Department of Pharmaceutics, Biopharmaceutics and Biotechnology[1], Free University of Berlin, and Beiersdorf AG[2], Hamburg, Germany

Scaling up feasibility of the production of solid lipid nanoparticles (SLN™)

S. H. GOHLA[2] and A. DINGLER[1]

Solid lipid nanoparticles (SLN™/Lipopearls™) are widely discussed as colloidal drug carrier system. In contrast to polymeric systems, such as polylactic copolyol capsules, these systems show up with a good biocompatibility, if applied parenterally. The solid lipid matrices can be comprised of fats or waxes and allow protection of incorporated active ingredients against chemical and physical degradation. The SLN can either be produced by "hot homogenisation" of melted lipids at elevated temperatures or a "cold homogenization" process. This paper deals with production technologies for SLN formulations, based on non-ethoxylated fat components for topical application and high pressure homogenization (APV Deutschland GmbH, D-Lübeck). Based on the chosen fat components, a novel and easy manufacturing and scaling up method was developed to maintain chemical and physical integrity of encapsulated active and carrier.

1. Introduction

Solid lipid nanoparticles (SLN) are a carrier system for cosmetic ingredients and drugs [1], which combines advantages of emulsions, liposomes and solid polymeric nanoparticles [2]. As no satisfactory and accepted scaling up method exists for polymeric nanocapsules, liposomes and emulsions can be produced easily at large scale. Disadvantage of both technological approaches is their weak chemical and physical protection capacities of sensitive ingredients, such as vitamins [3]. Due to their composition, solid lipid nanoparticles can combine physical integrity of particle shape [4] as well as chemical and physical stabilization of fragile ingredients [5]. This is demanding a standardised manufacturing and scaling up procedure for these carriers.

Solid lipid nanoparticles are produced by high-pressure homogenization, therefore basically scaling up to medium scale level and industrial production level should be possible [6]. This paper describes a standardized scaling up and production method to manufacture drug-free and drug-loaded SLN at medium scale.

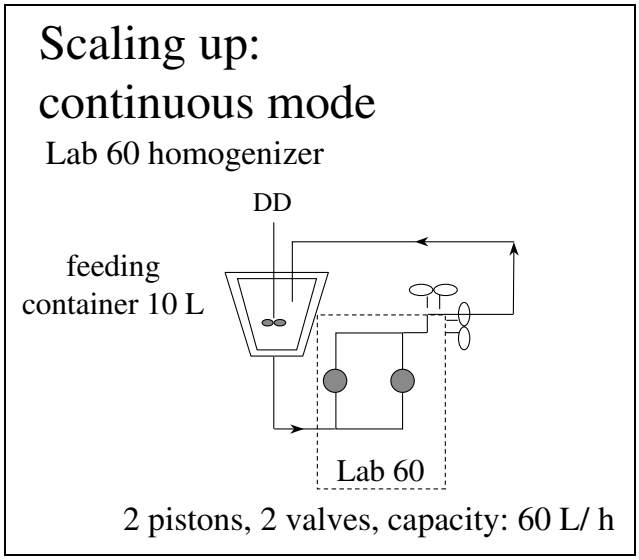

Fig. 1: Production of SLN in a continuous homogenisation mode using an Lab 60 homogenizer

2. Investigations, results and discussion

2.1. 2–10 kg Batches

SLN batches of 2–10 kg were produced by high-pressure homogenization using a modified Lab 60 device (Fig. 1). The production is generally possible with either the circulating or the discontinuous mode (Fig. 2). The circulating mode is characterized by the product feed back directly via a temperature controlled double-walled tube to the feed container. For the discontinuous mode the product is collected in the product container, after completing the first cycle the whole batch is fed back to the feed container to run a second cycle. This is continued until the required number of cycles has been performed [7].

Producing SLN in 2 kg batches the continuous production mode is superior to the discontinuous mode because of the high dead volume of 0.5 l. The variable production parameters, therefore, are production time and homogenisation pressure [8]. Fig. 3 shows the particle size of a drug-free and drug-loaded SLN dispersion produced with 200 or 500 bar. It was demonstrated that limitation of dispersity is directly correlated to the homogenisation pressure. The limit is reached after 15 min of homogenization. Further homogenization has no further influence on the

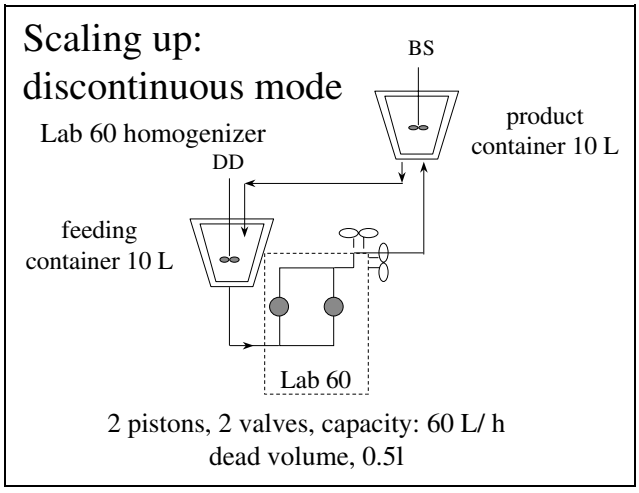

Fig. 2: Arrangement for the production of 50 kg batches: Gaulin 5.5 and Lab 60 are placed in series (fc – 60l feed container, pc – 60l product container, dd – dissolver disk, bs – blade stirrer)

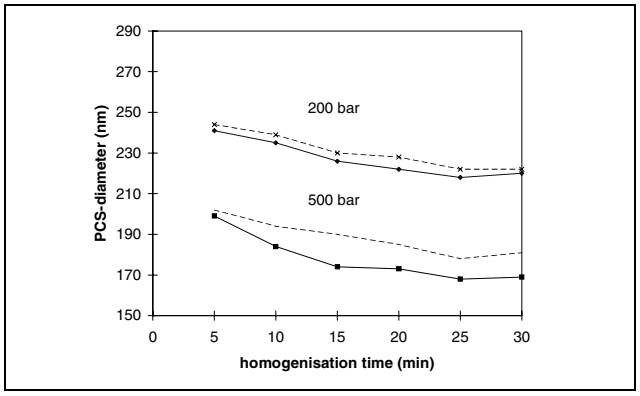

Fig. 3: PCS-diameter (nm) of drug-free or drug-loaded cetylpalmitate SLN produced in a continuous mode with a homogenization pressure of 200 or 500 bar, respectively (2 kg batches). – – – drug-loaded; —■— drug-free

particle size. The mean particle size achieved at 200 bar pressure is 225 nm (PCS-data). 500 bar pressure reduced the particle size down to 170 nm. Drug loading had only a minor impact on the mean particle size, as being shown with our model drug Ubiquinon Q10 [9].

2.2. 10 kg Batches

Production of 10 kg batches in a continuous model would require an extreme increase in the circulation time. Therefore, this batch size and higher can only be produced in the discontinuous mode using the modified Lab 60 (cf. Fig. 1). Fig. 4 shows the decrease in particle size as a function of cycle number or homogenization time if the Lab 60 (batch size 10 kg) was used [10]. A particle size of 255 nm is reached after the second cycle using the discontinuous homogenisation mode. Time optimum was reached after 20 min anticipating the discontinuous mode, whereas the same particle size using the continuous mode was received after 45 min of homogenization.

2.3. 50 kg Batches

A discontinuous production of 50 kg batches is not sensible due to the long and prominent heat exposure of the fats and incorporated actives. Therefore a continuous production mode was realised by combining two homogenizers in series. The first homogenizer had to guarantee a

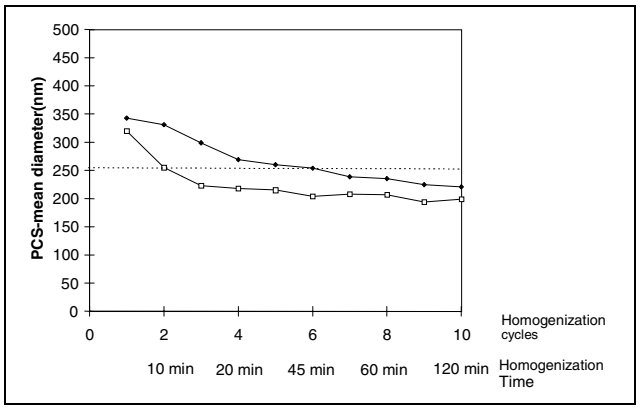

Fig. 4: PCS-mean diameter (nm) of two 10 kg SLN-batches as a function of the homogenization time under discontinuous and continuous homogenization conditions. —◆— Continuous mode; —□— Discontinuous

sufficient supply of dispersion being subsequently fed into the second homogenizer to realise final dispersity. To manage this procedure, a Gaulin 5.5 device was chosen as first homogenizer to transport the SLN dispersion into a Lab 60 as second homogenizer [11]. A computer network tacted these two machines controlled to adapt the production volume of homogenizer 1 according to the needs of the homogenizer 2 (Fig. 4).

The 50 kg feed and product containers allow the production of SLN dispersion under protective gas, e.g. nitrogen. The feed container contains a dissolver disk (DD) for preparation of the pre-emulsion directly in the container. The product container contains a blade stirrer (BS) to keep the SLN dispersion in motion during cooling and recrystallization of the o/w emulsion to obtain solid lipid nanoparticles.

Twenty kg of solid lipid nanoparticles with cetylpalmitate as lipid matrix was produced with the presented production line. The influence of the homogenization pressure of each applied homogenizer on the particle size of the product was investigated. Therefore three experiments were done. The first scaling up batch was produced with 200 bar homogenizer 1 (Gaulin 5.5) and 500 bar at the homogenizer 2 (Lab 60). The second batch investigated the particle size after producing with 500 bar at homogenizer 1 and 200 bar at homogenizer 2. The third experiment was performed with a homogenisation pressure of 500 bar at each homogenizer. Fig. 5 shows the results of the particle size measurements of the 20 kg scaling up batches.

Summing up the production with two homogenizers in series is an excellent way of production of larger batches. Production of 20 kg yielded a small particle size distribution with 99% of the particles smaller than 1.35 μm. A higher homogenisation pressure lead to a further decrease in the particle size. Comparing the particle size of the batches produced with 200/500 bar and 500/200 bar at the first and second homogenizer a similarity in particle size distribution is obviously. Consequently the total homogenisation pressure used for the production determines the particle size. Only an increase in the total homogenisation pressure (500/500 bar) leads to a smaller particle size distribution.

In conclusion the findings of the study show that solid lipid nanoparticles, based on different non-ethoxylated lipids, can be easily scaled up into the industrial scale. Homogenization of 500 bar were detected to be the ideal pressure condition, optimized dispersion rate was achieved with two to three cycles, depending on the size of batch. Introduction of ubiquinon Q10 as model ingredient showed that particle size as well as polydispersity index of the particles are hardly influenced. It could be shown that continuous homogenization has to be favoured with scales up to 10 kg, whereas the bigger scales have to be run discontinuously.

Computing several homogenizers in parallel offers opportunity to manage scale sizes of up to 300 kg.

Future investigations have to show, whether these findings can be transferred to other model ingredients besides Ubiquinone Q10 and can be expanded to other than the described lipids [12].

3. Experimental

Henkel (Düsseldorf, Germany) provided the emulsifier Tego Care 450 Cetylpalmitate, the emulsifier Tego Care 450 by Th. Goldschmidt AG (Essen, Germany). APV Deutschland GmbH (Lübeck, Germany) purchased the homogenizers (Lab series, Gaulin 5.5). Beiersdorf AG Hamburg provided UBIQUINON Q10 as active ingredient.

Table 1: Homogeniering devices and the conditions of work

	Micron LAB 40 (discontinuous)	modified Micron LAB 60	Gaulin 5.5
Batchsize	0.02 to 0.04 l	1 bis 10 l	*
Pump volume	0.04 l/cycle	60 l/h	150 l/h
Temperature control	Homogenizer-parts only	yes	yes
Homogenizer valves	1	2	2
Pressure	100 to 1600 bar	100 to 700 bar	100 to 700 bar

For 20 kg batches a Gaulin 5.5 is employed placed in series with the Lab 60 (Fig. 4). The feed and product containers, homogenization towers and tubes are all separately temperature controlled homogenisation was carried out as being noted in the Table.
Particle size was determined by laser diffractometry (Mastersizer E, Malvern, UK) and photon correlation spectroscopy (Coulter N4 plus, Coulter Electronics, UK).

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Dr. S. H. Gohla
Beiersdorf AG
Unnastr. 48
D-20245 Hamburg