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Influence of surfactants on the physical stability of Solid Lipid Nanoparticle (SLN) formulations

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The choice of surfactant or surfactant mixtures at suitable concentrations contributes to the stability of solid lipid nanoparticles (SLN). In this study, it was found that 1.5% TegoCare® 450 was the most effective stabilizer for the Witepsol® E85 SLN dispersion compared to Tween® 80, Tyloxapol® and Pluronic® F68 according to the data obtained from differential scanning calorimetry (DSC), zeta potential (ZP) measurements and particle size analysis.

Solid Lipid Nanoparticles (SLN) are a colloidal drug carrier system alternative to polymeric nanoparticles, liposomes and emulsions in various application routes due to their numerous advantages (Müller et al. 2000, 2002). SLN have been produced with the aims of controlling drug release and drug targeting, and increasing drug stability. Several production methods have been used. The high pressure homogenization technique is a more effective method for the production of submicron sized dispersions of solid lipids (below 500 nm and a low microparticle content) than other methods such as high shear mixing (Cavalli et al.1999) or solvent evaporation (Siekman and Westesen 1996) and is suitable for large scale production (Gohla and Dingler 2001). The choice of the suitable surfactant or surfactant mixtures and their concentrations have great impact on the quality of SLN, since surfactant affects surface properties of SLN (Mehnert and Mäder 2001). The best choice contributes to higher stability by preventing particle aggregation more efficiently.

The present study was done to determine the influence of surfactant on the physical stability of placebo SLN dispersions containing Witepsol® E85 (mono-, di- and triglycerides of saturated fatty acids from C10 to C18) as solid lipid. TegoCare® 450 (polyglycerol methylglucose distearate), Tween® 80 (polysorbate 80), Tyloxapol® (octyl phenol polyoxyethylene) and Pluronic® F68 (Poloxamer 188) were used to stabilize the SLN dispersions and compared to each other by means of particle size analysis, ZP measurements and DSC analysis performed at various storage temperatures (room temperature (RT), 4 °C and 40 °C) for a period of 3 months.

After 3 months of storage, particle size values were measured for all the formulations by photon correlation spectrometry (PCS). Polydispersity index (PI) values <0.3 indicate relatively narrow particle size distribution. However, the SLN dispersions containing TegoCare® 450, Tween® 80 and Tyloxapol® gave the best laser diffractometry (LD) results without aggregation and particles in the micrometer size range at room temperature. But, aggregation occurred in these formulations at 4 °C. For Pluronic® F68, aggregation could be prevented by storage at 4 °C (Table 1). Zeta potential (ZP) values were the highest with the formulation stabilized with TegoCare® 450 after 3 months (Table 1). It is known that a ZP greater than −60 mV is required for excellent, greater than −30 mV for a good electrostatic stabilization, thus indicating good physical stability (Freitas and Müller 1998).

The data obtained from DSC demonstrate that the formulation stabilized with Pluronic® F68 (4 °C) showed the highest crystallinity followed by TegoCare® 450 (RT), whereas the formulation containing Tyloxapol® (RT) led to the formation of a supercooled melt (Table 2).

It was found that TegoCare® 450 incorporated into the formulation at 1.5% was the most efficient surfactant to stabilize the Witepsol® E85 SLN dispersion after

Table 1: D_{50}, D_{90} and D_{95}, and ZAve with polydispersity index (PI) values obtained from laser diffractometry (LD) and photon correlation spectroscopy (PCS), respectively, and zeta potential (ZP) data of the SLN dispersions containing different surfactants at the production date (PD) and after 3 months of storage at various temperatures

Formulations		Mean diameter [μm]			ZAve [nm]	PI	ZP [nm]
		D_{50}	D_{90}	D_{95}			
TegoCare® 450	PD	0.163	0.360	0.486	228 ± 1	0.177	−47.3 ± 0.5
	RT	0.159	0.371	0.511	236 ± 5	0.226	−47.2 ± 0.8
	4 °C	0.460	27.07	64.68	250 ± 9	0.211	−49.6 ± 0.6
	40 °C	0.189	0.378	0.492	230 ± 3	0.198	−54.4 ± 0.4
Tween® 80	PD	0.213	0.389	0.502	190 ± 17	0.270	−41.3 ± 0.7
	RT	0.231	0.398	0.510	218 ± 4	0.144	−42.6 ± 1.0
	4 °C	3.460	49.09	84.61	274 ± 17	0.286	−34.1 ± 1.4
	40 °C	0.206	0.385	0.499	211 ± 3	0.152	−46.0 ± 0.8
Tyloxapol®	PD	2.268	150.0	194.6	200 ± 2	0.133	−38.3 ± 8.9
	RT	0.257	0.446	0.600	196 ± 27	0.188	−28.0 ± 0.4
	4 °C	15.55	42.72	67.06	251 ± 6	0.275	−28.9 ± 1.0
	40 °C	0.227	0.404	0.536	206 ± 3	0.162	−29.7 ± 1.1
Pluronic® F68	PD	0.198	0.379	0.486	248 ± 5	0.151	−35.2 ± 2.1
	RT	0.433	30.61	70.86	261 ± 8	0.192	−27.4 ± 0.7
	4 °C	0.211	0.397	0.513	261 ± 4	0.169	−26.9 ± 0.4
	40 °C	15.42	32.12	43.29	232 ± 4	0.295	−41.6 ± 1.8

Table 2: Crystallization behaviour of Witepsol® E85 in the formulations after 3 months of storage (standardized values) (CI: Crystallinity index)

Formulations	Melting point (°C)	Melting enthalpy (J/g)	CI (%)
TegoCare® 450 (RT)	41.2	29.6	24.9
Tween® 80 (RT)	42.8	1.9	1.6
Tyloxapol® (RT)	–	–	–
Pluronic® F68 (4 °C)	38.2	109.4	92.0

3 months of storage. DSC data, particle size data from PCS and LD and the highest ZP value among the others were in good agreement in the case of TegoCare® 450.
As conclusion, incorporation of a suitable surfactant is one of the critical points to provide the stabilization of a SLN dispersion, since it contributes to higher storage stability by efficiently preventing particle aggregation.

Experimental

1. Production of the formulations

The placebo SLN dispersions containing 10% Witepsol® E85, 1.5% surfactant and 88.5% distilled water were prepared employing the high pressure homogenization technique at a temperature of at least 5–10 °C above the melting point of the lipid to prevent lipid crystallization during production (500 bar, 3 cycles, 75 °C). TegoCare® 450, Tween® 80, Tyloxapol® and Pluronic® F68 were used as surfactants. After production, the SLN dispersions were filled into the clear siliconized glass vials (glass quality I, Bünder Glas, Münnerstädter Glaswaren, Schmidt, Germany) and stored at various temperatures (in the dark): room temperature, 4 °C and 40 °C. The samples were taken at determined time intervals (at the beginning of storage and subsequently on the 1st, 7th,14th, 28th, 60th and 90th day).

2. Particle size and zeta potential measurements

Size measurements of the particles were performed by PCS (Zetasizer 4, Malvern Intruments, UK) for the particles in the 3 nm – 3 μm size range and LD (Coulter LS 230, Beckmann-Coulter Electronics, Krefeld, Germany) for the particles in the 100 nm – 2000 nm size range. PI values for each sample as the width of particle size distribution were also obtained from PCS. LD data characterized the particles as the diameters 50%, 90% and 95% (D_{50}, D_{90} and D_{95}) volume. Particle charge in distilled water (pH 7) adjusted to a conductivity of 50 μS/cm with sodium chloride was measured as ZP using the Zetasizer 4 (Malvern Intruments, UK). MilliQ water was freshly prepared (FU, Berlin, Germany).

3. Crystallization behaviour of the lipid in the SLN dispersions

Crystallinity degree of the lipid was determined using the DSC (Mettler TA 3000 Controller and DSC821^e, Mettler, Switzerland). The samples weighed into 40 μl standard aluminium pans (amount containing 1–2 mg solid lipid) and heated from 25 °C to 85 °C with a heating rate of 5 K/min flushing with 80 ml N_2/min. Melting peaks and enthalpies were calculated using the Mettler Star Software.

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