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Note

The influence of the crystallinity of lipid nanoparticles on their occlusive properties

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Abstract

The aim of this study was the investigation of the correlation between the degree of crystallinity of solid lipid nanoparticle (SLN) dispersions and their occlusive effects. SLN dispersions with different crystallinity indices of the lipid matrix were produced, physicochemically characterized and their occlusion factor was determined after 6, 24 and 48 h. This study is based on the in vitro occlusion test by de Vringer. It could be shown that the occlusion factor depends strongly on the degree of crystallinity of the lipid matrix, i.e. this effect is proportional. Further, it could be shown that noncrystalline lipid nanoparticles, i.e. supercooled melts have no occlusive properties. Therefore, the desired degree of occlusivity can be achieved by choosing suitable lipids for the matrices of topical SLN formulations.

Keywords: Lipid nanoparticles; Occlusion; Creams

The penetration of active compounds into human skin depends strongly on skin hydration which can be influenced by occlusive compounds (Ziegenmeyer, 1992). The application of occlusives prevents water evaporation from the skin to the atmosphere and thus water is retained within the skin. Unfortunately, many commercially available occlusives have an unacceptable aesthetic appearance (Barry, 1983) so that there is a need for innovative occlusive systems.

Solid lipid nanoparticles are carriers for pharmaceutical and cosmetic compounds with various benefits, e.g. controlled release of incorporated compounds and protection of labile drugs against chemical degradation (Müller et al., 1995).

Additionally, it has been shown that solid lipid nanoparticles (SLN) have an improved occlusive effect compared to conventional emulsions or microparticles (de Vringer, 1992; Wissing et al., 2001). Their occlusive character is based on film formation after application to the skin. The extent of their occlusive properties depends on various factors, e.g. particle size and lipid concentration.

In this in vitro study, we investigated the influence of the crystallinity of the lipid matrix on the occlusion factor with a method developed by de Vringer (1992). For the study, different SLN for mulations were prepared, physico-chemically characterized and finally their occlusion factor was determined.

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Table 1
PCS and crystallinity data of investigated SLN formulations

Formulation	z-ave (nm)	PI	Crystallinity (%)
CF68	189 ± 2	0.202	95.0
ST	175 ± 2	0.155	62.9
D12T	167 ± 2	0.174	0.0

PCS parameters shown are average PCS size (z-ave) and polydispersity index (PI). Crystallinity data shown is the degree of crystallinity with respect to the bulk material.

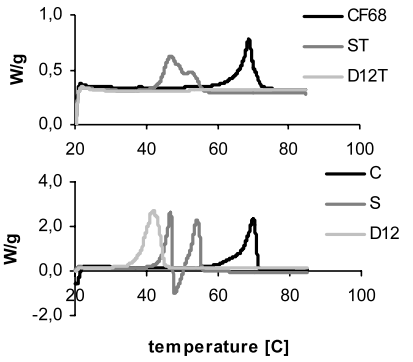

Fig. 1. DSC scans of the SLN formulations CF68, ST and D12T (top) and the corresponding bulk lipids (bottom).

Dynasan 112 (Condea, Germany), Compritol 888 ATO (Gattefossé, France) and Softisan 154 (Hüls, Germany) were used as lipid materials, Tyloxapol (Sigma, Germany) and Lutrol F68 (BASF, Germany) were used as surfactants. Water was supplied by a Millipore MilliQ-Plus.

The lipid nanoparticle dispersions were produced by the hot homogenization technique (500 bar, three cycles, 85 °C) on a Micron Lab 40 (APV Gaulin, Germany) as described by Müller et al. (1997). The formulations contained 20% Dynasan 112 (D12), Compritol (C) or Softisan 154 (S) as lipid and 5% tyloxapol (T) or Lutrol F68 (F68) as surfactant.

The particle size was analyzed by photon correlation spectroscopy (PCS) using a Zetasizer 4 (Malvern, Germany). The average size (z-ave) and polydispersity index (PI) as a means for the width of size distribution are given in Table 1.

In order to determine the extent of crystallinity, the samples were investigated by differential scanning calorimetry (DSC). Samples were scanned from 25 to 85 °C (10 K/min) and the melting enthalpy of SLN dispersions was compared to the bulk lipid. The degree of crystallinity is given in Table 1 and the DSC scans of the formulations and the bulk lipids are shown in Fig. 1. The bulk lipids were heated and cooled down twice in order to compare the data with the SLN formulations which are melted during production.

For the occlusion test, 100 ml beakers were filled with 50 ml water and sealed with cellulose acetate filter (Schleicher, Germany, cutoff size: 4–7 μm). Samples were spread on the filter (13.3 mg/cm^2) and stored at 32 °C and 50–55% r.h. for 48 h. The occlusion factor F was calculated according to Eq. (1) after 6, 24 and 48 h, where A is the water loss without sample (reference) and B is the water loss with sample. Every experiment was carried out in triplicate.

$$F = 100*((A - B)/A) \quad (1)$$

Three physically stable lipid nanoparticle dispersions with similar particle size and different degree of crystallinity of the lipid matrix were produced (Table 1). The particle size was kept constant in order to eliminate the influence of particle size on the occlusion factor.

The thermal behaviour of the SLN formulations and the corresponding bulk lipids was investigated with DSC (Fig. 1). While melting peaks can be detected in the scans of the nanoparticle formulations CF68 and ST, there are no exo- and endothermic effects visible for formulation D12T. This lipid forms a supercooled melt when used as matrix material in a SLN formulation.

The dependency of the occlusion factor F upon the crystallinity of the lipid matrix is shown in Fig. 2. Formulation CF68 forms highly crystalline lipid nanoparticles; in formulation ST, the lipid does not recrystallize completely at room temperature and formulation D12T forms supercooled melts upon cooling down.

Clearly visible, the occlusion factor depends strongly on the crystallinity of the lipid matrix. The highly crystalline nanoparticles (CF68) show a moderate occlusivity after 6 h which increases by more than 100% during the duration of the

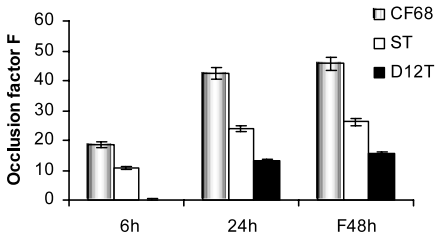

Fig. 2. Occlusion factor F of lipid nanoparticle dispersions CF68, ST and D12T after 6, 24 and 48 h (determined after de Vringer).

test. The occlusion factor *F* of formulation ST is proportional to the degree of crystallinity compared to CF68. For the non-crystalline formulation ST hardly an occlusive effect can be detected after 6 h. For this formulation, *F* remains below the values of the crystalline formulations throughout the experiment.

Concluding, it can be remarked that the extent of occlusivity of lipid nanoparticle dispersions correlates not only with particle size and lipid concentration but also with the degree of crystallinity of the lipid matrix. Therefore, when developing a new topical formulation based on SLN, it can be adjusted exactly to the desired degree of occlusion in a controlled way.

References

Barry, B.W., 1983. Skin transport. In: Barry, B.W. (Ed.), Dermatological Formulations. Marcel Dekker, New York, pp. 95–117.

de Vringer, T., 1992. Topical preparation containing a suspension of solid lipid particles. EP 91200664.

Müller, R.H., Mehnert, W., Lucks, J.S., Schwarz, C., zur Mühlen, A., Weyhers, H., Freitas, C., Rühl, D., 1995. Solid lipid nanoparticles (SLN)—an alternative colloidal carrier system for controlled drug delivery. Eur. J. Pharm. Biopharm. 41, 62–69.

Müller, R.H., Weyhers, H., zur Mühlen, A., Dingler, A., Mehnert, W., 1997. Solid lipid nanoparticles—ein neuartiger Wirkstoff–Carrier für kosmetika und pharmazeutika, 1. Mitteilung: systemeigenschaften, herstellung und scaling-up. Pharm. Ind. 59, 423–427.

Wissing, S.A., Lippacher, A., Müller, R.H., 2001. Investigations on the occlusive properties of solid lipid nanoparticles (SLN). J. Cosmet. Sci. 52, 313–323.

Ziegenmeyer, J., 1992. Biopharmazeutische Aspekte bei der anwendung von dermatika. In: Niedner, R., Ziegenmeyer, J. (Eds.), Dermatika. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, pp. 243–308.