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International Journal of Pharmaceutics 196 (2000) 183–185

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Influence of high pressure homogenisation equipment on nanodispersions characteristics

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Abstract

In this study a comparison of the influence of the homogenising equipment supplied by different manufacturers on the quality of the lipid nanodispersions is given. An Avestin EmulsiFlex-B3 (B3) and APV Micron Lab 40 (LAB 40) were used for high pressure homogenisation. Particle size and particle size distribution were chosen as quality parameters. The influence of different process parameters was evaluated. The two homogenisers were compared in their quality of nanoparticles-production by hot and cold homogenisation technique and in processing nanoemulsions. Working with the B3 appeared as useful for preformulation studies and processing of expensive or rare drugs and excipients. This first scaling up within laboratory scale is evaluated and the problems and remarkable aspects working with the B3 are pointed out.

Keywords: Nanoparticles; High pressure homogenisation; SLN; Nanoemulsions

In the last decade much effort has been spent on the development of solid lipid nanoparticles (SLN) and nanoemulsions. SLN are commonly produced by the hot homogenisation technique. Alternatively a cold homogenisation process can be used to incorporate temperature sensitive drugs or to increase drug encapsulation. In laboratory scale an APV Micron Lab 40 (LAB 40) is commonly used, which produces a sample volume of 40 ml. In preformulation studies with rare or expensive ingredients smaller sample volumes are desirable. These small volumes can be processed with an Avestin EmulsiFlex-B3 (B3) as its sample volume is 0.5–3.5 ml.

The use of different homogenisers raises the question of the comparability of the results. The results given below compare the two piston-gap homogenisers in their quality of nanoemulsion-processing and SLN-production by hot and cold homogenisation technique.

Medium chain triglycerides (Miglyol 812 by Caelo, Germany), Witepsol S58 (Contensio, Germany) and Compritol 888 ATO (Gattefossé, Germany) were used as lipid bases. Tween 80 (BASF, Germany), Poloxamer 188 (Synperonic PE/F68 by ICI Surfactants, Germany, or Lutrol F68 by BASF, Germany) and cholic acid, sodium salt (Sigma, Germany) were used as emulsifiers. Water was supplied by a Millipore MilliQ-Plus.

Nanoparticles were produced by either hot or cold homogenisation technique as described by Müller et al. (1997). Particle size was determined

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0378-5173/00/$ - see front matter
PII: S0378-5173(99)00417-2

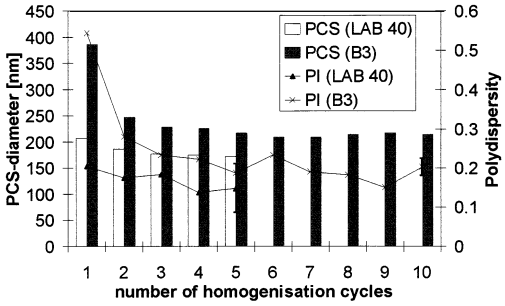

Fig. 1. Photon correlation spectroscopy (PCS)-values and polydispersity indices (PI) of Witepsol-particles produced at 500 bar.

within 24 h after production by photon correlation spectroscopy (PCS using a Malvern Zeta-Sizer4) and laser diffraction (LD using a Coulter LS230). PCS-values, polydispersity indices (PI) and LD50, LD95, LD99-values were used as quality parameters. The LD50-value means that 50% of the particles are smaller than the given size.

Witepsol-nanoparticles emulsified by a mixture of Poloxamer 188 and sodium-cholate were produced at 500 bar using the hot homogenisation technique. Samples were taken after every homogenisation cycle. PCS-values and PI are shown in Fig. 1. Results of laser diffraction measurements are given in Fig. 2. The number of homogenisation cycles necessary to decrease the polydispersity and to get a small particle population was slightly different. In detail, three runs on the LAB 40 and two more using the B3 lead to a plateau in the particle size measurements. So in practice, three runs at the LAB 40 and five at the B3 lead to reproducible and satisfying results.

Additionally, a significant difference in particle size measurements is visible. Although the particles produced with the B3 are in the same size range as those produced with the LAB 40 they are slightly larger.

Cold homogenisation studies were done with a system consisting of Compritol 888 ATO as lipid base and Lutrol F68 as emulsifier. The results are shown in Fig. 3. Comparison of the laser diffraction data shows that the particle sizes achieved with both types of homogeniser are similar. The LD50-values after five cycles are 4.389 μm for the LAB 40 and 3.671 μm for the B3, respectively. Clearly visible, the LD50-values decrease with increasing cycle number (for the LAB 40, LD50-value decreases from 19.07 μm after one cycle to 4.389 μm after five cycles and for the B3 from 8.119 to 3.671 μm).

An additional study was performed with medium chain triglycerides (MCT) to evaluate the effects of temperature in more detail. Miglyol was chosen because it is possible to process it both at room temperature and at higher temperatures in an identical, e.g. liquid state. It was processed at room temperature both on the LAB 40 and the B3 and at 50°C at the LAB 40 for comparable results. The data measured are given in Fig. 4.

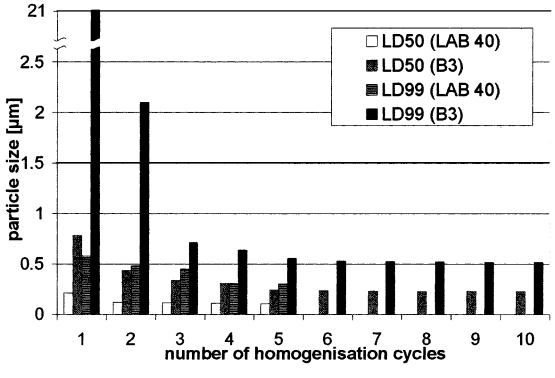

Fig. 2. Laser diffraction (LD) 50 and LD99-values of Witepsol-particles produced at 500 bar.

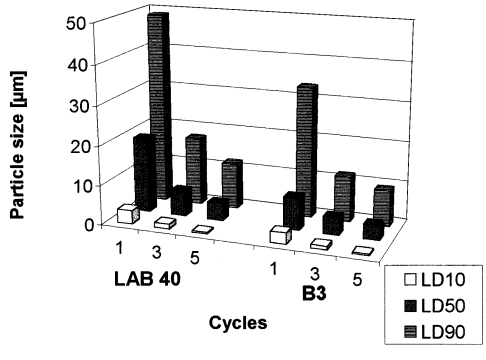

Fig. 3. Laser diffraction (LD)-values of Compritol-particles produced at 1000 bar.

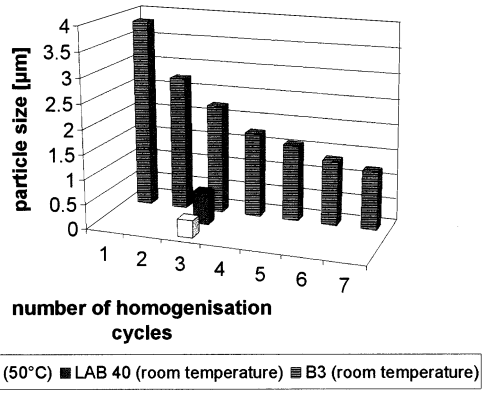

Fig. 4. Laser diffraction (LD) 50-values of medium chain triglycerides (MCT)-emulsions produced at room temperature and 50°C.

The comparison of the droplet sizes shows another behaviour than the Compritol cold homogenisation. The particles produced with the B3 are in the same size range but distinctly larger than those produced with the LAB 40. In addition, a higher number of cycles is necessary to achieve this size range. The comparison of the emulsions produced with the LAB 40 indicates the influence of temperature on the homogenisation result. Higher temperatures lead to smaller droplet sizes.

Summarising these data no general rule was found to prefer one of the homogenisers over the other. Regarding the homogenisation of a liquid dispersed phase (liquid or melted lipids) the LAB 40 achieved better results throughout the study. In contrast to that the B3 appeared more effective in cold homogenisation of a solid dispersed phase. A plateau in particle size distribution is reached with less cycles.

With regard to the practical handling of the machines the geometry and manual adjustment of the gap of the B3 have to be mentioned. Due to the horizontal flow inside the B3, flotation of particles and thus a blocking of the gap occurred frequently. This is avoided working with the LAB 40 because the pre-suspension passes the homogeniser in a vertical way.

Additionally a decreasing flow of the sample with one adjustment of the gap of the B3 was observed. It was not possible to process the whole sample with one adjustment as prescribed in the manual. The changing width of the gap could lead to worse dispersing conditions within one cycle due to reduced shear forces in the widened gap. This would explain the worse results of the B3 in homogenising a liquid dispersed phase. However, it does not give any conclusion concerning the better results in cold homogenisation of solids. No full explanation of the differences was found but it is possible that the different construction of the homogenisers leads to a different partition of the homogenising principles. A satisfying separation and evaluation of the two main dispersing principles (shearing and cavitation) and their influence on the dispersed phase was not possible by these data.

Nevertheless, both homogenisers are able to produce particles in the nanometre range and thus give comparable results. To minimise the blocking of the gap of the B3, it is suggested to place the homogeniser in a vertical position. Concerning special questions such as drug inclusion and lipid recrystallisation studies, the small differences in particle size have to be considered because of the rapidly changing proportion of inner core to particle surface in that size range. Considering the data in Fig. 1 surface per volume ratios of 0.028 nm^{-1} for the B3 and 0.035 nm^{-1} for the LAB 40 were found.

References

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