The number of poorly soluble drugs – in classical and pharmabiotech NCEs – is steadily increasing. A poor solubility is generally associated with poor bioavailability. Nanocrystals are a novel formulation approach for these compounds, this paper describes production of patient-convenient oral dosage forms.

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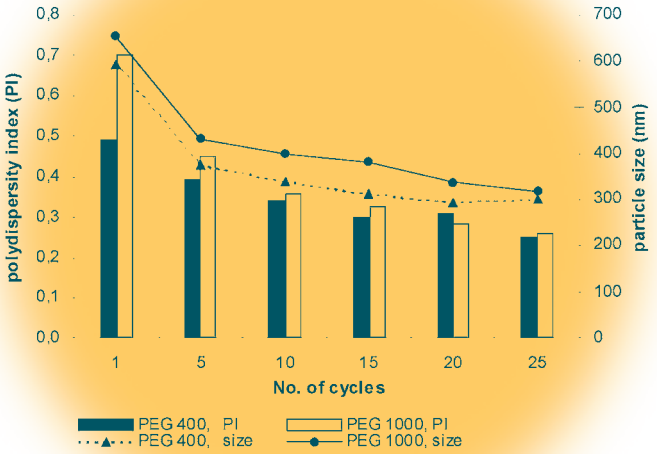
Nanocrystals of Poorly Soluble Drugs *for Oral Administration*



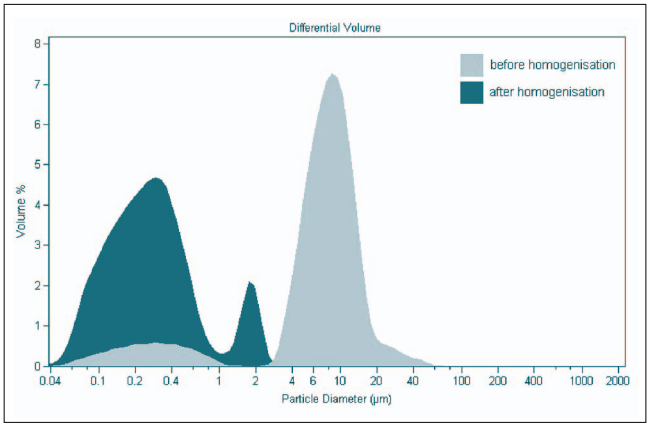
1 *PCS diameter and polydispersity index of Amphotericin B nanosuspension in PEG 400 and PEG 1000 as a function of homogenisation cycles (homogenisation pressure: 1500 bar)*

At present about 40% of the drugs being in the development pipelines are poorly soluble, even up to 60% of compounds coming directly from synthesis are poorly soluble [1]. Poor solubility is in most cases associated with poor bioavailability. According to the Noyes-Whitney law the dissolution velocity dc/dt depends on the saturation solubility c_s. There are two basic approaches to overcome the bioavailability problems of these drugs:

1. Increase of saturation solubility (e.g. by complex formation)
2. Increase of dissolution velocity.

The first approach was of limited successs as clearly demonstrated by the low number of products on the market based on such technologies. A much more straight forward way is increasing the dissolution velocity by increasing the surface area of the drug powder, i.e. micronisation leading to mean particle sizes of approximately 3 - 5 µm. However, many of the new compounds show such a low solublility that micronisation does not lead to a sufficient increase in bioavailability after oral administration. Therefore the next step taken was nanonisation. The drug powder is transferred to drug nanocrystals, typical sizes are around 200 - 600 nm.

The main production technologies currently in use to produce drug nanocrystals yield as a product a dispersion of drug nanocrystals in a liquid, typically water (so called "nanosuspension"). However, the most convenient dosage form for the patient is a dry product, e.g. tablet or capsule. This paper describes the formulation of drug nanocrystals to tablets and capsules.



2 *Laser diffractometry size distributions of the Amphothericin B powder in PEG 400 prior homogenisation and after homogenisation with 25 cycles*

Materials and methods

Amphotericin B was obtained from B. Braun Melsungen AG (Melsungen, Germany), polyethylene glycoles of different molecular weight were kindly supplied by BASF (Ludwigshaven, Germany). Homogenisation was performed

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using a lab scale Micron LAB 40 (APV Systems, Unna, Germany). Particle size analysis was performed by photon correlation spectroscopy using a Mastersizer 4 (Malvern Instruments, Malvern, U.K.) and laser diffractometry using a Coulter LS 230 (Beckman Coulter, Krefeld, Germany). PCS yields the mean diameter of the bulk population (z-average) and a polydispersity index quantifying the width of the size distribution. The polydispersity index (PI) ranges from theoretically 0 (monodisperse population) to 0.50 (relatively broad distribution), e.g. fat emulsions for parenteral nutrition have PI values between 0.10 and approximately 0.25. Laser diffractometry yields a volume distribution, the diameters d25%, d50% and d99% were taken as characterisation values for the size distribution.

Results and discussion

Production of drug nanocrystals (Nanopure)

Drug nanocrystals can be produced by bottom up techniques (i.e. precipitation) [2] or alternatively by bottom down technique (i.e. disintegration, milling). The bottom up technique is the classical precipitation approach, the drug is dissolved in a solvent which is subsequently added to a nonsolvent to precipitate the crystals. A priori this technique is difficult to handle, the crystal growth needs to be stopped to avoid formation of microcrystals. In addition this technology cannot be applied to the increasing number of drugs beeing poorly soluble in all media. From this, disintegration technologies are the method of choice for industrial production.

There are three basic technologies currently in use owned by different companies:

1. Pearl milling (Nanocrystals – élan prev. Nanosystems) [3, 4]
2. Homogenisation in water (Dissocubes - SkyePharma; Nanoedge - Baxter) [5, 6]
3. Homogenization in nonaqueous media or in water with water miscible liquids (Nanopure - PharmaSol Berlin) [7-13]

Approaches 1 und 2 yield aqueous nanosuspensions, the water needs to be removed to formulate tablets and capsules, e.g. by using the aqueous nanosuspension as granulation fluid in the tablet production process. One variant of the Nanopure technology is to produce drug nanocrystals dispersed in liquid PEG or in oils. The obtained suspensions can directly be filled into soft gelatine capsules or into hard gelatine or HPMC capsules which are then being sealed. In addition drug nanocrystals in solid PEG can be used as powder for tablet production.

Amphotericin B powder was dipersed in liquid PEG 400 resp. in melted solid PEG 1000 and homogenised at 1500 bar up to 25 homogenisation cycles. Figure 1 shows the decrease in PCS particle size as a function of the cycle number. As can be seen, a distinct reduction in particle size was already obtained after one homogenisation cycle. The mean diameter changes little from cycle 10 to cycle 25, however during further cycles the fraction of remaining microparticles is further reduced. A fine product was obtained after 25 homogenisation cycles with a PCS diameter of 299 nm (PEG 400) resp. a PCS diameter of 331 nm (PEG 1000) and laser diffractometry diameters 25% of 0.147 µm, diameter 50% of 0.258 µm and diameter 99% of 2.251 µm (PEG 400). Figure 2 shows the size distribution of the starting material and a homogenised final product, table 1 gives the diameters.

3 *Amphotericin B nanosuspension in liquid PEG 400 (left), as solid dispersion in solidified PEG 1000 (middle) and in form of milled solid PEG 1000 yielding a powder (right)*

Production of tablets

Homogenisation can be performed in polyethylene glycoles being liquid at room temperature, e.g. PEG 200 and PEG 400 typically used for capsule filling. Alternatively semisolid or solid PEG can be used, e.g. PEG 1000 or PEG 6000, both

4 *Appearance of solid PEG nanocrystal dispersion milled to a fine powder*

also suitable for capsule filling. In this case the solid PEG is melted by heating to 85°C, the drug powder is dispersed and the obtained pre-suspensions are homogenised at 85°C. This results in a hot nanodispersion which solidifies to a block of PEG. It is a solid dispersion of drug nanocrystals in solid PEG as outer phase. In a subsequent step milling can be performed yielding a flowable powder (Figure 3 and 4).

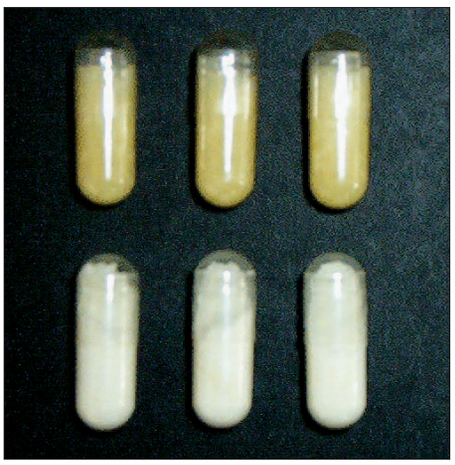
The powder can be admixed to a standard mixture used for direct compression. This is the most cost effective way to produce tablets containing nanocrystals.

Production of capsules

As lined out above, the liquid PEG nanosuspensions can be filled into soft gelatine capsules or alternatively into hard gelatine capsules which are subseqeuntly being sealed. Production of soft gelatine capsules is a more sophisticated technology, easier to perform is filling of hard capsules. Sealing is relatively easy to perform when applying the smart filling and sealing technology developped by Capsugel. However, still easier is the filling with a solid material requiring no sealing. Figure 5 (upper) shows capsules produced by filling the hot PEG nanosuspension directly into hard gelatine capsules which subsequently then solidify in the capsule. Alternatively the drug nanocrystal containing PEG powder was filled into the capsules (Figure 5, lower).

Release of nanocrystals from solid dosage forms

Production of drug nanosuspensions using the above mentioned techniques is very straight forward. Especially homogenisation is a very simple production technique. A more difficult step is to transfer the aqueous nanosuspensions in a solid dosage form which releases the drug nanocrystals again as ultrafine dispersion. It needs to be avoided that excipients used in the formulation lead to aggregation or let crystals fuse under the compaction pressure used in tabletting. The company NanoSystems could demonstrate in an impressive way pos-



5 *Capsules directly filled with hot PEG nanosuspension (upper) and with granulated solidified PEG nanosuspension (lower)*

sible achievements in increasing the bioavailability (e.g. Danazol nanosuspension 82.3%, Danazol microcrystals 5.2% bioavailability (Ref. NanoSystems)). However NanoSystems could also show a strong reduction in bioavailability improvement when aggregated nanosuspensions are administered (Ref. Liversidge IIR Köln). The mean PCS diameter of the drug nanocrystals in liquid PEG 400 before solidification of the melt was 299 nm, after dissolution of solidified PEG in water a diameter of 286 nm was measured.

Conclusions

The productions of drug nanocrystals in non-aqueous media leads to a smart intermediate product for straight forward production of the final dosage form capsule or tablet. One important quality criterium is the release of the drug nanocrystals as fine dispersion.

Table 1

Laser diffractometry diameters before and after homogenisation

Volume %	before homogenisation	after homogenisation
25	5.154 µm	0.147 µm
50	7.649 µm	0.258 µm
99	32.63 µm	2.251 µm

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