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Research paper

# Spray-drying of solid lipid nanoparticles (SLN$^{TM}$)

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**Abstract**

Aqueous dispersions of solid lipid nanoparticles (SLN$^{TM}$) were converted by spray-drying into dry, reconstitutable powders which could be stored over a long period. After redispersion, the resulting granulates were still acceptable for i.v. administration with respect to the particle size distribution and toxicity. Therefore only physiologically acceptable excipients such as carbohydrates and alcohols (ethanol and methanol) were added to the SLN dispersions before spraying. The particle size was influenced by the applied spraying parameters and by the chemical nature of the lipid phase, the type of carbohydrate and the spraying, and the redispersion medium. An identical size distribution before and after the spraying process, followed by subsequent redispersion was achieved by: reducing the temperature by spraying alcoholic dispersions, reducing the lipid concentration while increasing the sugar concentration, and by redispersion in a poloxamer 188 solution. 

*Keywords:* Solid lipid nanoparticles (SLN$^{TM}$); Spray-drying; Long-term storage; Poloxamer 188

## 1. Introduction

Solid lipid nanoparticles (SLN$^{TM}$) [1] are interesting colloidal drug delivery systems, since they have all the advantages of fat emulsions (large scale production, no organic solvents, low systemic and cytotoxicity) and polymeric nanoparticles (controlled drug release due to a solid lipid matrix) [2]. They open a broad field of applications including i.v., oral and dermal administration.

For some of these applications, the conversion of the liquid dispersion into a dry product is useful, or often necessary. SLN granulates or powders could be put into capsules, pressed into tablets or incorporated into pellets [3]. Aqueous SLN dispersions possess a long-term stability of at least three years [4]. Nevertheless, a prolonged long-term stability especially for i.v. administered systems can be achieved when stored as a dry product. This may be of interest for SLN containing drugs that are susceptible to hydrolysis or are exposed to elevated temperatures or light in aqueous dispersion [5].

The less cost-intensive spray-drying technique was investigated for SLN as an alternative method to lyophilization. Spray-drying is widely used in the chemical, the food and the pharmaceutical industries. It is commonly used to process milk, eggs, ceramics and fertilizers [6]. It converts a liquid into a dry system in a one-step process and can produce fine, dust-free powders as well as agglomerated ones, to precise specifications.

In general, the process consists of four steps [6]: (1) atomization of the feed into a spray, (2) spray-air contact, (3) drying of the spray and (4) separation of the dried product from the drying gas.

Preparation of both polymeric as well as lipid microparticles by spray-drying or spray-congealing has been reported [7,8]. For heat sensitive materials, an organic solvent was used in most cases to achieve the required lowering in temperature [7–9].

In this study, the development of an SLN system which was still suitable for i.v. administration after spray-drying was performed. The fraction of particles $>5$ $\mu$m, causing a

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possible capillary blockade, should not increase. Furthermore, the SLN powders should be reconstitutable to the identical particle size distribution of the original dispersion. No organic solvents were used, to avoid toxic residues. The number of additives was kept as low as possible. The formulation should not be too complex with respect to the acceptance by the regulatory authorities.

## 2. Materials and methods

### *2.1. Materials*

#### *2.1.1. Lipids*

Cetylpalmitate (m.p. 47°C) was purchased from Caelo (Hilden, Germany). Compritol 888 ATO (glycerol behenate containing ~15% monoglyceride, m.p. 72°C) was provided by Gattefossé (Weil, Germany) and Synchrowax HRSC (glyceroltribehenate and calcium behenate, m.p. 105–115°C) by Croda (Nettetal, Germany).

#### *2.1.2. Emulsifier*

Pluronic F68 (poloxamer 188) was donated by BASF AG (Ludwigshafen, Germany) via the distributor Tensidchemie (Düren, Germany).

#### *2.1.3. Carbohydrates and alcohols*

The carbohydrates (mannitol, lactose, trehalose, sorbitol, glucose and mannose) as well as ethanol and methanol were obtained from Sigma (Deisenhofen, Germany).

### *2.2. Methods*

The SLN dispersions were prepared by high pressure homogenization (APV Micron Lab 40, APV Gaulin, Lübeck, Germany). The melted lipid was added to a surfactant solution of distilled water at elevated temperature (see below). After treatment with an Ultra-Turrax T25 (Janke und Kunkel, Staufen, Germany) at 9500 rev./min, the crude pre-emulsion was homogenized by application of optimized pressures and number of homogenization cycles [10] (see below).

Three exemplary formulations were chosen (all weight percent):

1. Cetylpalmitate 10.0% (m.p. 47°C), poloxamer 188 5.0% (70°C, 500 bar, three cycles)
2. Compritol 888 ATO 10.0% (m.p. 72°C), poloxamer 188 1.2% (90°C, 500 bar, three cycles)
3. Synchrowax HRSC 5.0% (m.p. 105–115°C), poloxamer 188 1.2% (95°C, 1500 bar, five cycles).

Particle size was determined after production, by photon correlation spectroscopy (PCS) (Zetasizer 4, Malvern, UK) and laser diffraction particle size analysis (LD) (Mastersizer E, Malvern, UK). The obtained LD data were always evaluated using the volume distribution, being a sensitive tool to detect even a few larger particles. To characterize the content of large particles the volume diameters 90% or 99% were used, i.e. 90% (99%) of the particles are below this size value.

The carbohydrates were added in concentrations from 2% to 30%. To reduce the lipid content, the 10% SLN dispersions were diluted with water, methanol or ethanol (yielding final concentrations in the SLN dispersion for spray-drying of 10% or 20% alcohol).

Spray-drying was performed with a Mini Spray-dryer Büchi 190 (Büchi, Göppingen, Germany) as it is commonly used in pharmaceutical research. The Büchi 190 has a two-fluid nozzle and operates in a co-current manner. Co-current is preferable for the drying of heat sensitive materials because the dry product is only in contact with the coolest air. Applied spraying parameters were: inlet temperatures from 90°C (water-alcohol mixtures) to 110°C (aqueous systems), outlet temperatures from 50°C (water-alcohol mixtures) to 60°C (aqueous systems), spray-flow 550 Nl/h, aspirator setting 10, pump setting 5 ml/min. A 0.5-mm nozzle was used.

The achieved granulates were redispersed in water and in solutions of poloxamer 188 (being simultaneously an ingredient of the SLN formulations) in concentrations of 0.1% to 1%. Redispersion by shaking or using a Decapeptyl®-redispergator was not successful. Only sonication (sonic bath Sonorex Super RK 255 H-R, Bandelin electronic, Germany) at 40 kHz for 2.5 min was able to break down the aggregates.

The reconstituted systems were analyzed with the same sizing methods as outlined above.

## 3. Results and discussion

### *3.1. Influence of lipid type and concentration*

Generally, SLN are prepared by high pressure homogenization of a molten lipid (hot homogenization technique) [10]. Depending on the chemical nature of the lipid matrix, the recrystallization of the lipid fraction occurs rapidly, or can be retarded over weeks or months [4]. Concerning lyophilization of SLN, formulations containing a lipid with a low recrystallization index proved to be optimal [10]. The microparticle content increased only slightly.

A general difficulty when spraying aqueous solutions was the risk of the SLN melting during the spraying process. Due to the comparatively short falling rate drying period of the Büchi 190 the time for recrystallization of the liquid lipid droplets is limited. Consequently a dry product could not be achieved either in water (inlet temperature 110°C) or in alcoholic solutions (inlet temperature 90°C) with the Cetylpalmitate formulation (m.p. 47°C). The lipid droplets coalesced and adhered as a film to the glass equipment. This formulation had been chosen because of the very narrow particle size distribution and excellent physical stability

[11]. As toxicologically problematic organic solvents should be avoided (regarding i.v. administration) the inlet temperature must be high enough to remove solvent from the particle.

Kecht-Wyrsch postulates that spray-drying of lipid particles is only possible when the boiling point of the spraying medium is below the melting point of the lipid [12]. In contradiction to this finding, spray-drying of Compritol SLN 10% (m.p. 72°C) could be performed successfully with several carbohydrates dissolved in water (b.p. 100°C). Further experiments led to the conclusion that a minimum melting point of at least 65°C is necessary for spraying aqueous SLN dispersions.

During spraying, the evaporated moisture forms a skin around the droplets, which absorbs most of the heat. Hence, a temperature increase, and subsequent degradation of heat-sensitive materials, is prevented. Generally, particles reach a maximum temperature during spraying, which is 15–20°C below the outlet temperature of a co-current dryer [6]. With aqueous SLN dispersions outlet temperatures of 60–65°C were reached, which means a maximum temperature load of 40–50°C. Lipids such as Cetylpalmitate with a melting point in this range cannot solidify during the falling rate period. On the contrary, Compritol, with a melting point of 72°C should not melt during the spraying process.

The redispersability of the spray-dried 10% Compritol SLN dispersion was sufficient for e.g. a peroral formulation but was not satisfactory for i.v. administration. To determine whether partial melting of the lipid matrix triggered particle growth, SLN were prepared with Synchrowax HRSC. The extent of melting was reduced when spraying

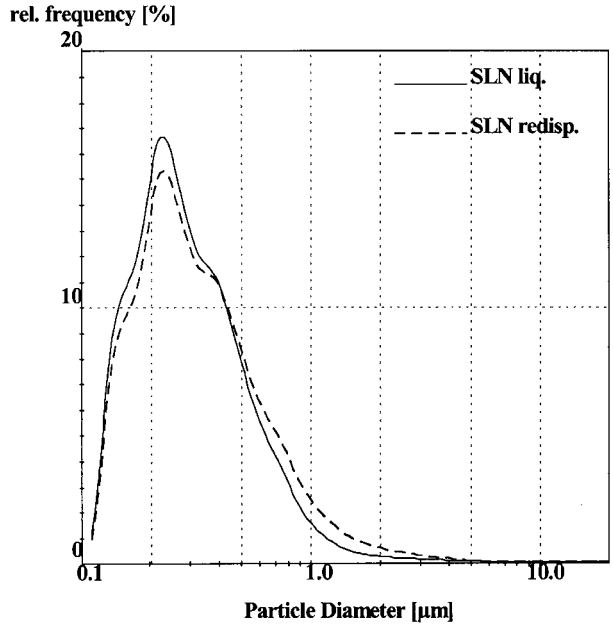


Fig. 1. Volume distribution of 5% Synchrowax SLN stabilized with 1.2% poloxamer 188 and 15% mannitol before (SLN liq.) and after spray-drying (SLN redisp.) (LD data).

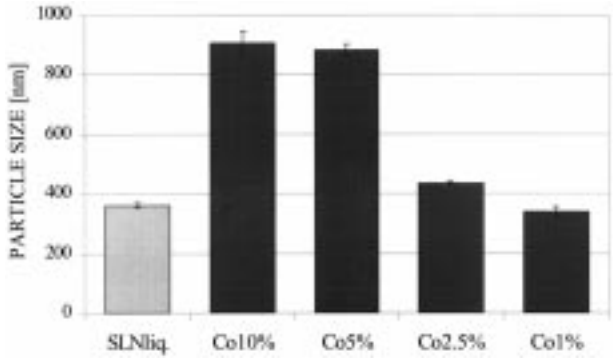


Fig. 2. Mean diameter of Compritol SLN before (SLN liq.) and after spraying with 15% mannitol. Lipid content: 10%, 5%, 2.5%, 1% (Co10%, Co5%, Co2.5%, Co1%) (PCS data).

an aqueous solution (inlet temperature 106°C) of SLN with a melting point of about 110°C. Fig. 1 shows that Synchrowax SLN remained almost unchanged in particle size distribution after the spraying process. However, the yield was poor (about 10%) since the granulate adhered to the glass equipment of the Büchi 190.

Although Synchrowax SLN were homogenized at an increased temperature of 95°C (analogous to the hot homogenization technique [13]), it can be concluded that due to its high melting point the wax remained solid during the production process. Generally, homogenization of lipids in the solid state leads to larger particles and broader size distributions [4]. Synchrowax dispersions can be readily spray-dried but it is difficult to produce SLN with a particle size distribution acceptable for i.v. administration. To obtain SLN which are i.v. injectable and can simultaneously be spray-dried, the following optimization steps were carried out with the Compritol formulation.

Higher temperatures and shear forces induced particle growth and subsequent gelation of aqueous 10% Compritol SLN stabilized with poloxamer 188. Reducing the lipid concentration improved the stability [5]. Generally, dispersed particles will collide if their velocity or kinetic energy is high enough. Both higher temperatures and shear forces increase the kinetic energy of a system. Particle collision can damage partially the surfactant film which coats the interface. Hence, the aggregation tendency will be enhanced. A lower particle concentration means a lower probability of particle contact and subsequent particle growth.

Spray-drying distinctly increases the kinetic energy of a system. When the feed has passed the nozzle and comes into contact with the hot air, both temperature and shear forces are at their maximum and promote the above mentioned effects.

Consequently, reducing the lipid concentration from 10% to 5%, 2.5% and 1% improved the redispersion result. PCS measurements show that with decreasing Compritol content the mean diameter was reduced to the level before spraying (Fig. 2).

From the PCS mean diameter, one cannot draw conclu-

sions about the number of microparticles possibly causing capillary blockade on the i.v. route. Therefore, LD measurements were performed. The amount of larger particles decreased with decreasing lipid content but was still higher than in the original dispersion (Fig. 3). A further reduction to 0.1% lipid did not improve the redispersion result (Fig. 3, right column).

### 3.2. Influence of the carbohydrate type and concentration

Although having reduced the lipid content, particle growth during spraying of Compritol SLN could not be completely avoided. Covering of the particle surface could protect the dispersion against the destabilizing effect of shear forces. Lyophilization of SLN also destroys the surfactant film around the nanoparticles [10]. Carbohydrates have been used successfully as cryoprotectants for SLN reducing particle aggregation. Concerning lyophilization of liposomes, a direct interaction between carbohydrate and liposome surface, as well as a spacer function has been reported [14]. Polyols, mono- and disaccharides are generally considered suitable cryoprotectants. Based on this, two exemplary representatives of each cryoprotectant group were chosen for spray-drying: sorbitol and mannitol (polyols), glucose and mannose (monosaccharides), lactose and trehalose (disaccharides).

Spraying Compritol SLN with mannitol, lactose or trehalose lead to dry, non-sticking, fine-grained powders with limited particle growth after redispersion. All three formulations appeared acceptable for i.v. administration with a maximum LD diameter 99% of $5.03 \pm 0.50$ $\mu$m. That means 99% of the particles are below 5 $\mu$m (Fig. 4). When using volume instead of number distribution for evaluation, the diameter 99% is highly sensitive to even minimal aggregation. The best results were achieved with trehalose. Trehalose also has the best properties for lyophilization of SLN [15]. Sorbitol, glucose and mannose were not suitable. The powders sprayed with sorbitol were not dry, because of its hydroscopicity. The yield with glucose and mannose was too low (below 10%).

Increasing the carbohydrate content increased the protective effect during spraying. A thicker sugar layer, which formed a crust after evaporation of the water, prevented the SLN particles from aggregation and protected them against the heat. Trehalose, possessing a higher water solubility than mannitol or lactose, could be used in much higher concentrations. In Fig. 5 the LD-diameter 90% and 99% of Compritol SLN before and after spraying and reconstitution are compared. Twenty-five percent trehalose led to readily redispersable granulates. The diameter 90% remained unchanged, i.e. 90% of the particles were smaller than $0.94 \pm 0.01$ $\mu$m. The same value was found for freshly prepared SLN. There is only a slight increase in the diameter 99%, from $1.87 \pm 0.09$ $\mu$m (before spraying) to $2.69 \pm 0.10$ $\mu$m (after spraying and reconstitution). These observations with trehalose are in agreement with results found for freeze-drying of SLN, liposomes and emulsions [10,16, 17].

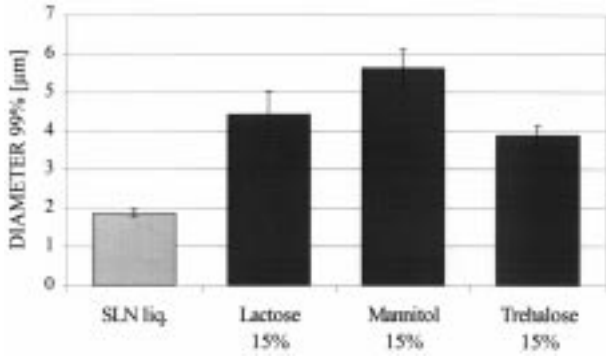


Fig. 4. Diameter 90% (volume distribution) of Compritol SLN before (SLN liq.) and after spraying with 15% lactose, mannitol and trehalose respectively (LD data).

### 3.3. Influence of the redispersion medium

Of all the obtained spray-dried SLN powders, none could readily wet with water. This effect, which makes reconstitution more difficult, has been observed for spray-dried and for lyophilized SLN previously [12,18]. When the spraying feed passed the nozzle, frequent particle collision took place. The surfactant film around the lipid globules was

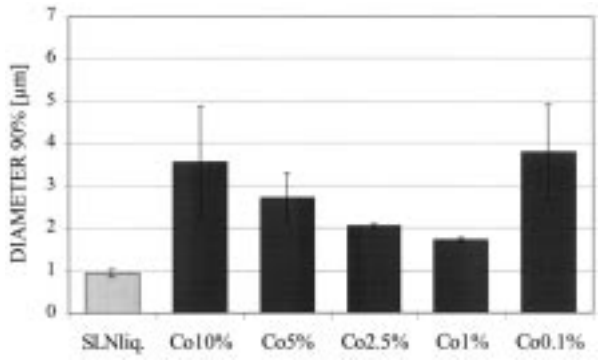


Fig. 3. Diameter 90% (volume distribution) of Compritol SLN before (SLN liq.) and after spraying with 15% mannitol. Lipid content: 10%, 5%, 2.5%, 1%, 0.1% (Co10%, Co5%, Co2.5%, Co1%, Co0.1%) (LD data).

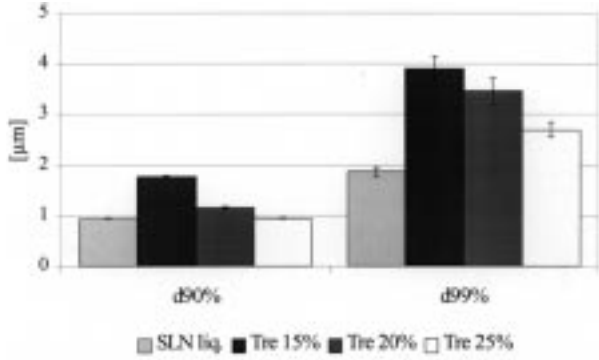


Fig. 5. Diameter 90% (d90%) and 99% (d99%) (volume distribution) of Compritol SLN before (SLN liq.) and after spraying with 15%, 20% and 25% trehalose (Tre15%, Tre20%, Tre25%) (LD data).

shorn off partially and the uncovered hydrophobic surface of the lipid particles reduced the wettability.

Further improvement was achieved using a low concentrated aqueous solution of Pluronic F68 instead of pure distilled water as the redispersion medium. The surfactant reduced the surface tension of the redispersion medium and therefore increased the wetting. Pluronic F68 is also a stabilizing excipient of the aqueous SLN dispersion (see Section 2.1). The effects of the redispersion medium were very small with use of a relatively good reconstitutable system (e.g. Compritol SLN with 25% trehalose, Fig. 5). Therefore, for better detection of improvement in redispersability a non-optimal system (Compritol SLN with 15% trehalose) was chosen. The optimum surfactant concentration was found to be 0.2% (Fig. 6). Higher concentrations of poloxamer 188 resulted in foaming of the systems without any further improvement in reconstitution.

### *3.4. Influence of the spraying medium*

The protective effect of highly concentrated sugar solutions has been shown above. However, the yield when spraying good redispersable systems with 25% or 30% trehalose was much lower (10%) than when spraying with 20% trehalose (37%) or 15% mannitol (45%). These relatively low yields can be explained as follows: due to the short falling rate period of the Büchi 190, the air-jet (regulated by the aspirator setting) had to be high. Only with a high aspirator power was a sufficient drying rate achieved, preventing the granulate from adhering to the glass equipment. A high aspirator power, however, leads to a loss of especially small particles. The particles are taken away with the gas stream [12,19]. Spraying with highly concentrated trehalose solutions increases in general the amount of small particles as it prevents aggregation. That means that compared with other formulations, a larger fraction of small particles is in the spraying chamber. Consequently, a larger fraction is taken away with the air-jet, leading to a lower yield.

To improve the yield, and further minimize particle aggregation, the carbohydrate was dissolved in water-alcohol mixtures. Ethanol and methanol were used in concentrations yielding 10% and 20% final alcohol concentration of the system to be sprayed. The alcohol accelerated the evaporation of the dispersion medium. This decreased the drying time and the amount of humid granulate which could adhere to the glass equipment. The aspirator setting (increased yield) and the inlet temperature (minimization of melting) could be reduced.

Spraying aqueous Compritol dispersions with 20% trehalose lead to a maximum detectable particle diameter of about 3.5 $\mu$m (LD diameter 99% of the volume distribution) (Fig. 7) and a spraying yield of about 37%. Increasing the sugar content to 25% reduced the LD diameter 99% to 2.7 $\mu$m (Fig. 5) but simultaneously reduced the yield to 10%. With the use of ethanolic SLN dispersions with 20% treha-

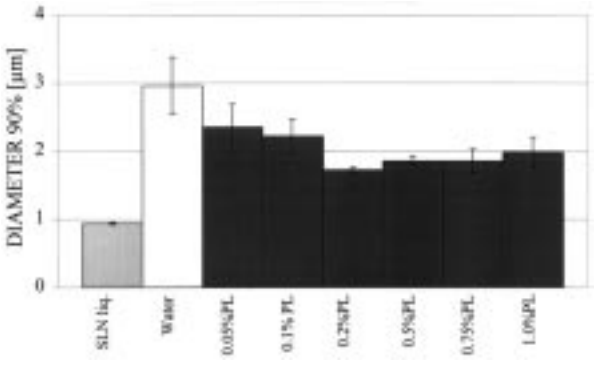


Fig. 6. Diameter 99% (volume distribution) of Compritol SLN before (SLN liq.) and after spraying with 15% mannitol and redispersion in aqueous solutions of Pluronic F68 (0.05% PL–1.0% PL) (LD data).

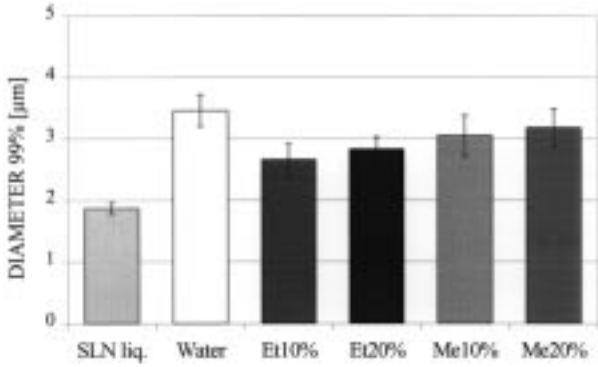


Fig. 7. Diameter 99% (volume distribution) of Compritol SLN before (SLN liq.) and after spraying with a solution of 20% trehalose and 10% respectively 20% ethanol (Et10%, Et20%) and methanol (Me10%, Me20%) (LD data).

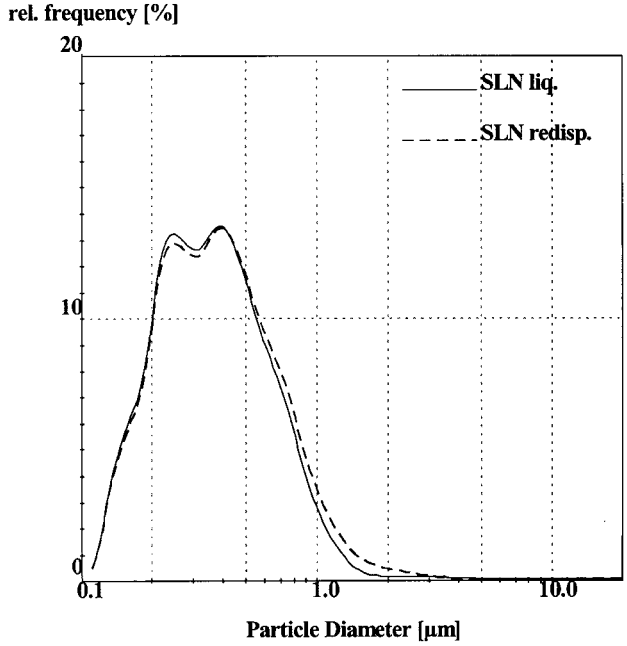


Fig. 8. Volume distribution of Compritol SLN before (SLN liq.) and after spraying with an aqueous solution of 30% trehalose (SLN redisp.) (LD data).

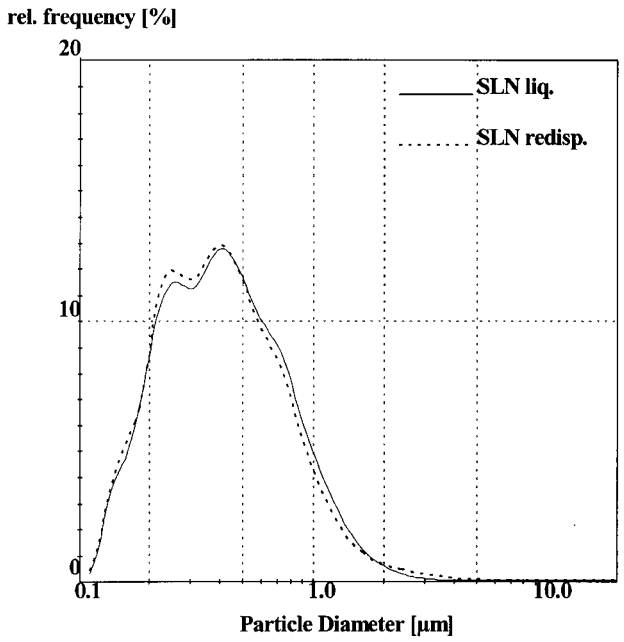


Fig. 9. Volume distribution of Compritol SLN before (SLN liq.) and after spraying with a solution of 10% methanol and 20% trehalose (SLN redisp.) (LD data).

lose the maximum particle size was also reduced to 2.7 $\mu$m (Fig. 7) but the yield was much higher (35%).

### *3.5. Optimized formulations*

After several optimization steps, the SLN powders showed no, or only very little, particle growth after redispersion. This represents an improvement, especially concerning Compritol SLN, which could not be lyophilized without particle growth up to now [10,12]. When combining the optimal parameters, e.g. spraying 1% Compritol SLN with 30% trehalose in water, the particle size distribution after reconstitution is almost identical to that before spraying (Fig. 8). When using a lower trehalose concentration, of 20%, in a solution of 10% methanol, the redispersability remained (Fig. 9) and the spraying yield improved from approximately 10% to 35%.

## 4. Conclusion

Aqueous SLN dispersions can be transferred into dry, fine-grained powders by spray-drying. Many parameters influence the quality of the SLN granulate and its redispersion properties.

Destabilization of the systems during the spraying process is mainly caused by the elevated temperature and by shear forces. Both increase the kinetic energy, leading to frequent particle collision. Additionally, partial melting of the lipid phase during spraying is one of the major reasons for particle growth.

The influence of temperature during spraying of SLN dispersions could be reduced by (1) addition of carbohydrates, the sugar layer around the particles prevented the coalescence of molten lipid droplets, (2) spraying alcoholic instead of aqueous SLN dispersions, due to lower inlet temperatures the extent of melting was reduced.

The influence of shear forces could be reduced by (1) addition of carbohydrates, the sugar layer around the particles protected the emulsifier film against shearing off from the particle surface, (2) decreasing the lipid content, a lower particle content reduces the probability of particle contact and subsequent aggregation, (3) redispersion in solutions of poloxamer 188, uncovered hydrophobic lipid surfaces (shearing off of the emulsifier film) reduced the wettability of the resulting SLN powders. A surfactant solution increased the wettability again.

The aim of the study was to produce spray-dried SLN which were suitable for i.v. administration after redispersion. Only toxicologically acceptable additives were used. Particle growth during spraying could be minimized despite the relatively low melting point of the lipid phase. The granulates were reconstitutable to the identical particle size distribution of the original dispersion.

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