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Investigation on the viscoelastic properties of lipid based colloidal drug carriers

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Abstract

The rheological behaviour of solid lipid nanoparticle dispersions (SLN) prepared by high pressure homogenization was investigated using a Haake RS-100 rheometer. Four preparations differing in their lipid content and macroscopic consistency were tested by continuous shear rheometry and oscillatory testing. Rheological data from continuous shear measurement reveal plastic flow for systems with low lipid content as well as for systems with high lipid content. By using oscillatory testing more detailed information concerning the structure could be achieved. Rheological measurements of 40% lipid dispersions show viscoelastic properties comparable to the data from standard dermal preparations. Therefore high concentrated lipid dispersions might constitute a promising vehicle for topical administration.

Keywords: Continuous flow rheometry; Rheology; Oscillatory testing; Viscoelasticity; Solid lipid nanoparticle dispersions (SLN)

The determination of rheological properties of lipid based colloidal drug carriers like ointments, gels etc. provides essential information regarding the physicochemical nature of the vehicles (Ceulemans et al., 1999). Rheology measurements are valuable tools for quality control of ingredients and final products together with manufactoring processes, such as mixing, pumping, stirring, filling and sterilization (Davis, 1969; Barry, 1983). Apart from that effects on the product by changes of the formulation, temperature or storage time can be studied and the influence of viscosity on the release of drugs from the vehicle can be monitored (Michailova et al., 1999).

Different SLN formulations consisting of 10–40% Precifac ATO (cetylpalmitate) (Gattefossé, Weil a. R., Germany), 5% sucrose fatty acid ester (Mitsubishi–Kagaku Foods, Tokyo, Japan) and water added up to 100% (m/m) were produced by high pressure homogenization (APV Micron Lab 40, APV Homogenizer GmbH, Lübeck, Germany). The melted lipid was dispersed in the hot surfactant solution (85°C), a pre-emulsion prepared by an Ultra-Turrax T25 (Janke and Kunkel GmbH KG, Staufen, Germany) at 8000 rpm for 1 min, and this emulsion was homogenized by high pressure homogenization (3 cycles, 500 bar, 85°C). The rheological measurements were performed

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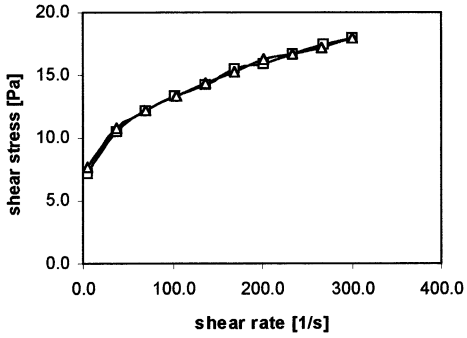

Fig. 1. Shear stress of 20% (m/m) lipid dispersion as a function of shear rate at 20°C: up-curve, square symbols; down-curve, triangle symbols.

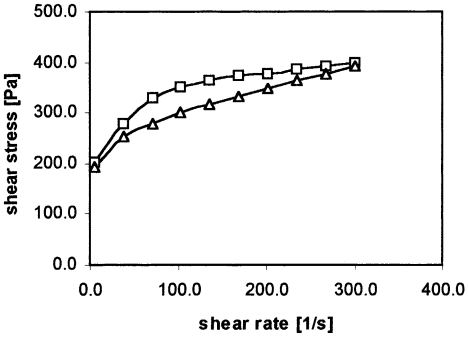

Fig. 2. Shear stress of 40% (m/m) lipid dispersion as a function of shear rate at 20°C: up-curve, square symbols; down-curve, triangle symbols.

with a Rheo Stress RS 100 (Haake, Karlsruhe, Germany) equipped with a cone and plate fixture (diameter 20 mm, angle 4°). All measurements were carried out at a temperature of 20 ± 0.1°C.

For the rheological charcterization of the lipid based colloidal drug carriers continuous shear rheometry as well as oscillatory testing were applied.

1. Continuous shear rheometry

In the continuous shear investigations the shear rate started at 0.5 s^{-1} (measuring limit of the rheometer) up to a maximum shear rate of 300 s^{-1} and back again to 0.5 s^{-1}. The resulting shear stress was measured.

Fig. 1 shows the flow curve of a 20% lipid dispersion with plastic flow characteristics, where the viscosity decreases with increasing shear rate. Ascending and descending flow curve overlap and show no time effects like, e.g. thixotropy. The lipid particles in the dispersion tend to align with increasing shear stress which is alleviating the flow.

Increasing the lipid content of the system from 20 to 40% leads to different flow characteristics, presented in Fig. 2. Unlike the 20% dispersion the

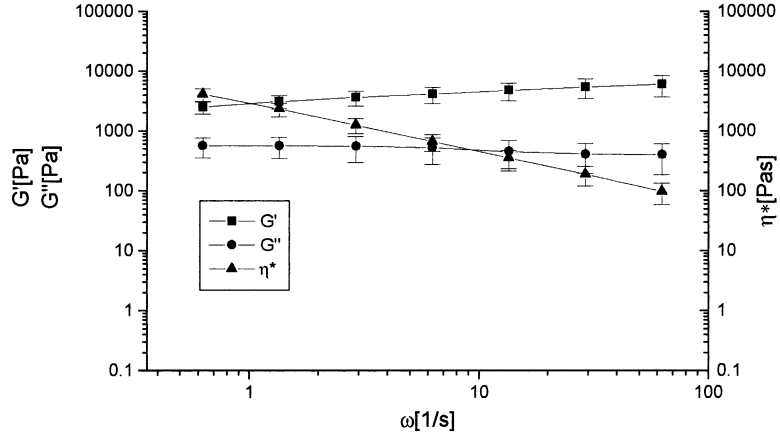

Fig. 3. Storage (G') (squares), loss modulus (G'') (circles) and complex viscosity (triangles) of 40% (m/m) lipid dispersion as a function of the radial frequency (ω) at a stress of 5 Pa at 20°C.

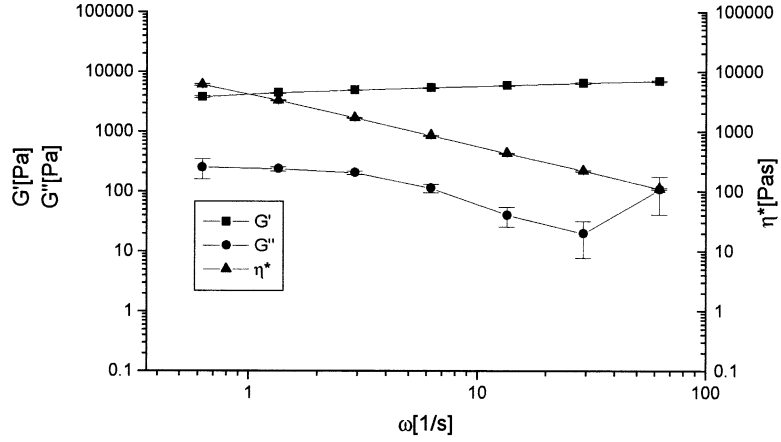

Fig. 4. Storage (G') (squares), loss modulus (G'') (circles) and complex viscosity (triangles) of 15% (m/m) bentonit gel as a function of the radial frequency (ω) at a stress of 5 Pa at 20°C.

ascending and descending curve of the 40% dispersion did not overlap. The flow curve shows thixotropy.

2. Oscillatory testing

Rheological test parameters like storage (G') and loss (G'') moduli, as well as complex viscosity (η^*) were obtained under dynamic conditions of non-destructive oscillatory tests in the frequency range of 0.1–10 Hz. First the linear viscoelastic region for all different systems was determined by a strain sweep. The complex modulus was measured as a function of strain at a constant frequency. Being in the linear viscoelastic region in all tested systems, 5 Pa was chosen as stress amplitude in all the following studies.

Fig. 3 displays a frequency sweep which provides a 'fingerprint' of a viscoelastic system under non-destructive conditions. It reveals the storage modulus, loss modulus and complex viscosity as a function of radial frequency of a 40% lipid dispersion 1 day after production. As the storage modulus is higher by about one order of magnitude than the loss modulus the system is more elastic

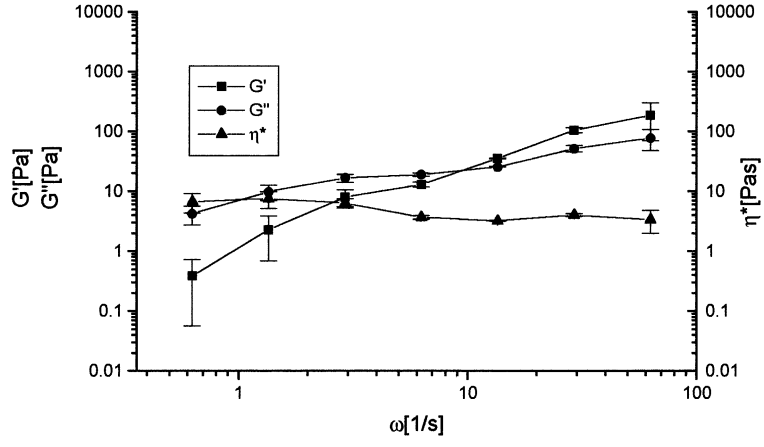

Fig. 5. Storage (G') (squares), loss modulus (G'') (circles) and complex viscosity (triangles) of 20% (m/m) lipid dispersion as a function of the radial frequency (ω) at a stress of 5 Pa at 20°C.

than viscous in the investigated frequency range and both parameters show weak dependence on the the applied frequency. The complex viscosity on the other hand depends very much on the applied frequency. Complex viscosity is decreasing with increasing frequency.

Compared to the oscillatory tests on the 40% lipid system the rheological data derived from tests on a 15% Bentonit gel, often described as having a 'cardhouse'-structure (Niedner and Ziegenmeyer, 1992) look very similar as demonstrated in Fig. 4. The storage modulus is also higher than the loss modulus and complex viscosity and moduli lie in the same range of magnitude apart from the loss modulus at higher frequencies.

A completely different rheological behaviour as a function of frequency can be seen with 10 and 20% lipid dispersions, exemplary shown in Fig. 5 for a 20% dispersion. Here complex viscosity and the moduli are much lower, which exhibits the much weaker structure of the system having a more liquid like character. In contrast to the 40% dispersion storage and loss modulus ascend with increasing frequency. Exceeding the radial frequency of 10 rad s^{-1} the former plastic feature of the 20% system transforms into a more elastic one.

Looking at the values of tan δ (measured at a frequency of 1 Hz) a change can be observed from the 20 to the 40% dispersion. The 40% dispersion with $\tan \delta = 0.12 \pm 0.02$ has more elastic properties than the 20% system which is more viscous ($\tan \delta = 1.47 \pm 0.06$). This can be explained by the more dense packing of the particles in the 40% lipid dispersion in contrast to the 20% dispersion.

Storage modulus and tangent of the phase angle (δ) of the 40%lipid dispersion are comparable with data from standard topical preparations, e.g. Unguentum emulsificans aquosum (Rose and Daniels, 1999).

In conclusion, it was found that increasing the lipid concentration from 20 to 40% leads to a dramatic change in the rheological properties. The low viscous solution turns into a elastic gel, which shows viscoelastic properties comparable to standard dermal preparations. Therefore these lipid dispersions might constitute a promising vehicle for dermal delivery.

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