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Research paper

Sucrose ester nanodispersions: Microviscosity and viscoelastic properties

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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.

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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.

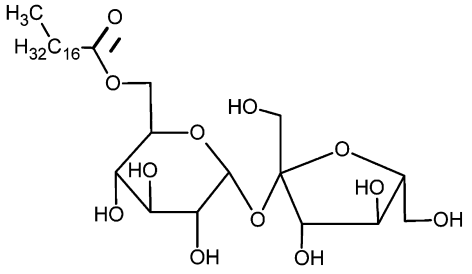

Fig. 1. Molecular structure of sucrose monostearate: the main ingredient (approx. 57%) in Ryoto Sugar Ester S1170F.

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