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Comparison of wax and glyceride solid lipid nanoparticles (SLN®)

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Abstract

The present study compares solid lipid nanoparticles (SLN) formulated with either wax or glyceride bulk material. While most published data deal with glyceride SLN, little knowledge is reported on wax carriers. The two types were compared with respect to drug encapsulation efficacy, particle size distribution after production and storage, and crystal packing. The inclusion of retinol as a model drug was investigated. Retinol is chemically unstable in water and rather stable in lipid phases. Thus, rapid degradation of retinol indicates rapid drug expulsion from the carrier. Good stability indicates an effective drug encapsulation in the lipid phase of the nanoparticles. Particle size distribution was measured by laser diffractometry. Subcell packing and assignment of polymorphic forms was investigated by WAXS measurements. Glyceride SLN showed good drug encapsulation, while physical stability was poor. In contrast, wax SLN possessed good physical stability but lacked sufficient drug encapsulation in the solidified state. These differences were attributed in part to different crystal packing. Less ordered crystal lattices favour successful drug inclusion, as in the case of glyceryl monosterate and glyceryl behenate SLN. The highly ordered crystal packing of wax SLN comprised of beeswax or cetyl palmitate, for instance, leads to drug expulsion, but also to superior physical stability.

Keywords: Solid lipid nanoparticles; Glyceride; Wax; Drug encapsulation; WAXS

1. Introduction

Most of the published papers on solid lipid nanoparticles (SLN) suspensions report on particles formulated with glyceride matrix material and stabilized with blockpolymers or phospholipids (Heiati et al., 1996; Müller et al., 1996). Glycerides are triglycerides or partial glycerides and, with respect to the fatty acid composition, monoacidic or polyacidic (Sato et al., 1999). However, waxes and paraffins can be used as core materials as well. Waxes can be defined as simple esters of fatty acids with alcohols. In contrast to glycerides, the alcohol represented is *not* glycerol (Venturella, 1990). Waxes may contain free hydroxy groups within the molecule (e.g. hydroxyoctanosyl hydroxystearate) or free fatty acid functions (e.g. beeswax). Besides differences in chemical composition, glyceride and wax bulk

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material feature different physical properties. Waxes are plastic solid at RT and shine after polishing (Dorgan, 1983). After melting at moderately elevated temperatures, they become a low-viscosity liquid. In contrast, glycerides are often obdurate and dull. Furthermore, these materials display striking dissimilarities in their crystal order. Glycerides crystallise in different subcell arrangements — hexagonal, orthorhombic and triclinic. They exhibit marked polymorphism with three and often more individual forms (Larsson, 1966). The polymorphism of waxes is drastically reduced. Mainly, an orthorhombic subcell prevails and the polymorphic transition rate is low (Dingler, 1998).

Because of these chemical, physical and crystallographic differences, an influence on properties of lipid nanoparticles is expected. The present study highlights differences of glyceride and wax SLN. The possibilities of encapsulating drugs were investigated using the model lipophilic compound, retinol. This is very unstable in water and at light exposure. A much higher but even insufficient stability is observed in oil phases (Tsunoda and Takabayashi, 1995). As long as retinol is encapsulated within a carrier like SLN, it is protected from chemical degradation inside the water phase. If the molecule is not inserted in the particle or expelled from the carrier (Westesen et al., 1997), rapid degradation of the active takes place. Thus long term stability of the sensitive drug is an indicator of good and sustained encapsulation efficacy. Furthermore, physical stability of the nanoparticles was assessed by laser diffractometry (Mastersizer E, Malvern Instruments, UK). Physical stability of nanoparticulate dispersions can be defined as (A) a formation of small particles having a narrow (monomodal) size distribution after production, and (B) the absence of aggregates and considerable particle growth on long-term storage. Additionally, the crystal packing of the molecules was investigated by wide-angle X-ray scattering (WAXS) analysis (Philips X-ray generator PW1830, NL-Amelo, copper anode). These measurements allow the determination of subcell packing and, thus, the assignment of the polymorphic form of the nanoparticles.

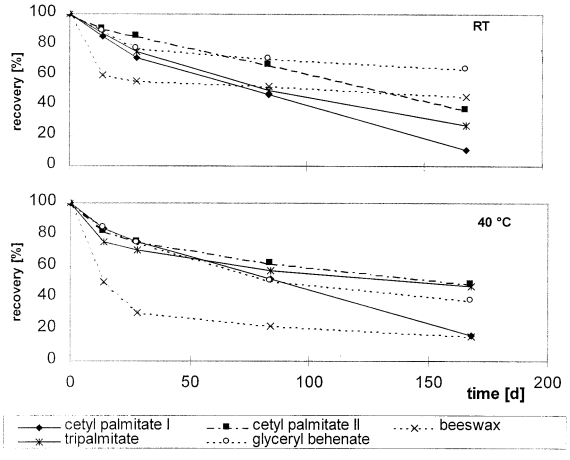

Fig. 1. Chemical stability of retinol in different SLN formulations at room temperature (RT) and 40°C storage. Cetyl palmitate I mainly represents crystalline SLN, and cetyl palmitate II mainly a supercooled melt. Arithmetic means of n = 3 experiments. S.D. is within 10%.

The following materials were chosen:

- Glycerides: Imwitor 900 (glyceryl monostearate, Hüls AG, D-Witten), Compritol 888 ATO (glyceryl behenate, Gattefossé, D-Weil a. Rhein) and Dynasan 116 (tripalmitate, Hüls AG, D-Witten).
- Waxes: Cutina CP (cetyl palmitate, Henkel, D-Düsseldorf) and beeswax (conforms to German pharmacopoeia DAB10, Caelo, D-Hilden).

SLN dispersions were prepared by the hot homogenisation technique, as described elsewhere (Müller and Lucks, 1996). Briefly, the molten lipid phase containing retinol was dispersed in a surfactant mix (1.5% Tween 80 in bidistilled water) and dispersed using an Ultra Turrax (Ika, D-Staufen). This crude premix was passed through a high-pressure homogenisator Lab 40 (APV, D-Lübeck) for three cycles. All procedures were carried out at temperatures above the melting point of the lipid. The retinol content was determined by an HPLC assay (Kontron, D-Neufahrn).

Fig. 1 represents the results of the chemical stability of retinol-loaded SLN based on the aforesaid different matrix materials. A poor stability indicates poor encapsulation quality of the active. Comparable good stability at RT and 40°C was obtained with the lipid glyceryl behenate

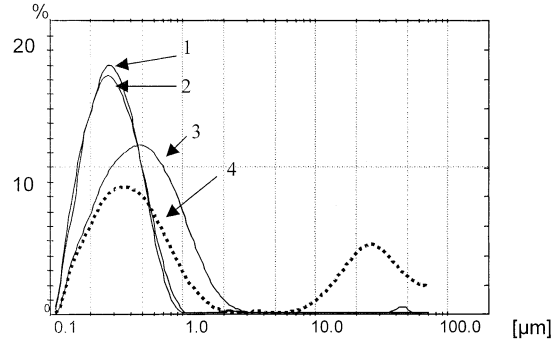

Fig. 2. Size distribution (volume distribution, laser diffractometry) of Tween 80-stabilised SLN dispersions after 84 days storage at RT. (1) cetyl palmitate SLN; (2) beeswax SLN; (3) tripalmitate SLN; (4) glyceryl behenate SLN.

(Compritol) revealing its suitability for encapsulating retinol. Similar good encapsulation can be obtained with glyceryl monostearate (Imwitor 900, data not shown in Fig. 1). In contrast, beeswax SLN showed the poorest stability at 40°C storage. Two different Cutina formulations are listed in Fig. 1. Drug-loaded Cutina SLN displayed a high tendency to form supercooled melts rather than solid particles. Recrystallisation of these particles can be induced by storage at 4°C. The cetyl palmitate II (Cutina CP) was the original dispersion, whereas cetyl palmitate I was stored at 4°C for 24 h. Cetyl palmitate II displayed only weak and broad WAXS reflexes, showing its supercooled state. More intense reflexes and, thus, more crystalline particles were obtained with the sample stored at 4°C, indicating the beginning of recrystallisation. Stored at RT for another 168 days, the higher crystalline carrier exhibited drug expulsion, as can be seen by the rapidly degrading retinol. At 40°C these differences were less pronounced, probably because recrystallisation is slower at this temperature. Similar results were obtained with tripalmitate (Dynasan 116) carriers. By increasing production temperature or pressure, smaller particles with a pronounced supercooling tendency resulted. These supercooled carriers, comprised of tripalmitate (not shown in Fig. 1), exhibited the better protection of retinol. The recrystallising tripalmitate matrix expelled the molecule from the lipid phase into the aqueous phase; thus, degradation was accelerated. Obviously, in carriers like cetyl palmitate and tripalmitate, drug encapsulation is poor. Heterogeneous glycerides like Compritol and Imwitor displayed the best protection for the model drug. Beeswax is rather heterogeneous in chemical composition too. Its poor encapsulation efficacy will be discussed below.

Measurements of particle sizes by laser diffractometry right after production revealed little difference between the different lipids. However, their long term stabilities were quite different. Fig. 2 depicts the size distribution of SLN suspensions stored for 84 days at RT. Wax SLN proved excellent long term stability, whereas glyceride particles showed particle growth and micrometer aggregates. Within glycerides, the best physical stability was obtained for Dynasan, followed by Compritol. Imwitor is extremely unstable, and considerable particle growth takes place within a few days. Possibly, increasing amounts of partial glycerides like monoglycerides are responsible for this physical destabilisation. The amount of monoglycerides is approximately 0% for tripalmitate, 15% for glyceryl behenate and 50% for glyceryl monostearate. On the other hand, mono- and diglycerides possess surfactant properties (HLB 2–5). It was proposed (Westesen et al., 1993) that these partial glycerides improve the surfactant film around the nanoparticles and thus prevent particle aggregation.

Fig. 3 reveals WAXS measurements of beeswax (lower graph) and Compritol SLN (graph in the middle and top). The diffraction pattern of Cutina was most similar with the one of beeswax,

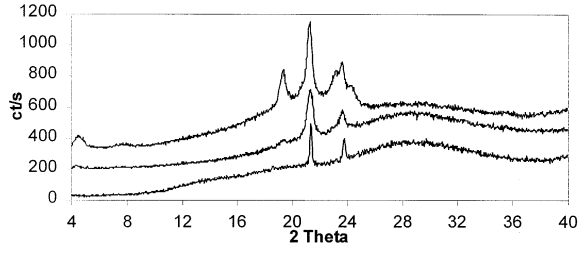

Fig. 3. WAXS diffraction pattern of beeswax SLN (lower graph) and fresh glyceryl behenate SLN (graph in the middle) and glyceryl behenate SLN after water evaporation from the dispersion (upper graph).

while Imwitor and Dynasan resembled more the X-ray behaviour of Compritol (data not shown). Reflexes of waxes like beeswax were found at 0.38 nm and 0.42 nm, which is typical for an orthorhombic subcell. The graph in the middle shows fresh Compritol SLN, also displaying orthorhombic subcell packing (β′ polymorph). After long term storage, or under-stress conditions such as shaking, exposure to electrolytes or water evaporation, the metastable β′ form transformed to the β_i polymorph (upper graph, spacings at 0.46, 0.42 and 0.38 nm). For waxes, no such transition, even under stress conditions, was observed. Furthermore, the peaks of beeswax SLN were sharper than those of Compritol SLN, despite the chemically heterogeneous composition of beeswax. In general, the short spacings of glycerides are broader than wax spacings. Broader peaks result from less crystal order and crystal defects. Comparing the three glycerides, Dynasan showed the sharpest lines and Imwitor the broadest ones. This relation again corellates well with the physical storage stability and encapsulation efficacy discussed above.

In conclusion, wax-comprised SLN can be characterised by excellent particle size distribution and physical long-term stability. Glyceride SLN are well suited for the incorporation of the active retinol. Preferentially, retinol is included in the lattice of complex glycerides, like glyceryl monostearate and glyceryl behenate. The pure triglyceride tripalmitate, possessing a higher ordered crystal packing, expels the drug upon solidification, similar to wax SLN. The drug load of supercooled melts is good as well; however, controlled release can be neglected. Poor physical stability of polysorbate 80-stabilised glyceryl behenate SLN can be improved by choosing an optimised surfactant blend. These SLN combine high drug encapsulation and good physical stability.

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