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International Journal of Pharmaceutics 214 (2001) 21–24

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Production and characterisation of highly concentrated nanosuspensions by high pressure homogenisation☆

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Received 1 June 2000; accepted 10 October 2000

Abstract

Nanosuspensions produced by high-pressure homogenisation are a solution for the formulation of poorly soluble drugs with bioavailability problems. The typical solid concentration of the nanosuspensions is 10%. However, to transfer the nanosuspensions to a dry product (e.g. granulation, tablets, pellets), a higher solid content is required to remove less water. Nanosuspensions with 20 and 30% solid content were produced, the effect of surfactant concentration assessed and their quality (size data) compared with the lower standard concentrations of 1–10% solid.

Keywords: Nanosuspensions; High concentration; High pressure homogenisation; Surfactants

Solubility problems of many newly developed high-potential drugs are a severe obstacle in formulation development, especially when they show poor solubility simultaneously in aqueous and organic media. This leads, in many cases, to a poor and/or varying bioavailability after oral administration (Müller et al., 1996). Alternative intravenous injection is not possible if the particle size is not distinctly below 5 μm. One possibility to solve this problem is the transfer of coarse drug particles into nanoparticles, i.e. nanosuspensions. This improves their dissolution behavior due to increasing saturation solubility and dissolution velocity. Size reduction of the particles by high-pressure homogenisation leads to nanosuspensions (DissoCubes™) (Müller et al., 1999a). In this method, the aqueous dispersion of the drug powder passes through a narrow homogenisation gap of approximately 25 μm in width with a very high velocity. The particles are disintegrated by cavitation forces (Müller et al., 1999b).

By now, physically stable nanosuspensions with a narrow size distribution in the nanometer range have been achieved using drug concentrations between 1 and 10%. To avoid particle growth during storage time or for reasons of convenience, the nanosuspensions can be transformed into a dry product by lyophilisation or spray drying. More-

☆ Presented at the Third European Workshop on Particulate Systems, Utrecht, The Netherlands, 27–29 April 2000.

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0378-5173/01/$ - see front matter
PII: S0378-5173(00)00626-8

over, further processing to granulates or tablets might be convenient for oral administration of the suspensions. To avoid the need for removing a high percentage of water during these processes, highly concentrated nanosuspensions $\gg 10\%$ are very desirable.

This paper describes the production and characterisation of highly concentrated nanosuspensions with a drug content of up to 30%.

RMKK99 was used as a model drug for oral application. Potassium oleate and Tween 80 (Sigma Aldrich, Deisenhofen, Germany) were used as surfactants.

The preparation method of the nanosuspensions was identical for all formulations. The drug RMKK99 was dispersed in a solution of surfactants in different concentrations according to Table 1. The dispersion was premixed for 1 min using an Ultra Turrax (Jahnke and Kunkel GmbH and Co KG, Staufen, Germany) at 9500 rpm. This premix was prehomogenised using a Micron Lab 40 high-pressure homogeniser (APV Deutschland GmbH, Lübeck, Germany) applying the pressures 150 and 500 bar for two cycles each to avoid blocking of the gap by larger particles. Finally, high-pressure homogenisation was carried out applying 1500 bar for another 20 cycles.

Particle size measurements were performed using a laser diffractometer (LD) Coulter LS230 (Coulter Electronics, Krefeld, Germany) and a photon correlation spectrometer (PCS) Zetasizer 4 (Malvern Instruments, Malvern, UK).

The concentration of 10% solid is a frequently used standard concentration when producing nanosuspensions because there is no risk of blocking the homogenisation gap, especially when using finely milled drug particles or micronised drug to prepare the pre-suspension. To assess the upper limit of solid concentration to be processed, the concentration was stepwise increased to 20 and 30% solid content. Similar to parenteral fat emulsions being stabilised in general by 1.2% lecithin, approximately 1% surfactant/stabiliser concentration is sufficient to stabilise 10% nanosuspensions. In parenteral fat emulsion technology, even 20% emulsions are formulated with 1.2% lecithin only because there is still an excess of free lecithin in the water (formation of liposomes). Therefore, the 20% nanosuspension B was produced with identical stabiliser concentrations as the 10% nanosuspension A.

To assess potential effects of increased surfactant concentrations, higher stabiliser concentrations were used in nanosuspensions C and D. The 30% nanosuspension E was produced with highest surfactant concentration just to ensure complete coverage of the surface (Table 1). The particle size obtained during the homogenisation process for a given drug depends primarily on the power density applied (pressure) and the number of homogenisation cycles. The role of the surfactants is to stabilise the produced nanoparticles, thus avoiding particle aggregation. Differences observed between different surfactants or surfactant concentrations therefore correlate with their ability to prevent aggregation. This is confirmed by the mean PCS diameter of the nanosuspensions B–D being around 800 nm. Nanosuspension C has the lowest PCS diameter and, simultaneously, the lowest polydispersity index of 0.24. The polydispersity index of nanosuspension B is distinctly higher. This is attributed to aggregates also causing the increased PCS diameter (Fig. 1). Obviously, the medium stabiliser concentration leads to optimum coverage of the particle surface, and aggregation effects partially observed with higher stabiliser concentrations (e.g. anchoring) are avoided.

To produce nanosuspensions with a higher concentration of solid, it is preferential to start with a very fine drug powder. To avoid blocking of the homogenisation gap, it is recommended to perform so-called pre-milling. A few cycles are run at lower pressures, increasing the pressure from one

Table 1
Concentrations of RMKK99 and surfactants in different formulations

Formulation	RMKK99 (%)	Potassium-oleate (%)	Tween 80 (%)
A	10	1.0	0.5
B	20	1.0	0.5
C	20	1.5	0.75
D	20	2.0	1.0
E	30	2.5	1.25

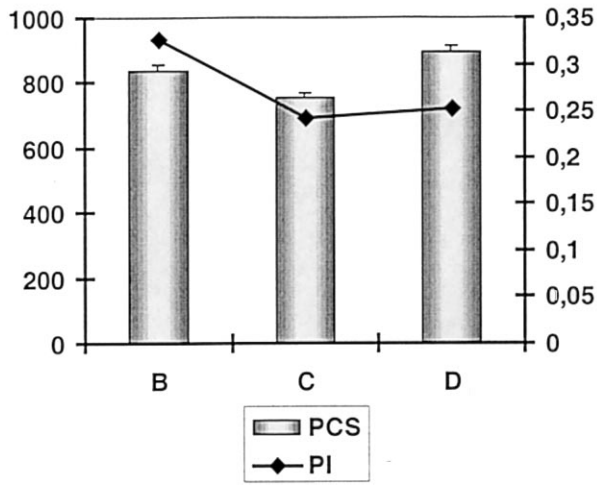

Fig. 1. Mean diameters of formulations with different surfactant concentrations measured by PCS.

cycle to the next until the final production pressure is reached. Typical sequence for pre-milling is two cycles at 100 bar, two cycles at 200 bar, two cycles at 500 bar and two cycles at 1000 bar. In this case, such an extensive pre-milling was not necessary due to the fineness of the product, only short pre-milling was applied (see earlier).

The particle size distribution of the three differently concentrated nanosuspensions A, C and E was compared using the diameters 50, 90 and 95% as characterisation parameters (Fig. 2). It should be noted that, in contrast to PCS, the LD data represent a volume distribution that weights more intensively large particles. Even if there are only a few large particles, especially the diameters 90 and 95% will increase distinctly. Compared with the 10% nanosuspension, the higher concentrated nanosuspensions showed slightly increased diameters; however, there was little difference between the 20 and 30% nanosuspensions. So far there was a tendency to obtain rather smaller particles when increasing the solid concentration (e.g. from 1 to 10%), which was attributed to increased collision of particles at higher concentrations during the homogenisation. The slightly increased diameters when increasing to 20% can be explained via the power density applied (work per dissipation volume and per time unit). The production conditions were kept constant for all concentrations, which means the energy to disintegrate particles was identical in all three productions despite the fact that the mass of material to be disintegrated doubled or tripled. To achieve a product of similar size as the 10% nanosuspension, more cycles (disintegration energy) need to be applied.

When increasing the solid concentration of RMKK99 to 40%, the viscosity of the suspension increased distinctly and it became pasty. Such high-viscosity suspensions are not suitable for homogenisation using the labscale instrument LAB 40. However, such viscous systems can be processed by larger homogeniser types, e.g. by applying a pressure in the feeding vessel. Piston-gap homogenisers especially for processing of viscous materials are available. Nanosuspensions of 40% solid content were, for example, prepared using a Stansted homogeniser 7400 series/4755 valve (Krause, 2001).

To summarise, nanosuspensions up to 30% solid content can be produced, and even higher concentrations are possible when using a modified homogeniser design (active transport of product). The obtained sizes are in a similar range to low-concentration nanosuspensions of 1–10%. Smaller particles can be achieved by increasing the applied total disintegration energy (increased cycle numbers).

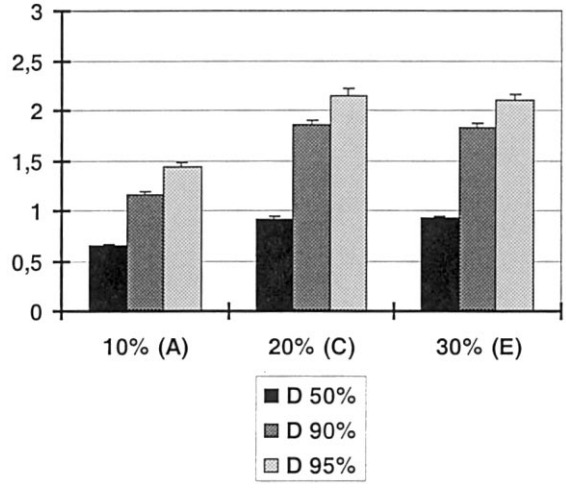

Fig. 2. The diameters 50, 90 and 95% of formulations A, C and E after 20 cycles of homogenisation directly after production measured by laser diffraction.

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