ABSTRACT

Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. Today many of the new drugs exhibit such a low solubility that micronisation does not lead to a sufficiently high bioavailability and so, the next step was taken to move from micronisation to nanonisation that means producing drug nanocrystals. To date, nanoscale systems for drug delivery have gained much interest as a way to improve the solubility problems. The production of drug nanocrystal by bottom up technologies starts from the molecules which are dissolved and precipitate them by adding the solvent to a non-solvent and the top down technologies are a disintegration method that means various types of wet milling as well as spray drying technique briefly described. Usually, the drug nanocrystals are generated in a liquid dispersion medium by precipitation or a disintegration process and the obtained product from this process is a suspension of drug nanocrystals in a liquid stabilized by a surfactant or polymer so-called ‘nanosuspension’. The present article describes the details about drug nanocrystals. Drug nanocrystals consist of the pure poorly water-soluble drug without any matrix material means carrier free drug delivery system. The review article includes the methods of preparation with their merits and demerits, special properties, important aspects the transfer of nanosuspension in to patient convenient dosage form, scaling up issues and applications in drug delivery.

KEYWORDS: Drug nanocrystals, solubility, bioavailability, drug delivery

INTRODUCTION

An increasing number of drug candidates synthesized each year by pharmaceutical companies are considered poorly water-soluble. Most of these compounds are dropped from development because they can’t be formulated properly. Presently about 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from synthesis are poorly soluble. The number of poorly soluble drugs increasing day by day requires innovative formulation approaches to reach a sufficiently high bioavailability after oral administration or at least to make available intravenously injectable forms. There are number of formulation approaches for drugs being poorly soluble in water, e.g. the use of solvent mixtures, solid dispersion, microemulsion, cyclodextrines or o/w emulsions for intravenous administration and salt formation etc. The drug needs to possess certain physicochemical properties is principle limitation of all these formulation approaches (e.g. solubility in oils) or to ‘fit’ to the solubilising principle (e.g. having the right molecular size to fit into the cyclodextrine ring). Limited success of these formulation approaches were clearly demonstrated by the relatively low number of products on the market being based on such formulation approaches. For example, there are only three main o/w emulsion products on the market with the drugs Diazepam, Etomidate and Propofol. It would be more elegant to have one universal formulation approach to process any poorly soluble drug.

A meanwhile classical formulation approach to process poorly soluble drugs is micronisation that means converting the coarse drug powder to an ultrafine powder with a mean particle size in the range of 2–5 μm and particle size distributions normally range from approximately 0.1 to 25 μm. Micronisation is a very simple technology achieved by jet milling or wet milling. Micronisation is a technology for class II drugs of the biopharmaceutical classification system (BCS), i.e. drugs having a good permeability but a low oral bioavailability...
due to their poor solubility and low dissolution velocity. The principle for enhancement of solubility was to increase the dissolution velocity by enlarging the surface area of the drug powder. Nowadays, many of the new drugs exhibit such a low solubility that micronisation does not lead to a sufficiently high bioavailability and so, the next step was taken to move from micronisation to nanonisation that means producing drug nanocrystals. Drug nanocrystals are nanoparticles being composed of 100% drug without any matrix material that means the drug nanocrystal as its own carrier. By definition drug nanocrystal is a crystalline particle with at least one dimension measuring less than 1000 nanometers (nm), where 1 nm is defined as 1 thousand-millionth of a meter (10⁻⁹ m). Nanocrystal particles have increased surface area which enhances dissolution rate and stabilized to prevent agglomeration.

(Figure 1)

Oral Nanocrystals formulations of poorly water-soluble drugs offer benefits like enhanced oral bioavailability, rapid onset of action, improved dissolution rate and also simultaneously the saturation solubility according to Noyes–Whitney, this also a function of the surface area, based on these correlations; there are two basic approaches to improve oral drug absorption:

1. Increase \( dc/dt \) by enlarging the drug powder surface and
2. Increase the saturation solubility, \( cs \), of the drug

Micronisation is a very simple traditional approach to increase the dissolution velocity by enlarging the surface. The particle size of normally sized drug powders (approximately 20–100 \( \mu \)m) is reduced to a size in a range between 2 and 5\( \mu \)m. However, many new drugs coming from synthesis or biotechnological processes exhibit such a low solubility that the increase in surface area is not large enough to achieve a sufficiently high dissolution velocity leading to therapeutic blood levels. Consequently, the next step was taken, moving from micronisation to nanonisation that means converting the drug microcrystal to drug nanocrystal. Drug nanocrystal possesses sizes of approximately 10–1000 nm; most production methods yield a main diameter somewhere between 200 nm and 400 nm.

Nanonisation has an additional effect compared to micronisation; it increases not only the surface area \( A \), but also simultaneously the saturation solubility \( cs \). The solubility of normally sized powders is a compound specific constant, depending only on the temperature and the solvent. But this changes when one goes below a size of approximately 1 \( \mu \)m. The dissolution pressure increases due to the strong curvature of the particles leading to an increase in \( cs \), the theoretical background being provided by the Ostwald–Freundlich and the Kelvin equations. According to Noyes–Whitney, this leads to a further increase in \( dc/dt \) in addition to the gain by an increased surface area. Therefore, the drug nanocrystals are a smart carrier free delivery system, a universal principle, which can be applied to any drug.
because any drug can be diminished to nanocrystals (Figure 2).
The saturation solubility increases which leads to the formation of a supersaturated solution compared to the solubility of normally sized drug powders (size >>1 μm). Crystal growth in suspensions can occur due to Ostwald ripening during storage however ostwald ripening was not yet observed in our nanosuspensions, which is explained by the relatively homogenous size of the homogenised products in combination with the a priori low solubility of the drugs.

Drug nanocrystals can be injected intravenously as an aqueous suspension. Stabilization of the nanosuspensions is performed applying classical suspension theory, by charged surfactants (electrostatic stabilization) and by nonionic surfactants or polymers (steric stabilization). Combination of both electrostatic and steric stabilization is favorable making the nanosuspension less susceptible towards electrolytes in the body. Regularly accepted stabilizers for i.v. injection should be used for e.g. lecithin, tween 80, poloxamer 188, sodium glycocholate and low molecular polyvinylpyrrolidone (PVP). The mean diameter of drug nanocrystal 200–400 nm is well below the size of the smallest blood capillaries in the range of 5–6 μm and so depending on the magnitude of the dissolution pressure, the injected particles either dissolve very fast in the blood, or in case of slower dissolution they can be taken up by the MPS or can be directed to other targets. Using the nanocrystal technology, any drug can be made 100% bioavailable.

From the definition, the absolute bioavailability is equivalent to the blood levels obtained after intravenous administration, the relative bioavailability (after oral administration) is defined as the fraction (%) of the area under the blood level curve obtained after non-i.v. injection compared to the AUC obtained after intravenous injection.

Nanoinisation has the advantage that it practically can be applied to more or less any drug material. In general, even highly water sensitive drugs can be reduced to drug nanocrystals, even stored in the form of an aqueous nanosuspension (drug nanocrystals dispersed in aqueous surfactant/stabilizer medium).

For example, aqueous Paclitaxel nanosuspension proved to be stable over a period of four years stored at 4°C, i.e., more than 99% of the drug was recovered intact<sup>10</sup>.

**PRODUCTION METHODS TO PRODUCE DRUG NANOCHRYSALS**
The existing technologies can be divided into two called ‘bottom up’ and the ‘top down’ technologies. The bottom up technologies starts from the molecules which are dissolved and precipitate them by adding the solvent to a non-solvent and the top down technologies are a disintegration method that means various types of wet milling. Usually, the drug nanocrystals are generated in a liquid dispersion medium by precipitation or a disintegration process and the obtained product from this process is a suspension of drug nanocrystals in a liquid stabilised by a surfactant or polymer so-called ‘nanosuspension’.

1. Precipitation methods
The hydrosol technology was developed by Sucker and the intellectual property owned by the company Sandoz, now known as Novartis<sup>11</sup>, 12. Basically, the drug is dissolved in a solvent and this solution is added to a non-solvent leading to the precipitation of finely dispersed drug nanocrystals. In the case of Nanomorph by the company Soliqs/Abbott, amorphous drug nanocrystals are produced to further enhance dissolution velocity and solubility<sup>13</sup>. A nice example is carotene nanoparticles in food industry. The precipitation technique is simple and required low cost equipment. A problem associated with this technology is that the formed nanocrystals need to be stabilized to avoid growth in micrometer crystals. In addition, the drug needs to be soluble at least in one solvent which creates problems for the newly synthesized or discovered drugs, being poorly soluble in water and simultaneously in organic media. To sum up, the bottoms up techniques are not actually widely used for drug nanocrystal production. Nowadays, the top down technologies of various milling techniques are more frequently used.

2. Pearl/Ball Milling (Nanocrystals or Nanosystems)
In pearl milling, the drug macrosuspension is filled into a milling container containing milling pearls made up from glass, zircon oxide or special hard polystyrene derivatives. The pearls are moved by a stirrer and drug ground to nanocrystals in between the pearls. This technology developed by G. Liversidge and coworkers and nowadays used by the company Nanosystems and presently owned by élan. First product on the market is Rapamune launched in 2002, based on this technology and for reasons of convenience for the patient; the aqueous nanosuspensions have to be transferred to tablets. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles<sup>14</sup>, 15, 16. The basic advantage of pearl milling technique is applicable to the drugs are poorly soluble in both aqueous and organic media. In addition, very dilute as well as highly concentrated nanosuspension can be prepared by handling 1mg/ml to 400mg/ml drug quantity. Problems associated with this technology is that nanosuspension contaminated with
materials eroded from balls may be problematic when it is used for long therapy, time consuming method, some fractions of particles are in the micrometer range and scale up is not easy due to mill size and weight.

3. High pressure homogenisation methods

The second most frequently used disintegration method is milling by high pressure homogenisation. A simple process high pressure homogenisation in water developed by R.H.Muller and homogenisation in water-free media and water mixtures developed by the company PharmaSol GmbH/Berlin (pure nanocrystals). The company Baxter introduced a combination technology called NANOEDGE in which precipitation is followed by a second high energy step, typical high pressure homogenisation\(^1\). The two homogenisation principles applied are:

1. Microfluidisation
2. Piston-gap homogenisers

**Microfluidisation**

Microfluidisation technique is based on a jet stream principle; the suspension is accelerated and passes with a high velocity an especially designed homogenisation chamber. In the ‘Z’ type of chamber, the suspension changes a few times the direction of its flow leading to particle collision and shear forces. In the second ‘Y’ type of chamber, the suspension stream is divided into two streams which then collide frontally. The microfluidisation technique for drug nanocrystal production has been acquired by SkyePharma PLC\(^8\). A drawback of this technology is sometimes high number of passes through the microfluidiser, not very production friendly. In addition, the product obtained by microfluidisation can contain a relatively large fraction of microparticles thus losing the special benefits of a real homogeneous drug nanocrystal suspension.

**High pressure homogenisation in water (Dissocubes)**

A simple process of particle diminution by high-pressure homogenisation was developed by R.H.Muller at the beginning of 1990s. The instrument can be operated at pressure varying from 100 – 1500 bars and up to 2000 bars with volume capacity of 40ml (for laboratory scale). The drug powder is suspended in a surfactant solution; the obtained macro suspension is then passed through a high pressure piston gap homogeniser. In piston gap homogeniser particle size reduction is based on the cavitations’ principle. The cavitations forces in the homogenisation gap are strong enough to dimunite the drug microparticles to nanocrystals (Figure 3). Particles are also reduced due to high shear forces and the collision of the particles against each other. The dispersion contained in 3cm diameter cylinder; suddenly passes through a very narrow gap of 25\(\mu\)m. According to Bernoulli’s Law the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3cm to 25\(\mu\)m leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap and normal air pressure, are reached. The final size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenisation cycles, and power density of homogeniser and homogenisation pressure\(^4\).

Trade name of the obtained aqueous nanosuspensions is Dissocubes\(^\circledR\) for the reason that the particles have special dissolution properties and a cuboids shape. This technology does not cause the erosion of processed material\(^1\), contamination from the production equipment is typically below 1 ppm that means within a suitable range, very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity\(^20\), applicable to the drugs that are poorly soluble in both aqueous and organic media and allows aseptic production of nanosuspensions for parenteral administration.\(^21\) Preprocessing step like micronisation of drug is required and high cost instruments are major drawback of this technology.

**Homogenisation in water-free media and water mixtures (Nanopure)**

For some administration routes or purposes, it is more convenient to have drug nanocrystals dispersed in nonaqueous media. For the transfer of liquid nanosuspensions into dry products it can also be desirable to have suspensions with reduced water content and a more volatile dispersion medium (e.g. water–ethanol mixtures). Examples are drug nanocrystals in oils for filling of soft gelatin capsules or alternatively dispersed in liquid PEG 400 or 600. Highly chemically labile drugs could be produced in such non-aqueous media (e.g. water–glycerol mixtures) at very mild conditions and diluted prior to i.v. injection with water to yield an isotonic suspension\(^4\).

When developing the second generation of drug nanocrystals (Nanopure), drug suspensions in non-aqueous media such as propylene glycol were homogenised. In addition to homogenisation at room temperature, the process was performed at 0°C and well below freezing point (e.g. -20°C), so called ‘deep-freeze homogenisation’. The result was against the teaching that particle disintegration was similarly effective in non-aqueous media which opens the perspective to prepare non-aqueous nanosuspensions for further direct processing, e.g. oral dosage forms.
**Combination technology (NANOEDGE) precipitation and homogenisation**

The company Baxter introduced a combination technology called NANOEDGE. Precipitation is followed by a second high energy step, usual high pressure homogenisation. Precipitated drug nanoparticles exhibit the tendency to continue crystal growth to the size of micrometer crystals. In addition, depending on the precipitation conditions the particles are completely amorphous, partially amorphous or completely crystalline. To ensure the long-term stability of the crystalline status, the easiest approach is to have particles in the low energy crystalline modification. Amorphous or partially amorphous particles bear the risk of re-crystallisation of this amorphous fraction followed by a decrease in bioavailability.

Both problems, avoidance of further crystal growth in micrometer size and uncertainty of crystalline/amorphous state were solved by combining the precipitation with a second high energy addition step\(^2\). In general, the precipitated particle suspension is subsequently homogenised which can preserve the size range of the particles obtained after the precipitation step. In addition, this ‘annealing’ process converts all precipitated particles to crystalline material. This removes all concerns about physical stability of amorphous material and obtained drug nanocrystals possess a definite crystalline state. This combination technology overcomes some problems of the precipitation process, but others such as the solvent remain. In addition, combination processes are more costly than one step processes, especially for producing sterile parenteral products.

**4. Production of drug nanocrystals by Spray Drying**

For the production of tablets, an aqueous nanosuspension can be used as granulation fluid or a dry form of the nanosuspension, powder, or granulate can be employed. Starting from an aqueous macrosuspension containing the original coarse drug powder, surfactant, and water-soluble excipient, the homogenisation process can be performed in an easy one step yielding a fine aqueous nanosuspension, in a subsequent step the water removed from the suspension to obtain a dry powder. There are two methods for removing the water from the formulation. Freeze drying, but it is complex and cost intensive leading to a highly sensitive product\(^{23,24}\). Spray drying is another simple and most suitable method for the industrial production. In which drug nanosuspension directly produced by high pressure homogenisation in aqueous solutions of water-soluble matrix materials, e.g., polymers (PVP, polyvinyl alcohol or long chained PEG, sugars like saccharose and lactose, or sugar alcohols like mannitol and sorbitol). Subsequently the aqueous drug nanosuspension can be spray dried under adequate conditions; the resulting dry powder is composed of drug nanocrystals embedded in a water-soluble matrix\(^2\). (Figure 4) schematically represents the whole production process of drug nanocrystal loaded spray dried compounds. One aim of a solid nanoparticulate system is releasing the drug nanocrystals after administration in the gastrointestinal tract (GI) as a fine nonaggregated suspension; the other is to increase the physical stability for long term storage. Contact of the drug nanocrystals is averted by fixation within the matrix.

Thereby, the probability of physical instabilities as, e.g., aggregation and ripening are in principle clearly avoided or minimized to a negligible extent. However, appropriate investigations have shown a relation between the loading capacity of the compounds and the releasing behavior, as well as the storage stability. Exceeding a certain maximum loading capacity of the matrix with drug nanocrystals has an increasing negative effect on particle crystal growth and on release as fine dispersion\(^2\).

**SPECIAL PROPERTIES OF DRUG NANOCRYSTALS**

The rationale of producing micronised drugs for oral administration is the enhancement in bioavailability for BCS class II drugs and the limiting step of oral absorption is the dissolution velocity. For micronised drug the dissolution velocity is enhanced by their enlarged surface area. The same effect observed for nanonised drug, but much more pronounced. The surface area is more enlarged, the dissolution velocity further enhanced.

Another most important aspect is the increase in saturation solubility which is a compound-specific constant only depending on the temperature and the properties of the dissolution medium. This is valid for powders of daily life with a size in the micrometer range or above. However, below a size of approximately 1–2 μm, the saturation solubility is also a function of the particle size. The theoretical backgrounds are the Kelvin equation\(^2\), the Ostwald–Freundlich equation and the Prandtl equation\(^4\). The saturation solubility is equilibrium between dissolving molecules and recrystallising molecules. Increasing the dissolution pressure shifts the equilibrium, the saturation solubility increases. The dependence of the saturation solubility on the particle size is also expressed in the Ostwald–Freundlich equation. The increase in saturation solubility has two effects:
1. Based on the Noyes–Whitney equation an increase in saturation solubility leads to an increase in dissolution velocity.

2. Increased saturation solubility in the lumen of the gut increases the concentration gradient between lumen and the blood, thus accelerating drug-diffusion, promoting absorption.

There is a third special feature of drug nanocrystals, the general adhesiveness of nanoparticles. Due to their large surface area, the nanoparticles tend to stick to surfaces. Based on physics this can be explained by the larger surface area providing more interactive forces between the particles and the surface\(^2\). The effect can be nicely demonstrated referring to daily life. Relatively large crystalline sugar does not stick that well to bakery compared to iced sugar. Iced sugar (fine particle) scan cover bakery in a very sticky layer. The adhesiveness of the particles to the gut wall after oral administration further enhances the bioavailability. The drug dissolves exactly at the place of its absorption. This process was found to be very reproducible, there is very little dependence on the nutritional state of the patients, i.e. between fed and fasted state\(^4\).

To sum up, special features of drug nanocrystals are: the further enlargement in surface area compared to micronised powders, the increase in saturation solubility, both leading to a distinctly increased dissolution velocity. In addition, due to their ultrafine character and adhesiveness, they further enhance oral bioavailability of drugs and reduce variability in bioavailability due to the reproducibility of their adhesion process to the gut wall.

**FINAL FORMULATIONS OF DRUG NANOSUSPENSIONS**

Aqueous or non-aqueous drug nanosuspensions exhibit a physical long term stability which in theory should be adequate to place them on the market as liquid products. This might be suitable for certain groups of patients, e.g. children or elderly patients, but not for the ‘normal’ patient. Dry oral dosage form is preferred for the ‘normal’ patient that means a tablet or a capsule. In case of drug nanosuspensions in pure water (Dissocubes) or in water containing mixtures (Nanopure) they can be used as granulation fluid in the granulation process for the production of tablets or on the other hand as wetting agent for the extrusion mass to produce pellets. Spray-drying is also possible whereas water-ethanol mixtures will evaporate faster than pure water. The produced powders can then be used again for tablet or pellet production or alternatively be filled in hard gelatin or HPMC capsules.

The new feature of Nanopure is that drug nanocrystals can be produced in non-aqueous media such as oils or solid/liquid PEG which can directly be used for the filling of capsules. The dispersion of the crystals in oil promotes drug absorption exploiting the absorption enhancing effect of lipids\(^29,\ 30\). For the production of the final dosage form, the liquid PEG nanosuspensions can be filled into capsules. For the drug nanocrystals in PEG being solid at room temperature (e.g. 1000, 6000) there are two ways of processing:

1. Filling of the hot melted nanosuspension directly into hard gelatin capsules or HPMC capsules, the suspension solidifies inside the capsule or

2. Solidification of the PEG nanosuspension, grinding it to a white powder with subsequent filling of the powder into hard gelatin or HPMC capsules

The latter could have the advantage that the powder finely disperses faster in the GIT after dissolution of the capsule, thus accelerating dissolution of the PEG and redispersion of the drug nanocrystals. Of course, the drug nanosuspension product can also be used to produce tablets. Solid-PEG is a normal excipient in tabletting; it can be admixed to a mixture for direct compression\(^31\).

One more elegant method to transfer drug nanosuspensions to a solid dosage form is the preparation called ‘compounds’. Compounds are freely flowable powders, generally produced for mixtures for direct compression and Direct-Compress is a technology for the production of such compounds. For example, the excipient lactose is dissolved and a non-water soluble polymer (e.g. ethyl cellulose particles, Eudragit RSPO particles) is dispersed simultaneously, in an aqueous nanosuspension and this suspension is then spray-dried. The result is a freely flowable powder having particle size around 50–400 \(\mu\)m\(^32\). This compound can be used in a direct compression process to produce tablets and alternatively the product can be filled into hard gelatin or HPMC capsules.

To summarise, there are various different ways to transfer the drug nanocrystals to a final dry oral dosage form for the patient. With regard to parenteral products, the drug nanosuspensions can be used as they are; the shelf life of up to 3 years was shown for selected nanosuspensions\(^33\).

**LARGE SCALE PRODUCTION, SCALING UP ISSUE**

In general, scaling up encounters many problems, as the process parameters and process dimensions will change a lot within such a scaling up process. The lab scale machines used for the production of drug nanocrystals have a batch volume of about 3 ml (Avestin B-3) and 40 ml (Micron LAB 40, APV Homogenisers, Unna, Germany). Increasing the produced volume from 3 ml to a batch size of about half a ton (500 kg) means enlarging...
the production volume by a factor of approximately 165,000. Apart from having production capacities available, the first pre-requisite is to have available a qualified production unit to produce the batches for the clinical studies.

For the DissoCubes produced in water and the Nanopure nanocrystals produced in other dispersion media, the same equipment can be used. The principle of high pressure homogenisation is used in different areas ranging from food to pharma. High pressure homogenisation lines are accepted by the regulatory authorities for the production of emulsions for parenteral nutrition (e.g. Intralipid, Lipofundin). This is basically a very good starting position for establishing a new technology.

Another advantage is that the homogenisation valve is relatively similar at least the geometry, when moving from lab scale APV machines to production machines.

Use of larger volume machines proved to be beneficial for the product quality. Less homogenisation cycles and less pressure were required, at the same time the product was even smaller in size and more homogeneous in size distribution (lower polydispersity index). This can be attributed to the fact that the production parameters can be much better controlled using the larger volume machines, e.g. temperature.

In addition, these machines are more effective because they are not single punch but multiple punch machines, there are distinctly less fluctuations in the homogenisation pressure compared to the lab machine LAB 40. In addition, they are equipped with two homogenisation valves in series. The second homogenisation valve immediately disrupts the aggregates potentially formed when the particles leave the first homogenisation valve. This second valve typically operates at 1/10 of the pressure of the first homogenisation valve (e.g. 500–50 bar).

A modified LAB 60 homogenisation unit was built for the production of technical batches. It was modified such a way that the capacity of the product containers was extended from half a litre to 10 Litre and also can be placed under a laminar air flow unit mounted at the ceiling of the production suite.

In case larger volumes of nanosuspensions are required, it is recommended to use a Rannie 118 with a capacity of 1 ton/h at the maximum applicable pressure of 1500 bar. Alternatively, an Avestin 1000 could be used providing a homogenisation capacity of 1000 kg/h. The number of homogenisation cycles required for a fine drug nanosuspension is a minimum of 10, typically a maximum of 20. Consequently, it is recommended to place two or four homogenisers Rannie 118 in series.

Assuming a capacity of 1000 kg/h in case of one homogeniser, the production of one tons nanosuspension would require 20 h while in case of four homogenisers in series, this time would reduce to 5 h homogenisation time for 1000 kg of nanosuspension.

For production of sterile products, there are two possible approaches:

Thermal sterilisation by autoclaving can be performed in case the drug is temperature resistant and the stabiliser combination is suitable. In general, it was found that identical to parenteral fat emulsions stabilisation of nanoparticles by lecithin can lead to dispersions being stable at autoclaving conditions of 121 °C, 2 bar.

Aseptic production for parenteral nanosuspension on larger scale realized by company Baxter. Such production line has also the advantage that the highly potent drugs such as cytotoxics can be processed. In addition, it should be born in mind that high pressure homogenisation process itself has a germ reducing effect. Not only the crystals but also the bacteria are ‘disintegrated’. Therefore the high pressure homogenisation is used in food industry to reduce the microbial level in food to prolong its shelf life.

PRODUCTS ON THE MARKET/IN CLINICAL PHASES

Looking at the time between invention of a technology and the first products on the market, this time period is very short for the drug nanocrystals. The liposomes were invented in 1968 by Bingham; the first pharmaceutical products appeared on the market at the beginning of the 1990s. Whereas the first drug nanocrystal patents were filed at the beginning of the nineties by the company Nanosystems (nowadays e’lan).

The first product solid-dosage formulation of the immunosuppressant Rapamune® (sirolimus) received marketing approval from the U.S. Food & Drug Administration (FDA) in August 2000 by company Wyeth incorporating the Nanocrystal technology. Rapamune was previously available only as an oral solution which requires refrigeration storage, and must be mixed with water or orange juice prior to administration. The tablet has the advantage of being more user friendly than the solution. Compared to the solution, the tablet has 21% higher bioavailability. That means the drug nanocrystals perform even better than an oral solution.

Emend® (aprepitant) was approved by the FDA in March 2003 and launched in the United States by Merck in April 2003. The filling material of a capsule is pellets. Emend is a capsule containing 80 or 125 mg of apreptitant formulated as Nanocrystal drug particles. Whereas the first commercial product that utilized...
Nanocrystal technology (Rapamune) was a reformulation of an already marketed drug. Emend was developed as an NCE (new chemical entity) in a Nanocrystal formulation. 

TriCor® 145mg and 48mg (fenofibrate) was launched in December 2004 by Abbott in the U.S. The new formulation of TriCor® provides the benefits of a simplified, flexible dosing regimen and allows for administration with or without food as well as 9% improvement in bioavailability. The old formulation had to be taken with a meal. 

Megace® ES (megestrol acetate) concentrated oral suspension for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome approved by FDA in July 2005. Megace® ES utilizes Nanocrystal Technology to improve the rate of dissolution and bioavailability of the original megestrol acetate oral suspension. Apart from product being marketed more than 20 product based on nanocrystal technology are in clinical phase. 

PHARMACEUTICAL APPLICATIONS OF DRUG NANOCRYSTALS IN DRUG DELIVERY 

1. Parenteral administration 
Drug nanocrystals in the form of nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitonial to intravenous injection. Nanosuspensions have been found to increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspensions revealed their superiority over taxol in reducing the median tumor burden. Clofazimine nanosuspension, a poorly water-soluble anti-leprotic drug, revealed an improvement in stability and efficacy over the liposomal clofazimine in M. avium infected female mice. Rainbow and co-workers reported an intravenous itraconazole nanosuspension enhanced efficacy of antifungal activity relative to a solution formulation in rats. 

2. Peroral administration 
Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Aqueous nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets. Ketoprofen nanosuspensions have been successfully incorporated into pellets to release the drug over a period of 24 h. Amphotericin B, an antibiotic lacks good oral bioavailability. However, oral administration of amphotericin B as a nanosuspension produced a substantial improvement in its oral absorption in comparison to the orally administered commercial formulations such as Fungizone, AmbIsome and micronized amphotericin B. In addition, oral fenofibrate nanosuspensions showed bioavailability enhancement in comparison to conventional suspensions of micronized drugs.

3. Ophthalmic drug delivery 
Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high toxicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability. One example of a nanosuspension for ophthalmic controlled delivery was developed as a polymeric nanosuspension of ibuprofen. This nanosuspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone enhance rate, drug absorption and increase the duration of drug action.

4. Pulmonary drug delivery 
Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. The dispersions can be relatively high concentrated. Due to the presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanocrystals. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspenion for pulmonary delivery. In addition, bupravaquone nanosuspensions were formulated for treatment of lung infections by using nebulization.

5. Target drug delivery 
Nanosuspensions can also be used for targeted delivery. Targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone. Similarly, conditions such as pulmonary aspergillus can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes.

LIMITATION OF DRUG NANOCRYSTALS TECHNOLOGY 
High cost instruments are required for production of drug nanocrystal that increases the cost of dosage form. This technique is limited to BCS class II drugs only. Formation of nanocrystals and their stability depends on the molecular structure of the drug, so only certain classes of compound will qualify.
CONCLUSION
Drug nanocrystals are considered as one of the most important formulation approaches for poorly soluble drugs at the beginning of this new century. The smartness of technology is that it can be universally applied to practically any drug. Identical to micronisation, it is a universal formulation principle, but limited to BCS class II drugs. The striking advantage is that the drug nanocrystals can be applied to various administration routes, that means oral but also parenteral, especially i.v. administration. Other administration routes are dermal delivery to create supersaturated solutions, that means oral but also parenteral, that the drug nanocrystals can be applied to various administration routes, that means oral but also parenteral, especially i.v. administration. Other administration routes are dermal delivery to create supersaturated systems with high thermodynamic activity, ophthalmic administration to create systems with prolonged retention times, nasal administration to stick nanocrystals to the nasal mucosa, vaginal administration to create systems evenly spreading throughout the therapeutic area, and aerosols containing drug nanocrystals for pulmonary delivery. Based on these criteria, the drug nanocrystal technology is successful emerging technology.

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Figure 1: The nanocrystal technology
Figure 2: Dissolution velocity $dc/dt$ and saturation solubility $c_s$ as a function of the size of drug powders ranging from normally sized to nanonised drugs.

Figure 3: Change of diameter of the streaming dispersion in a piston-gap homogeniser from the cylinder containing the bulk suspension to the narrow homogenisation gap.

Figure 4: Two-step process of the production of drug nanocrystal loaded compounds.