized. Especially this was the first time that aqueous dispersions solely composed of SE were investigated.

By application of gentle heat and only moderate shear stress it was possible to produce nanosized, physiologically acceptable SE dispersions without using organic solvents. The formulations were macroscopically stable over months. Diverse history of fabrication led to the differences in the macroviscosity of SE dispersions with equal chemical composition.

The main focus of this study was the characterization of the viscosity phenomena.

Three orders of magnitude difference in macroviscosity between the dispersions containing 2 wt% of the amphiphilic SE were obtained. Whereas, the viscosities at the molecular level investigated noninvasively by the EPR technique were all close to the viscosity of water.

Investigations by light microscopy and PCS indicated to structures below the micrometer range. TEM experiments visualized coexisting irregular micelles and lamellar structures. Although lamellas in the high viscous 2% sample were in a more ordered state, it is not clear whether this result can be attributed to the high macroviscosity. Further investigations are ongoing to describe the systems and their inner structures.

The findings are important to understand the LDDS based on amphiphilic SE. The interesting properties, which were shown by the described systems, make them an addition to other established lipidic systems.

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