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Nanosuspensions as a new approach for the formulation for the poorly soluble drug tarazepide

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Abstract

Poorly soluble drugs are often a challenging problem in drug formulation, especially when the drug is not soluble in either aqueous media or organic solvents. Attempts to overcome the solubility problem are, e.g. solubilisation with mixed micelles or forming a complex using cyclodextrines, but these approaches are of limited success. Another problem with new high potential drug is that these drugs often show bioavailability problems. One tried to improve the in vivo performance of poorly soluble drugs by reducing the particles size of the drug thus leading to an increased surface area and an increased dissolution velocity (Müller et al., 1994, 1999). Some of these problems occurred with tarazepide and therefore it was tried to create a formulation with this drug as nanosuspension which is suitable for intravenous administration.

Keywords: Nanosuspension; Tarazepide; Long-term stability

Tarazepide (Fig. 1), provided by Solvay Pharmaceuticals GmbH (Hannover, Germany), is a highly potent selective CCK_a-antagonist, poorly soluble in aqueous systems but orally active. The aim of this study was to obtain a formulation, which is suitable for i.v. administration and long term storage (Müller et al., 1995a). The nanosuspensions were produced for animal testing for the purpose of determining tarazepide toxicity. Therefore the aim was to obtain a product of good quality, that means homogeneity of the nanosuspension with a very small amount of microparticles, especially under 5 μm to prevent capillary blocking. With high pressure homogenisation it is possible to obtain a uniform product with a very low fraction of particles in the micrometer range. To avoid effects, such as anaphylactic shock or other allergic reactions, because of presence of surfactants, it was important to reduce the amount of surfactant without loosing a stable suspension.

First of all a screening of formulations was designed with different types and concentrations of commonly used surfactants. The drug powder was dispersed in an aqueous surfactant solution using an Ultra Turrax (Jahnke und Kunkel GmbH, Staufen, Germany) for 1 min at 9500

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Table 1
Composition of tarazepide formulation A–C

Formulation	Compounds	Percentage (w/w)
A	Tarazepide	10.0
	Lutrol F68®	0.5
	Tween 80®	0.25
	Aqua ad inject.	ad 100
B	Tarazepide	10.0
	Lutrol F68®	1.0
	Tween 80®	0.5
	Glycerol	0.61
	Aqua ad inject.	ad 100
C	Tarazepide	10.0
	Lutrol F68®	1.0
	Tween 80®	0.5
	Aqua ad inject.	ad 100

rpm. The obtained premix was homogenised using an APV Gaulin Micron LAB 40 homogeniser (APV Germany, Germany). At first two cycles at 150 bar and two cycles at 500 bar as a kind of premilling were applied, then ten homogenisation cycles at 1500 bar were run to obtain the final product. Glycerol, to adjust the osmotic pressure, was added after production. Based on an initial screening, the most successful surfactants in stabilising this drug as nanosuspension were selected to produce three formulations (A–C) for further stabilising testing. The surfactants were used in two different concentrations. The surfactants Lutrol F 68® (poloxamer 188) were obtained from BASF (Ludwigshafen, Germany), Tween 80® and glycerol from Merck (Darmstadt, Germany), Aqua ad injectabilia: was purchased by B. Braun Melsungen AG (Melsungen, Germany).

Production was performed under a laminar air flow (LAF) cabinet to get a sterile product. Long-term stability was determined by measuring particle size and increase of particle diameter over a period of 6 weeks (Müller et al., 1995b). From these data following, surfactant and concentration were assessed for optimal stabilization of tarazepide as nanosuspension: a combination of Lutrol F68® and Tween80®.

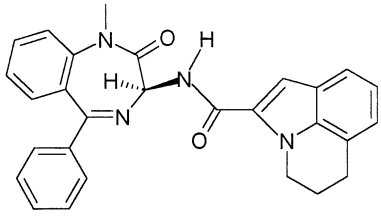

Fig. 1. Chemical structure of tarazepide.

In a continued work, formulations, as presented in Table 1, were produced (Böhm et al., 1998) to observe the stability over a period of 4 months. All compositions were stored at room temperature, no preservatives were added. Particles size analysis was again performed by laser diffraction (LS 230, Coulter Electronics, Krefeld, Germany). The diameters were calculated using the volume distribution. Additionally photon correlation spectroscopy (PCS) (Malvern Zetasizer 4, Malvern Instruments, UK) was used to detect the mean PCS diameter of the bulk particle population and the polydispersity index (PI). Zeta potential measurements were performed in distilled water with conductivity adjusted to 50 μS, field strength 20 V/cm (Malvern Zetasizer 4, Malvern Instruments, UK).

To sum up the results: after production all formulations showed a similar size distribution. A narrow size distribution is essential to prevent particle growth due to Ostwald ripening being caused by different saturation solubilities in the vicinity of differently sized particles. In these three formulations only a small amount of microparticles occurred, what is demonstrated in Fig. 2.

Zeta potential was also measured 1 day after production. The zeta potential of formulation A was −33 mV, formulation B −29 mV and formulation C −30 mV. A zeta potential of at least approximately 30 mV is required for a stable dispersion. In this case stability for nanosuspension A–C was found for at least a quarter of a year (analysis time by now). The PCS data for this period are given in Fig. 3.

As shown in Fig. 3 the mean particle of the three formulations ranged from 347 to 517 nm. This is in an acceptable range and did not change very much within 91 days. Of importance was that glycerol had no impact on the stability of these nanosuspensions. With regard to the production process it is much easier to add the required amount direct to the nanosuspension

rather than adjusting the osmotic pressure just before application to the patient.

It should be noted that the LD data are volume based, the PCS mean diameter is light intensity weighted size. Therefore the PCS mean diameter and the diameter 50% from the LD are not identical, LD data are generally higher.

The data show, that for long-term stability a higher concentration of surfactant is essential. Nanosuspension formulation A showed particle growth after 90 days of storage, whilst no particle growth of nanosuspension B and C (double concentration of surfactants) occurred (Fig. 4). These data confirm that the addition of glycerol had no

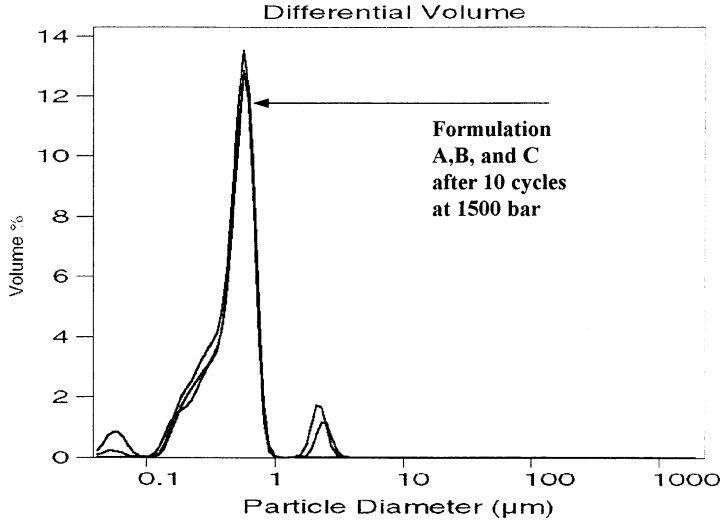

Fig. 2. LD size distribution of tarazepide formulation A, B, and C 1 day after production.

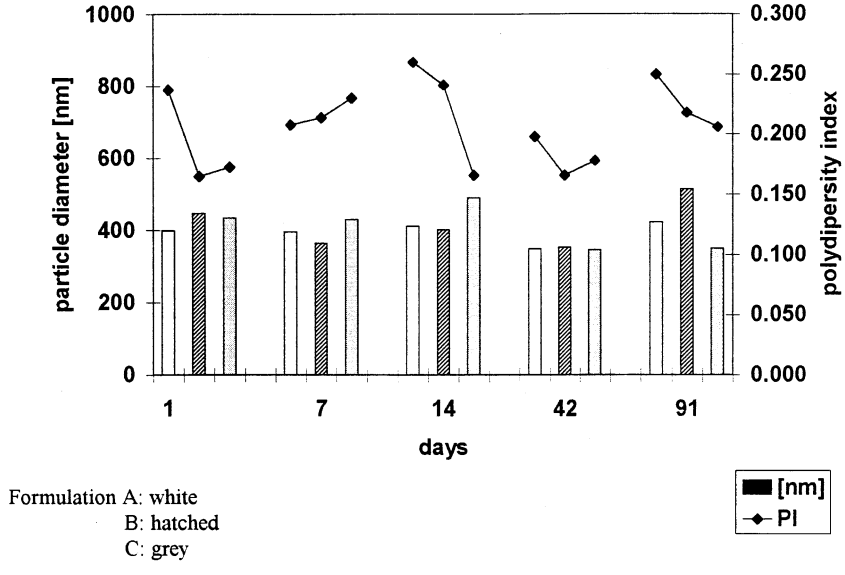

Fig. 3. Photon correlation spectroscopy (PCS) mean diameter and polydispersity index (PI) of the formulations A–C as a function of storage time (stored at room temperature).

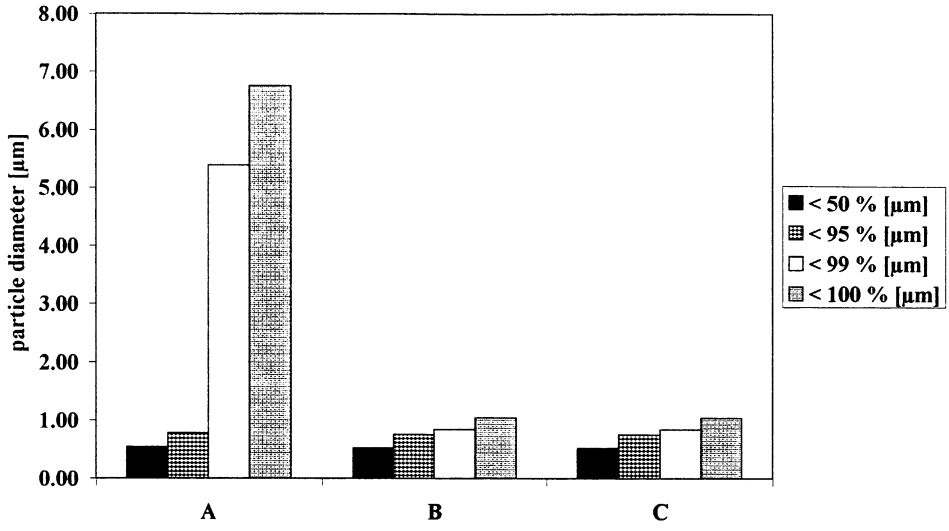

Fig. 4. Laser diffraction diameters 50, 95, 99 and 100% of tarazepide nanosuspension formulation A–C day 91 (storage at room temperature).

impact on the long-term stability of these formulations.

A product of high quality, in this case homogeneity of nanoparticles with a low fraction of microparticles was obtained for tarazepide using the optimised formulations. The nanosuspension was well tolerated when administered intravenously in rats and mice (data unpublished). It was also demonstrated that a long-term stable nanosuspension, when using a sufficient high concentration of surfactant, can be obtained.

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