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Nanosuspensions of poorly soluble drugs — reproducibility of small scale production

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Abstract

The major problem of many newly developed pharmaceutical drugs is their poor solubility in water and simultaneously in organic media. To solve these problems formulation as nanosuspensions is an attractive alternative. During the drug development process screening for an optimal formulation by homogenisation is essential. Time and cost effective production in an initial phase of R&D can be conducted on lab scale by using the Micron Lab 40 in its discontinuous version. In this report reproducibility of small scale production parameters (particle size, size distribution, content of microparticles) was exemplary studied for the drug RMKP22.

Keywords: Drugs; Nanoparticles; Polydispersity index

One approach for the formulation of poorly soluble drugs is the transfer to drug nanoparticles. Drug nanoparticles can be prepared by a precipitation process leading to hydrosols (List and Sucker, 1988) or alternatively by ultra-fine milling. The milling techniques which can be employed are very limited, in general techniques like jet milling lead to a product possessing a too broad size distribution (e.g. 0.1–25 μm) and only a very small fraction of particles in the nanometer size range (Müller et al., 1996). Using a pearl mill leads to the product NanoCrystals® (company NanoSystems, Liversidge et al., 1991) and the use of a high pressure homogeniser to nanosuspensions/DissoCubes® (Skye Pharma PLL, UK, Müller et al., 1999). A limitation to hydrosols is the prerequisite that the poorly soluble drug needs to be at least soluble in one solvent which is miscible with a non-solvent to perform the precipitation step. However, many drugs are simultaneously poorly soluble in aqueous and organic solvents. A critical parameter in the production of hydrosols is the need to stop the growth of the precipitated nanoparticles by controlled addition of surfactants to avoid formation of micrometer particles.

Control of the precipitation conditions and the need to take measures against the particle growth can effect the reproducibility of the particle size and size distribution obtained. Basically a milling

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process appears to be much easier to control. The aim of this study was therefore to investigate the reproducibility of the production of DissoCubes® by high pressure homogenisation.

Production of DissoCubes® on lab scale is typically performed by using a Micron Lab 40 in its discontinuous version (APV Deutschland GmbH, Germany). This yields a batch size of 20–40 ml. However, reproducibility is of little use when it can only be achieved on lab scale. Therefore, for this study a continuous Lab 40 was employed yielding a batch size of 200–500 ml in its standard version but allowing also the production of a few litres in its modified version (use of larger product containers).

RMKP22 4-[*N*-(2-hydroxy-2-methyl-propyl)-ethanolamino]-2,7-bis(cis-2,6-dimethylmorpholin-4-yl)-6-phenyl-pteridine was provided by Dr Karl Thomae GmbH (Biberach, Germany). The surfactant Tween 80 and glycerol were purchased from Merck AG (Darmstadt, Germany).

The drug microparticles were dispersed in the surfactant solution and passed through a continuous Micron Lab 40. Homogenisation was performed at room temperature applying a variable pressure profile. Two cycles were performed at 150 bar, two cycles at 500 bar and finally ten subsequent cycles at 1500 bar. Samples were drawn after each second cycle for particle size analysis.

Particle size analysis was performed by laser diffractometry (Coulter LS 230, Coulter Electronics, Krefeld, Germany) and by photon correlation spectroscopy (PCS) (Malvern Zetasizer4, Malvern Instruments, UK).

Laser diffractometry yields a volume size distribution. As characterisation parameters the diameters 10, 50, 90, 95 and 99% were used. For example diameter 99% means that 99% of the particles are below the given size value.

PCS yields the mean diameter of the bulk population (*z*-average, measuring range: 3 nm–3 μm) and a polydispersity index (PI) as measure for the width of the distribution. The PI ranges from zero (monodisperse particles) to 0.500 (broad distribution), values above 0.5 do not allow allocation to a logarithmic normal distribution to the PI. The nanosuspension was composed of 1% RMKP22, 0.3% Tween 80, 2.2% glycerol and water.

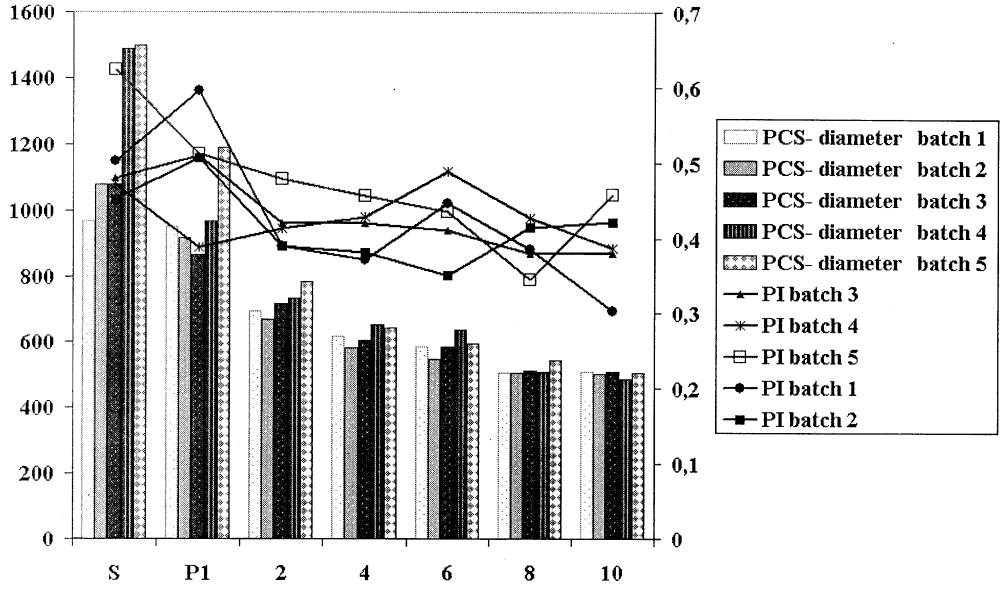

Fig. 1. Photon correlation spectroscopy (PCS) diameter and polydipersity index (PI) of nanosuspensions as a function of the number of homogenisation cycles (pre-milling: one cycle (P1); milling: cycle 1–10; reference: stock dispersion (S) before homogenisation).

Table 1
Photon correlation spectroscopy (PCS) diameter and polydispersity index (PI) of batches 1–5 obtained after two, six and ten homogenisation cycles and calculated mean values of these batches

Batch no.	Cycle 2		Cycle 6		Cycle 10	
	mean (nm)	PI	mean (nm)	PI	mean (nm)	PI
1	692	0.389	585	0.447	508	0.303
2	667	0.390	547	0.351	504	0.421
3	717	0.420	585	0.410	508	0.38
4	733	0.414	635	0.489	486	0.387
5	781	0.479	596	0.436	506	0.458
Mean	718	0.418	590	0.427	502	0.390

A total of five batches of 200 ml nanosuspension were produced applying the described production parameters. In general it is beneficial to start with a powder size as small as possible, that means RMKP22 was used in jet milled form. The applied pressure profile of 150/500/1500 bar is an optimised profile to avoid blockade of the homogenisation gap. Homogenisation at 150 and 500 bar is a pre-milling to disintegrate relatively large microparticles in the drug powder, that means > approximately 20 μm. Jet milled drug powders are typically in the size range 0.5–25 μm, that means this pre-milling step is specially essential when processing larger sized normal drug powders.

The width of the homogenisation gap is a function of the applied pressure, that means it decreases with increasing pressure. At 1500 bar the width of the gap is approximately 25 μm, therefore application of this special pre-milling step.

In general, the particle size decreases with an increasing number of cycles and increasing homogenisation pressure. Fig. 1 shows the effect of the pre-milling after one cycle at 150 bar (P1) compared to the mean PCS size of the stock dispersion (S) before homogenisation. The relatively small size of the stock dispersion can be explained by the limited measuring range of PCS, particles above 3 μm are not detected leading to an artificially low PCS mean diameter.

Applying the production pressure of 1500 bar leads to a continuous decrease with increasing cycle number. There is no further decrease after eight cycles because the maximum dispersitivity at the given power density has been reached. There is also a decrease in the PI from P1 to cycle four to cycle six. The product is getting more homogeneous in size, due to the disintegration of micrometer drug particles which were still in the suspension. To sum up: the number of cycles required for a nanosuspension (e.g. 2, 5 or 10) depend on the desired size and uniformity of the product which depends of course on the envisaged route of administration (e.g. oral vs. parenteral, s.c. and i.m. vs. intravenous).

Table 1 shows mean PCS diameters and PI values obtained with the five different batches exemplarily for homogenisation cycles 2, 6 and 10. It shows a high reproducibility of the mean size in-between the batches and at each cycle number. For example, the mean diameter of the five batches after ten cycles is 502 nm, the size variation observed ranges from 486 to 508 nm.

To obtain maximum physical stability (avoidance of Ostwald ripening) the nanosuspension should be as homogeneous as possible, that means reduction of the number of micrometer particles. A low content of micrometer particles is also essential when the product should be injected intravenously, that means especially the content of particles larger 5 μm to avoid capillary blockade. Table 2 shows the diameters 10–99% measured by laser diffractometry. Typically, after ten homogenisation cycles 99% of the volume of the

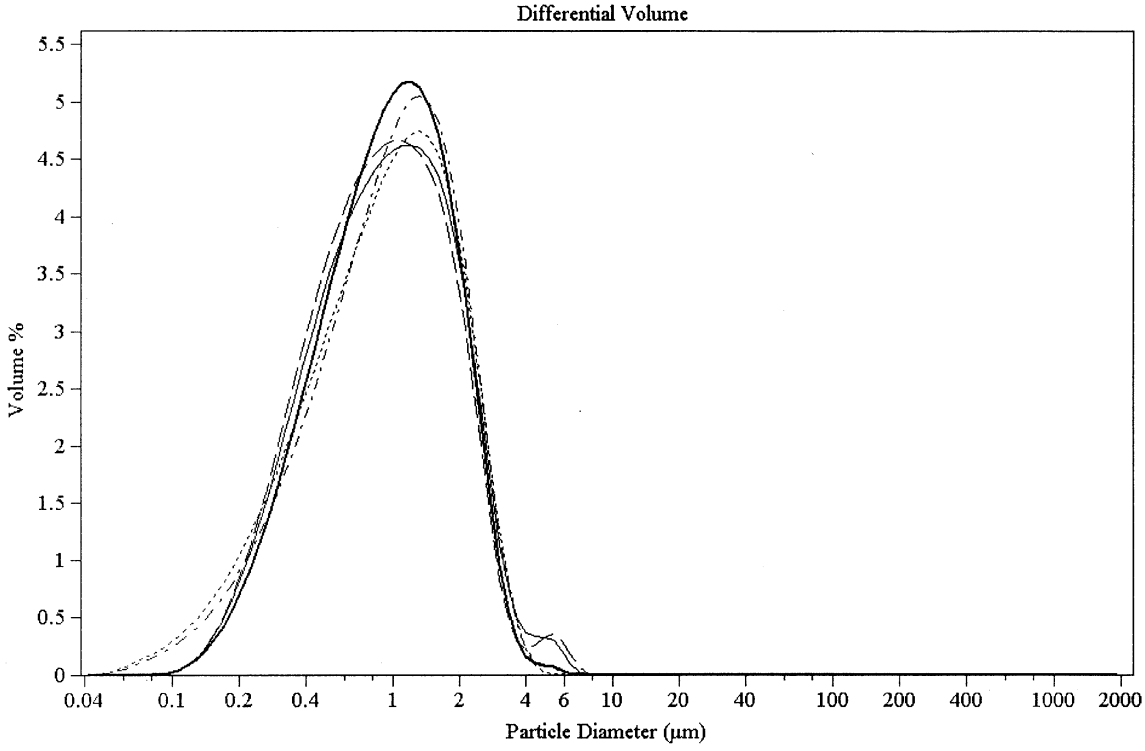

Fig. 2. Size distributions of the five batches after the last ten homogenisation cycles at 1500 bar.

Table 2
Laser diffractometry data: diameters 10–99% [µm] measured in the five batches after ten homogenisation cycles

Batch	Diameters after ten cycles				
	10%	50%	90%	95%	99%
1	0.33	0.94	2.27	2.77	4.61
2	0.32	0.91	2.18	2.65	4.84
3	0.27	0.94	2.21	2.63	3.46
4	0.30	0.99	2.22	2.62	3.49
5	0.35	0.96	2.13	2.52	3.36
Mean	0.31	0.95	2.20	2.64	3.95

particles is below 5 µm. It should be noted that the laser diffractometry data are a volume distribution and that the size range used for calculating the diameters is broader than for PCS. Therefore, the diameter 50% needs to be higher than the mean PCS diameter. Comparing the calculated mean diameters of Table 2 with the observed variation from batch 1 to 5 confirms again the high reproducibility of the production process.

Fig. 2 shows an overlay of the size distributions of the five batches determined by laser diffractometry demonstrating also the reproducibility of the production process.

In conclusion, the milling process by high pressure homogenisation for the production of drug nanoparticles is highly reproducible with regard to the mean size and width of the distribution of the bulk population (PCS data) but also regarding the low content of micrometer particles (LD data).

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