Stability studies and characterization of SLN formulations

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Introduction

Aqueous SLN dispersions, introduced in 1991, consist of a matrix composed of a lipid being solid at both room and body temperatures, having a mean particle size between 50 nm and 1 μm (Rawat M. et al. 2006). SLN are biodegradable, easy to produce (even in large scale) and biocompatible (Muller R.H. et al. 1995).

A clear advantage of the use of lipid particles as drug carrier systems is the fact that the matrix is composed of physiological components and/or excipients of accepted status (e.g. GRAS status). This approach reduces the risk of acute and chronic toxicity (Muller R.H. et al. 2005).

SLN represent an alternative carrier system to achieve a controlled drug release (Hu F.Q. et al. 2004), in comparison to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. SLN possess properties of emulsions (lipid composition) and polymeric particles (solid matrix). The solid matrix offers the possibility to improve the stability against coalescence and the reduced mobility of incorporated drug molecules is a requirement for protecting these latter against chemical degradation, and also to achieve a controlled release. Drug release can take place either by diffusion or by degradation of the lipid matrix which occurs mainly by enzymes such as lipases, and by hydrolytic processes only to a very little extent (Olbrich C. et al. 1998).

SLN are a colloidal carrier system for topical, oral and parenteral administration, which are used to improve the bioavailability of mainly lipophilic drugs (Cavalli R. et al. 1996).

The purpose of this work was to develop new SLN formulations using different solid lipids and surfactants to study their physicochemical properties and to assess their long term stability. To develop such formulations a new production procedure has been applied.

Materials and methods

Cetyl palmitate and Compritol 888 ATO were a gift from Gattefossé (France). Hexadecyl Hexadecanoate, Pluronic F-68, Sodium deoxycholate and Tyloxapol were provided by Sigma-Aldrich (Germany). Tego Care 450 was obtained by Degussa (Germany). MilliQ-water was home supplied.

Briefly, the mixture of lipid and surfactant was heated 5-10ºC above the melting point of lipid, followed by addition of 20 mL of deionized water heated at the same temperature and put in the ultra-turrax during 20 min. The recently prepared emulsion was further diluted with 20 mL of hot water under magnetic stirring until the temperature reached 33ºC. Finally, 4 mL of ethanol was added and stirred for more 30 min.

The mean particle size of SLN was analyzed by photon correlation spectroscopy and the electrophoretic mobility was measured by Laser Doppler Anemometry using a Malvern Zetasizer

5000. The samples were diluted with MilliQ-water having a conductivity adjusted to 50µS/cm by dropwise addition of 0.9% NaCl solution.

SLN stability was determined by measuring the mean diameter of SLN stored at three different temperatures (4, 22 and 40ºC) for six months.

SLN morphology was observed under scanning electron microscopy (SEM) and particle aggregation was assessed by optical microscopy. For SEM the samples were mounted on metal stubs, gold coated under vacuum and then examined. For optical microscopy a sample drop was observed at ampliation of 100x.

Results and discussion

Different lipid/surfactant concentrations were tested (data not shown) and the maximum lipid concentration of each lipid that allows a stable dispersion was stored and the mean diameter was determined.

Immediately after production, the macroscopic appearance of the aqueous dispersions was similar to milk, of low viscosity and with white colouration.

Table I summarises the properties of the developed SLN formulations (production day) composed of different proportions of the constituents.

	Formulations	Diameter ± SD (nm)	Zeta Potential ± SD
A	15% Cetyl palmitate 0.9% Tego Care 450	630.3 ± 135.9	-28.3 ± 0.4
B	5% Compritol 888 ATO 0.9% Pluronic 0.05% Sodium deoxicholate	299.8 ± 26.8	-18.8 ± 0.2
C	10% Hexadecyl hexadecanoate 1% Tyloxapol	324.1 ± 39.9	-34.0 ± 1.5

Table I Characteristics of different SLN

As expected, the mean diameter of SLN formulations increased with the increase of the lipid concentration. Cetyl palmitate formulations (A) were composed of 15% of lipid, while Compritol (B) and Hexadecyl hexadecanoate (C) formulations were of 5% and 10%, respectively. These differences were significant, meaning that the SLN size was dependent on both lipid composition and concentration.

SLN formulation having a higher zeta potential value was formulation C with approximately -34.0, which means that this formulation should be the most stable.

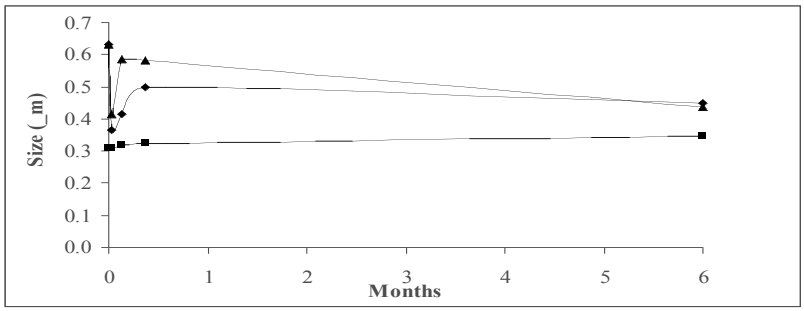


Figure 1. Effect of temperature of storage on the mean size of SLN formulations A (♦), B (■) and C (▲) at room temperature during 6 months.

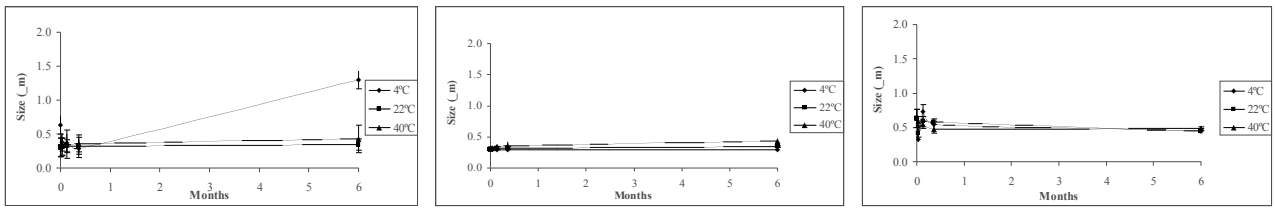
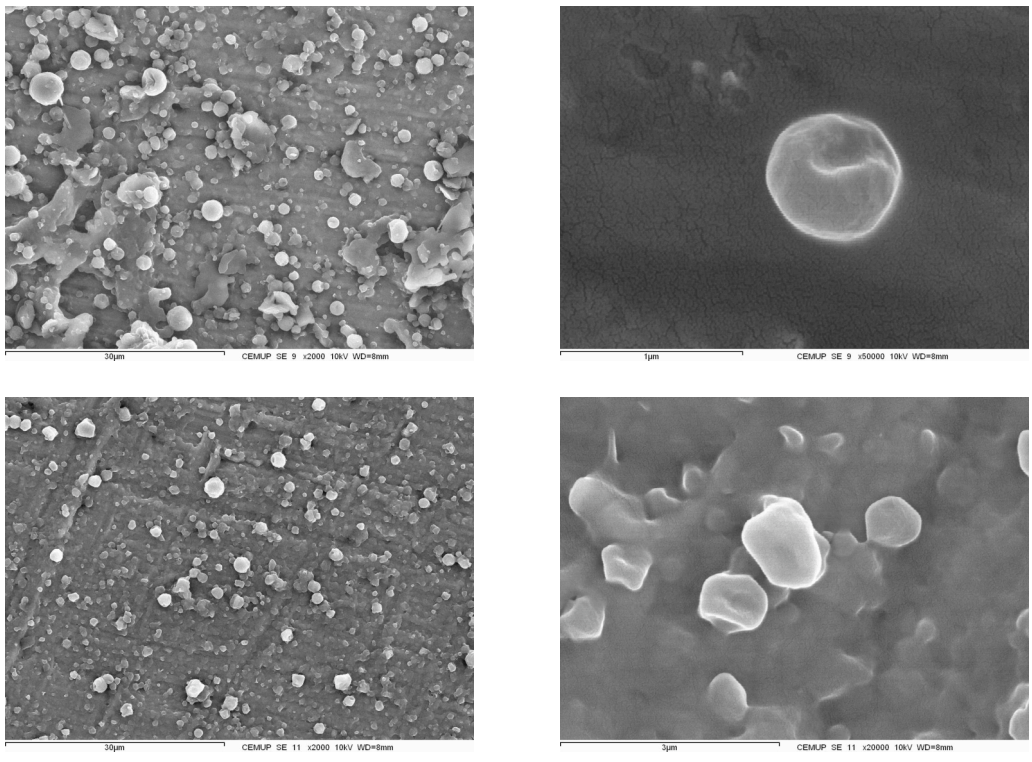


Figure 2. Effect of storage temperature on the mean size of SLN formulations A (left), B (middle) and C (right) during 6 months.

Under SEM analysis a globular or ellipsoidal shape of SLN with a smooth surface was observed. The irregular shape of the produced SLN is due to the nature of the solid lipid used, including solubility properties, crystal lattice and film forming capacity (Hu F.Q. et al. 2002).



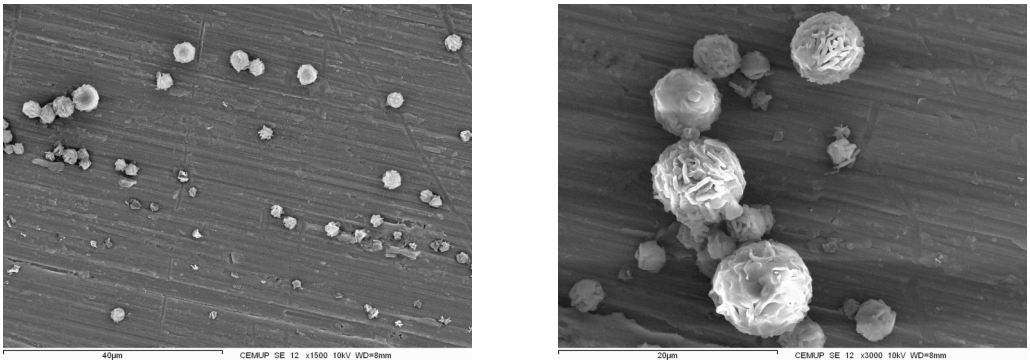


Figure 3. SEM micrographs and detail of the surface morphology of SLN formulation A (up), B (middle) and C (down).

The occurrence of particle aggregation was discarded after analysis of samples using optical microscope.

Conclusions

A new production procedure for SLN has been described. Nanosized particles have been produced using Cetyl palmitate, Compritol 888 ATO or Hexadecyl hexadecanoate as solid lipids.

After six months of storage these SLN showed similar sizes on the day of production revealing that these particles are a promising drug delivery system.

References

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