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Pure Drug Nanoparticles for the Formulation of Poorly Soluble Drugs

At present about 10% of the drugs under investigation have bioavailability problems due to poor solubility. It is estimated that about 40% of the newly developed drugs will be poorly soluble in the future. The poor solubility even makes it very difficult to perform the pharmacological screening of compounds for potential drug effects. Therefore there is a high need for intelligent drug formulations to achieve a sufficiently high bioavailability.

Many different approaches have been developed to overcome the solubility problem of poorly soluble drugs, e. g. solubilisation, inclusion compounds, complexation. A basic disadvantage is that these formulation approaches can only be applied to a certain number of drugs exhibiting special features required to employ the formulation principle (e. g. molecule fits into the cavity of the cyclodextrin ring). The use of solvent mixtures is also very limited due to toxicological considerations. In addition, more and more newly developed drugs are poorly soluble in aqueous media and simultaneously in organic media, thus excluding the use of solvent mixtures. Ideally the formulation principle should be able to be applied to all or at least most of the poorly soluble drugs.

An alternative to other methods developed was the production of drug nanoparticles by high pressure homogenisation (Fig. 1) [1]. In contrast to pearl milling, high pressure homogenisation is a continuous production process. Contamination from the production equipment is within the regulatory limits, for example contamination with iron was found to be less than 1 ppm [2]. The next development step was Nanopure, drug nanoparticles produced by high pressure homogenisation applying special features and conditions [3]. This article provides an overview of this technology.

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Formulation characteristics - basic aspects

In the first development step by Müller et al. [1] drug nanoparticles were produced by dispersing the drug powder in an aqueous surfactant solution, the obtained pre-suspension was passed through a high pressure piston-gap homogeniser, e. g. 5-20 homogenisation cycles at typically 1000-1500 bar. The development based on the principle that cavitation occurs in the aqueous phase. The particle suspension has a very high flow velocity when passing the tiny gap of the homogeniser, the static pressure on the water decreases below the vapour pressure of water, the water starts boiling at room temperature leading to the formation of gas bubbles, at the exit of the gap the gas bubbles implode. The implosion shock waves disintegrate the drug particles to drug nanoparticles. Due to the cavitation principle this process is more efficient, the higher the temperature is, that means the higher the vapour pressure of water is.

Special features of the developed Nanopure technology are that the homogenisation can be performed in a non-aqueous phase or phases with reduced water content. In addition it was found that - in contrast to more pronounced cavitation at higher temperatures – homogenisation was similar or more efficient at lower temperatures, even below the freezing point of water. Obviously shear forces of the turbulent flow are strong enough to break the drug microparticles. In addition, some compounds are getting more brittle at lower temperatures (e. g. especially polymers). Furthermore chemical stability of drugs is less impaired when homogenising in non-aqueous or water-reduced media at low temperatures.

Production technique: lab & industrial scale

The drug powder is dispersed in a non-aqueous medium (e. g. Peg 600, Miglyol 812) or a water-reduced mixture (e. g. water-ethanol) and the obtained pre-suspension homogenised in a piston-gap homogeniser. A suitable machine for lab scale is the Micron Lab 40 (APV Deutschland GmbH, Lübeck, Germany). It allows pressures between 100 bar and 1500 bar, the batch volume is 40 ml. The homogenisation tower is equipped with a temperature control jacket to allow homogenisation at 0°C or below. Figure 3 shows the LAB 40 being run in a homogenisation process at –20°C, the temperature control jacket is covered with ice formed by air humidity in the lab.

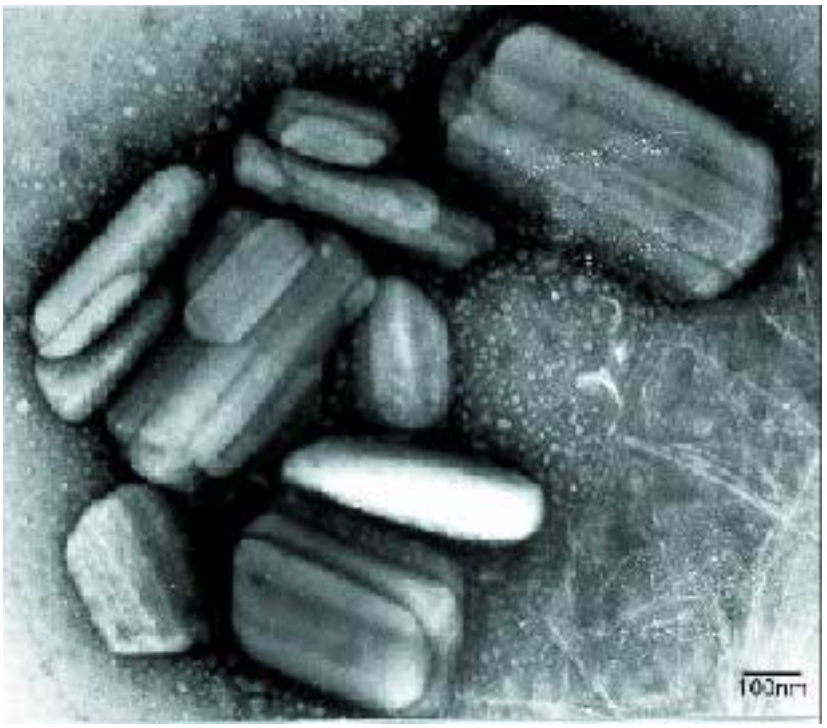
Larger lab scale batches can be produced using the continuous version of the Lab 60, e. g. 200-500 ml and more depending on the size of the product vessels.

Scale up is simple and straight forward because the high pressure homogenisation lines are used on large scale in food industry (e. g. 1 ton per hour) and also in pharmaceutical production lines (e. g. for the production of parenteral emulsions). The homogenisers are accepted by the regulatory authorities in production lines for parenterals. The machines can be qualified and validated [5]. High pressure homogenisers such as the Rannie 118 can process 1200 L per hour at 1500 bar. Placing two machines of this type in series and passing the batch 10 times through the machines (equal to 20 homogenisation cycles) will allow to produce 1000 kg drug nanoparticle dispersion within approximately 8,5 hours of homogenisation.

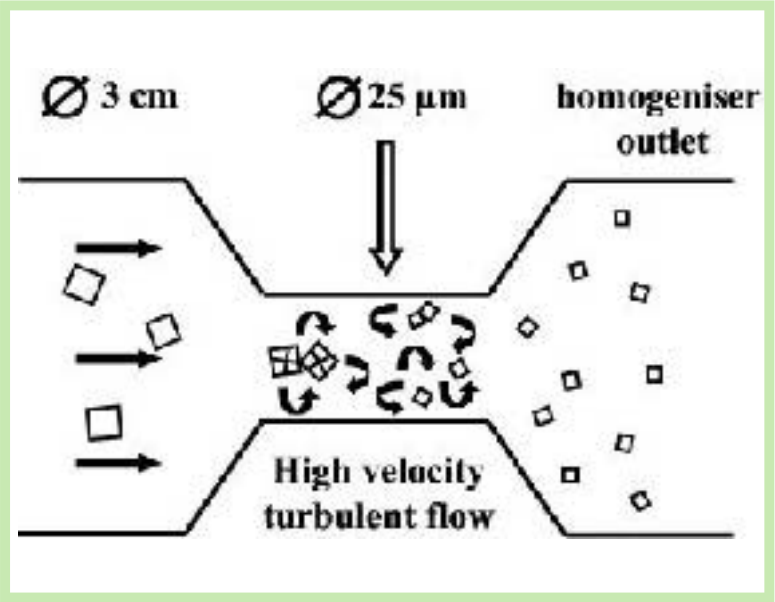
Physical & chemical stability

Having a mean particle diameter in the nanometer size range, the Nanopure suspensions represent an ultrafine, high-energetic dispersion. Of course the question arises: Is there no crystal growth due to Ostwald ripening or particle aggregation?

Ostwald ripening occurs due to different saturation solubilities in the vicinity of very small and of larger particles. The particles are produced by a homogenisation process, that means the particles produced are relatively homogeneous. The differences in the size in combination with the generally poor solubility of the drug nanoparticles are sufficiently low to avoid Ostwald ripening. Aqueous drug nanoparticle suspensions proved to be physically stable up to 3 years [6]. Figure 4 shows the physical stability data of tarazepide drug nanoparticles in aqueous suspension.



1 *Electron micrograph of paclitaxel nanoparticles produced by high pressure homogenisation (after [4]).*



2 *Homogenisation principle of Nanopure – the shearing forces and turbulences are strong enough to disintegrate the particles, especially brittle particles at lower temperatures.*

It is known that during homogenisation high temperature peaks can occur for periods of ms. There was always a discussion if this can impair drug stability. Actually, this is a function of the drug being processed. Homogenisation of cyclosporine at stress conditions (i. e. 1500 bar, 30 cycles) did not lead to any detectable decomposition by HPLC [8]. In contrast, processing the drug azodicarbonamide (ADA) led obviously to some limited decomposition as indicated by the carbondioxide formation and a foamy product [9]. Processing ADA under the production conditions of Nanopure at reduced temperature could avoid this. To summarise, even more sensible drugs than ADA can be processed applying the appropriate homogenisation conditions, e. g. low temperature (as in case of ADA) or water-reduced or non-aqueous medium.

3 *Micron Lab 40, the homogenisation tower (front left) is equipped with a temperature control jacket (middle of tower) controlling the actual homogenisation chamber. There is an ice layer formed on the temperature control jacket by condensation from air humidity.*

Mechanism of action

The basic principle of micronisation and nanonisation is the increase in surface area leading to an increased dissolution rate according to the Noyes-Whitney equation [10]. However, this is only one aspect. In general, one can read in textbooks that saturation solubility is a compound-specific constant only depending on the temperature. This is correct for powders of sizes handled in daily life, but it is different for drug nanoparticles. The dissolution pressure is a function of the curvature of the surface, that means it is much stronger for a curved surface of nanoparticles. Below a size of approximately 1-2 µm, the dissolution pressure increases distinctly leading to an increase in saturation solubility (fig. 5, upper). In addition the diffusional distance h on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient (cs – cx)/h. The increase in surface area and increase in concentration gradient lead to a much more pronounced increase in the dissolution velocity compared to a micronised product. In addition, the saturation solubility is increased as well.

Saturation solubility and dissolution velocity are important parameters affecting the bioavailability of orally administered drugs. From this, nanoparticles have the potential to overcome these limiting steps.

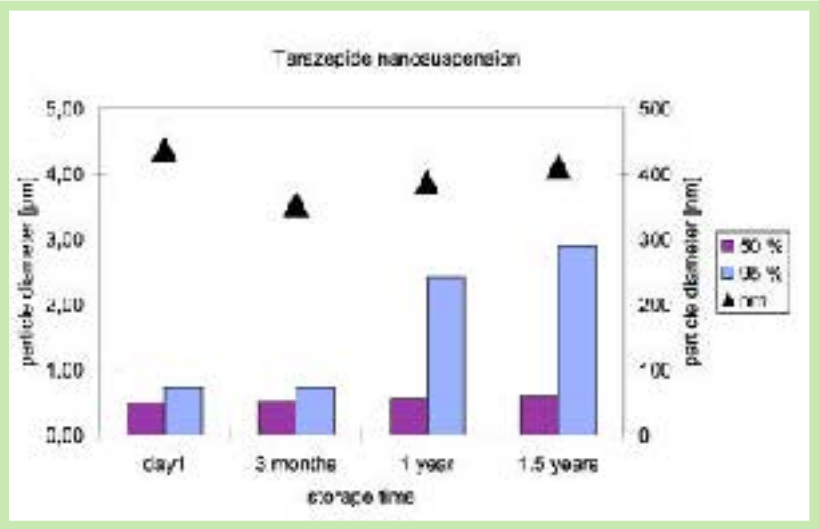
Effects in vivo

The commercially most attractive route for nanosuspensions is the oral one. Basic mechanisms of actions for drug nanoparticles are:

- general adhesiveness of nanoparticles to the gut wall,
- adhesion to the gut wall being a reproducible process thus minimising variation in drug absorption,
- increase in dissolution velocity overcoming this rate-limiting step and
- additionally increase in saturation solubility leading to an increased concentration gradient between gut and blood.

Interesting in vivo data have been generated by the people around Liversidge [12]. Administration of the analgesic Naproxen as a nanosuspension led to an area under the curve (AUC) (0-2h) of 79.5 mg x h/l, however only 44.7 mg x h/l were found for Naprosyn suspension and 32.7 mg x h/l for Anaprox tablets. The corresponding t_{max}

values were 1.69 h for the nanoparticles, 3.33 h and 3.20 h for the conventional commercial products (human study, postprandial). The gonadotropin inhibitor Danazol showed an absolute bioavailability of 82.3% when administered as drug nanoparticles, the conventional dispersion only 5.1%. For intravenous administration, another commercially most interesting route, the drug nanoparticles should possess a bulk population in the nanometer range by simultaneously having a low microparticle content, i. e. especially particles larger than 5 µm which can cause capillary blockade. The homogenisation process a definitionem yields a very homogenous product with minimised content of particles larger 1 µm. In vivo data prove the i. v. injectability of drug nanoparticles [4, 13]. In an in vivo tumour model (mamma tumour



4 *Mean PCS diameter (= bulk population) and laser diffractometry diameters 50% and 95% (= sensitive indicator for potential large crystals or aggregates) of tarazepide drug nanoparticle suspension as a function of storage time (with permission after [7])*

16C) i. v. injected 100 nm paclitaxel proved more efficient than 300 nm paclitaxel nanoparticles and the commercial product Taxol. Remissions at day 70 were 28%, 12% and 0%, respectively [13]. The higher efficiency of the 100 nm drug nanoparticles was explained by a higher uptake into the tumour tissue (passage of nanoparticles through the fenestrated endothelia of the blood capillaries within the tumour area).

To sum up: Orally administered drug nanoparticles can increase the bioavailability or are the only tool to achieve a sufficient bioavailability with poorly soluble drugs. Intravenous administration of drug nanoparticles allows achievement of sufficient blood levels, also for screening purposes of new developed compounds. In addition, toxicologically critical excipients such as Cremophor EL like in Taxol can be avoided when stabilising the drug nanoparticles with accepted emulsifiers, e. g. lecithin or Tween 80.

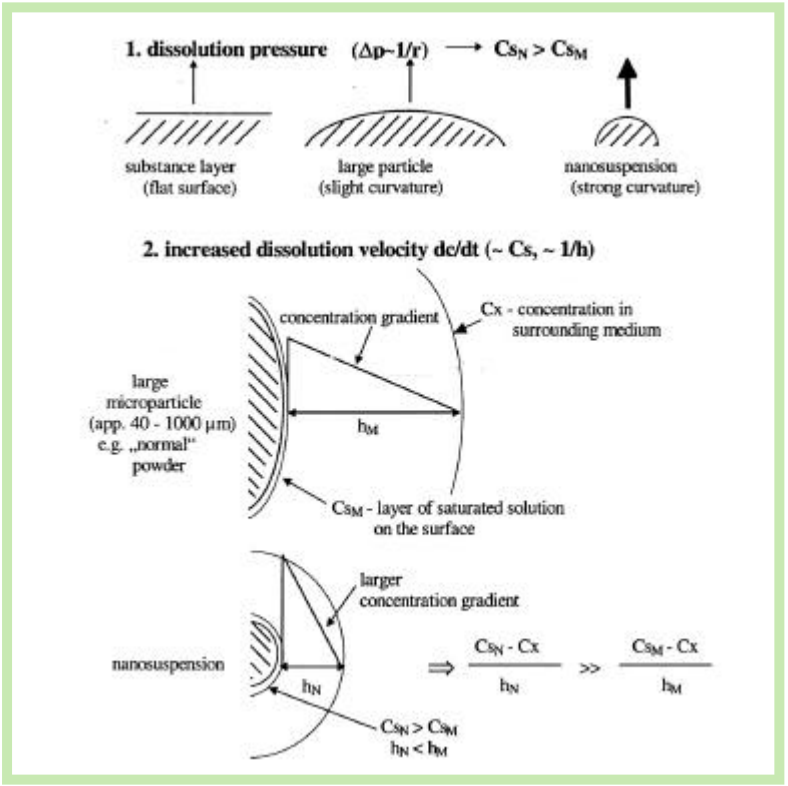
Not the smaller, the better, but: tailor-made particle sizes

There is a general tendency that people tend towards extremes. For example, the higher a skyscraper is, the better. Obviously there also seems to be the opinion, the smaller a drug nanoparticle is, the better. However, this has to be seen in a more differentiated way.

Considering the oral route of administration, there is a general adhesiveness of fine particles. Having achieved a certain degree of fineness (nanoparticle range), differences in adhesiveness are considered as being minor. Also limited difference was found between saturation solubilities when going below the critical threshold of 1-2 µm [1]. However, there are differences in dissolution velocity. In case of too small particles, the dissolution velocity might increase strongly leading to potentially undesired plasma peaks. From this it might be a more sensible approach to have an intermediate particle size providing sufficient bioavailability but still avoiding plasma peaks as occurring with too small particles.

For intravenous administration a small particle size below 150 nm is only desirable in case one wants to pass fenestrated endothelia (e. g. treatment of tumours), however, this is a very limited case. Normally, the original tumour being removed by surgery, it is not the main target of a chemotherapy. The critical metastases are not accessible by small drug nanoparticles anyway. From this example the general rule can therefore not be derived that smaller injected particles are better.

More realistic and on short-term achievable goals are passive targeting of drugs to treat MPS infections (i. e. targeting to the macrophages, e. g. treatment of M. tuberculosis and M. avium infections, especially in HIV patients). Here it is more desirable to have larger particles to ensure fast and efficient removal from the blood streams by the macrophages. Another therapeutic goal is the creation of stealth drug nanoparticles circulating in the blood, minimising free drug concentration but simultaneously prolonging the drug release by slow dissolution. For such a purpose, very small particles are not suitable because they will dissolve too fast. Another therapeutic goal is targeting to non-MPS targets, e. g. the brain and the bone marrow. Targeting of atovaquone drug nanoparticles to the brain could be achieved using the PathFinder technology [14] to treat toxoplasmosis infections [15]. The particles are taken up by the endothelial cells of the blood-brain-barrier, the particles dissolve and drug diffuses into the brain. To reach the therapeutic drug level it is highly desirable to have drug nanoparticles in the up-



5 *Increased dissolution pressure at stronger curvature of the surface (upper) and comparison of cs, h and resulting concentration gradient between a drug microparticle and a drug nanoparticle (after [11] with permission). Abbreviations: p - dissolution pressure, CX – concentration in surrounding bulk, CSM / CSN – saturation solubility of microparticles / nanoparticles, hM / hN- diffusional distance on surface of microparticles / nanoparticles*

per nanometer range than rather very small particles around 100 nm.

To sum up: The particle size should be tailormade depending on the therapeutic requirements and purpose.

Final formulations

The Nanopure suspensions are physically stable on long-term in case they are stabilised by emulsifiers/polymers in optimised composition. However, aqueous suspensions might not be the most convenient dosage form for the patient. The special feature is that the novel particles can be incorporated into traditional dosage forms well-known to the patient. The nanoparticle suspension can be used as granulation fluid to produce tablets or as wetting liquid for pellet production. The dispersions can also be spray-dried to be filled into hard gelatine capsules or sachets. Drug nanoparticles produced in Peg 600 or Miglyol can directly be filled into soft gelatine capsules. Lyophilisation of drug nanoparticles produced in water-reduced media can be used to produce FDDS (Fast Dissolving Delivery Systems).

For parenteral application Nanopure can be lyophilised and reconstituted prior to injection with isotonic media (e. g. water with glycerol).

There are also other areas of application, e. g. ocular delivery (prolonged retention time) or topical application (increased saturation solubility leading to increased diffusion pressure into skin).

Market perspectives

The number of poorly soluble drugs is steadily increasing, especially the drugs simultaneously poorly soluble in water and in non-aqueous media. Therefore there will be a high demand for formulations overcoming the problems related to these drugs. From this, the product Nanopure as drug nanoparticles – especially because it is broadly applicable – will have good market perspectives.

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