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Preparation of semisolid drug carriers for topical application based on solid lipid nanoparticles

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Abstract

Aqueous dispersions of solid lipid nanoparticles (SLN) show some interesting features in topical drug delivery. However, to get a semisolid carrier having the appropriate consistency for topical application, the liquid SLN dispersions have to be incorporated in convenient topical dosage forms like hydrogels or creams. This is a time-consuming production process with several disadvantages. A new one-step production process delivering a semisolid topical formulation including SLN is presented avoiding these disadvantages. The semisolid SLN dispersions were produced by high-pressure homogenization using an APV Lab 40 homogenizer. The resulting dispersions were characterized concerning their particle size and rheological properties. Despite the high lipid content of the SLN dispersions, they retained their colloidal particle size. Viscoelastic measurements proved the existence of a gel-like structure with a prevailing elastic component. © 2001 Published by Elsevier Science B.V.

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Solid lipid nanoparticles (SLN™) (Müller and Lucks, 1996) appear promising as drug carrier system for topical application. The carrier is composed of physiological and biodegradable lipids of low systemic toxicity and also low cytotoxicity (Müller et al., 1997). Most of the lipids used have an approved status, e.g. the GRAS status which includes accepted food additives for the human use due to their low toxicity or are excipients used in topical cosmetic or pharmaceutical preparations. Occlusion properties as a result of film formation on the skin which can enhance the penetration of drugs through the stratum corneum have been reported (Jenning et al., 1999). Stabilization of chemically unstable drugs by incorporation into a lipid matrix has been shown (Jenning, 1999). Sustained drug release is possible due to the solid matrix of the particles (Jenning et al., 2000a). Sustained drug release becomes important in dermal application concerning drugs that are irritating at high concentrations. Furthermore it provides the possibility to supply an active over a prolonged period of time and can reduce systemic absorption. Controlled

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triggered release of drugs is feasible due to polymorphic transitions of the lipids induced by water evaporation from the dosage form after application to the skin. Furthermore electrolytes present in the upper skin surface can initiate polymorphic transitions accompanied by drug expulsion due to the formation of a stable polymorph (Jenning et al., 2000b).

Liquid SLN dispersions possess a low viscosity (approximately 100 mPa s) and a yield value of practically zero (Freitas, 1998). Therefore, the liquid SLN dispersion usually has to be incorporated in convenient topical dosage forms like hydrogels or creams to obtain a topical application form having the desired semisolid consistency. This multistep production process however has a lot of disadvantages. The production process is time-consuming because SLN dispersion and dermal drug carrier have to be produced separately. Moreover, applying the hot homogenization process for the preparation of SLN dispersions (Müller et al., 1995) requires cooling down of the hot O/W nanoemulsion prior to adding it to the topical dosage form. Conventional SLN dispersions contain about 10% lipid and 80–90% water. Therefore, their loading into a topical dosage form is limited. Hence drug loading is also limited. Incompatibilities with ingredients from the hydrogel or cream may occur (e.g. gelling agent or surfactants). Aggregation of the nanoparticles is possible especially when using polar gelling agents like charged polysaccharides (Jenning et al., 2000a). Also the use of neutralizing agents like sodium hydroxide for the preparation of polyacrylic acid gels can affect particle size. Electrolytes like sodium ions can reduce the zeta potential of the particles leading to aggregation of the particles which is a well known fact also for lipid nanoemulsions (Freitas and Müller, 1999). Finally the total amount of excipients is very high. Avoiding these disadvantages the development of a new one-step production process delivering a semisolid topical formulation including SLN is presented in the following.

Fig. 1 illustrates the basic steps of production of semisolid SLN dispersions. The process starts with the melting of the lipid and dispersing it in a hot surfactant solution having the same temperature (about 20°C above the melting point of the lipid) using an ultra turrax T25 (Janke and Kunkel GmbH KG, Staufen, Germany) at 9500 rpm for 1 min. In contrast to SLN dispersions with 10–20% lipid, a higher lipid content of 30–50% is generally used. This liquid premix is then passed through a APV Micron LAB 40 high-pressure homogenizer (APV Deutschland GmbH, Lübeck, Germany). Three cycles at 500 bar and 85°C were performed. Already after one homogenization cycle the former liquid O/W dispersion became quite viscous. Despite the viscous consistency of the hot O/W emulsion, it was possible to process the material with the APV Micron Lab 40 high-pressure homogenizer without obstruction for another two cycles. The resulting viscous hot O/W nanoemulsion was left to cool down to room temperature. The lipid droplets recrystallize to solid nanoparticles forming a gel network with a semisolid consistency. No further time-consuming processing is necessary. By this new one-step production process no incompatibilities with ingredients (e.g. gelling agents from hydrogels) from previously used topical dosage forms can occur. The SLN load is quite high thereby providing the possibility of higher drug loading. Finally the developed topical drug carrier system consists of less excipients, i.e. one lipid, one emulsifier and water which is generally desirable in the development of new drug carrier systems.

To determine mean particle size and polydispersity index of the high concentrated systems photon correlation spectroscopy (PCS) with a

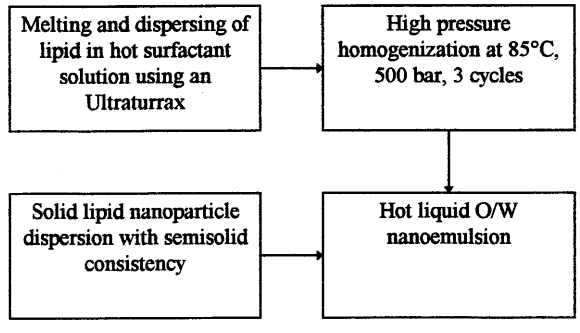

Fig. 1. Preparation of semisolid SLN dispersions by a one-step production process.

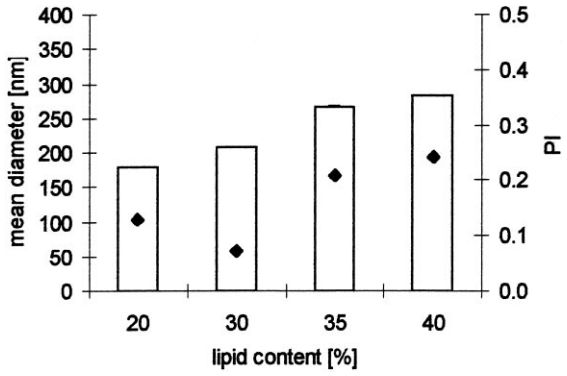

Fig. 2. Influence of lipid content on particle size and polydispersity index measured by photon correlation spectroscopy (PCS).

Zetasizer 4 (Malvern Instruments, UK) was performed. The solid lipid dispersions consisted of 30–40% Precifac ATO (cetylpalmitate) (Gattefossé, Weil a.R., Germany), 5% sucrose fatty acid ester (Mitsubishi-Kagaku Foods, Tokyo, Japan) and bidistilled water. Fig. 2 shows the mean particle size and the polydispersity index of some lipid dispersions only differing in their lipid content. Compared with a 20% SLN dispersion which is still a liquid dispersion with no yield value, the lipid dispersions with increasing lipid content differ only little concerning particle size. Also the polydispersity index increases only slightly but stays still below 0.3 indicating a narrow size distribution. These data demonstrate that despite the increasing lipid content and the viscous to semisolid character of the dispersions, the colloidal size is still preserved.

The rheological status of a semisolid drug carrier system is a very important physical parameter. Rheology measurements provide essential information about different aspects concerning semisolid preparations. Rheological properties therefore affect all stages of manufacture like mixing, pumping, filling etc. Moreover, rheological measurements are valuable tools in quality control of ingredients and final products. Concerning application and performance on skin they provide essential information. Furthermore, drug release from semisolid vehicles is influenced by the rheological behavior. To determine the rheological properties of the developed semisolid drug carrier, an oscillation frequency sweep test was carried out. Oscillation tests are dynamic methods for determining the rheological properties of the material in its rheological ground state without altering the static structure of the material (Barry and Warburton, 1968). These measurements can provide information on the intermolecular and interparticle forces in the material (Martin, 1993). An oscillation frequency test is a dynamic test in which the response of the tested material is measured as a function of frequency at a constant stress amplitude. It provides a so-called 'fingerprint' under non-destructive conditions. Information regarding the viscous and elastic behavior of the test material can be obtained. The storage modulus G' gives information about the elastic component, whereas the loss modulus G'' is a measure of the viscous component. The viscoelastic measurements were performed at 20 ± 0.1°C on a Rheo Stress RS 100 (Haake, Karlsruke, Germany) equipped with a cone and plate system (diameter 20 mm, angle 4°). The measurements were carried out in the linear viscoelastic region applying a constant shear stress of 5 Pa over a frequency range 0.1–10 Hz. Fig. 3 shows a frequency sweep test of a 40% SLN dispersion stabilized with 5% sucrose fatty acid ester. As can be seen from the diagram the storage modulus G' (elastic component) is far greater than the loss modulus G'' (viscous component) over the measured frequency range which indicates the pres-

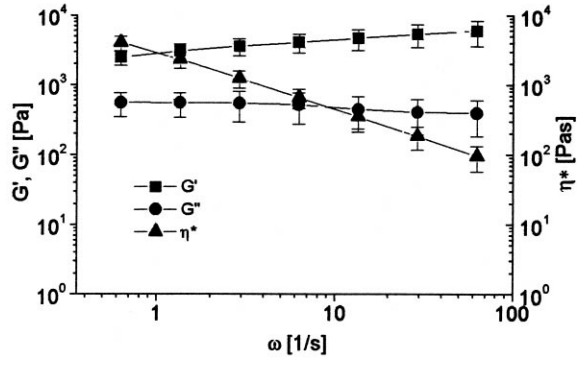

Fig. 3. Storage (G') (squares), loss modulus (G'') (circles) and complex viscosity η^* (triangles) of 40% SLN dispersion as a function of the radial frequency (ω) at a stress of 5 Pa at 20°C.

ence of a gel-like structure. Both parameters show weak dependence on the applied frequency. The complex viscosity η^* decreases with increasing frequency. This is also typical for viscoelastic solids and can be found for standard topical dosage forms like Unguentum emulsificans aquosum.

In conclusion, it could be shown that the production of semisolid SLN dispersions is possible by high-pressure homogenization with a Micron Lab 40 piston gap homogenizer. A one-step production method has been developed without the need of further processing. Surprisingly, it was found that despite the high lipid content and the semisolid consistency of the lipid dispersions, the colloidal size could be preserved. Viscoelastic measurements showed that these semisolid dispersions form a gel-like structure with a prevailing elastic component. This is in accordance with the results obtained from standard dermal preparations like Unguentum emulsificans aquosum. Therefore, these semisolid SLN dispersions present a promising topical dosage form.

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