DRUG NANOCRYSTALS: A NOVEL FORMULATION APPROACH FOR POORLY SOLUBLE DRUGS

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Abstract: During the last two decades, many modern technologies have been established in the pharmaceutical research and development area. The automation of the drug discovery process by technologies such as high-throughput screening, combinatorial chemistry, and computer-aided drug design is leading to a vast number of drug candidates possessing a very good efficacy. Unfortunately, many of these drug candidates are exhibiting poor aqueous solubility. The use of drug nanocrystals is an universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. Drug nanocrystals are crystals with a size in the nanometer range, meaning that they are nanoparticles with a crystalline character. This review article describes the physicochemical properties of drug nanocrystals, production methods & potential clinical advantages.

Keywords: Nanocrystals; Nanosuspensions; Bioavailability enhancement; Surfactants; Stabilizers.

Introduction
It is estimated that 40% or more of active substances being identified through combinatorial screening programs are poorly soluble in water (Lipinski, 2001, 2002) [1]. Poor solubility is not only a problem for the formulation development and clinical testing, it is also an obstacle at the very beginning when screening new compounds for pharmacological activity. From this, there is a definite need for smart technological formulation approaches to make such poorly soluble drugs bioavailable. Making such drugs bioavailable means that they show sufficiently high absorption after oral administration, or they can alternatively be injected intravenously. There is quite a number of formulation approaches for poorly soluble drugs which can be specified as "specific approaches". These approaches are suitable for molecules having special properties with regard to their chemistry (e.g. solubility in certain organic media) or to the molecular size or conformation (e.g. molecules to be incorporated into the cyclodextrin ring structure). Of course it would be much smarter to have a "universal formulation approach" applicable to any molecule apart from few exceptions. Such a universal formulation approach to increase the oral bioavailability is micronization, meaning the transfer of drug powders...
into the size range between typically 1-10µm. However, nowadays many drugs are so poorly soluble that micronization is not sufficient. The increase in surface area, and thus consequently in dissolution velocity, is not sufficient to overcome the bioavailability problems of very poorly soluble drugs of the biopharmaceutical specification class II. A consequent next step was to move from micronization to nanonization. Since the beginning of the 90s, the company Nanosystems propagated the use of nanocrystals (instead of microcrystals) for oral bioavailability enhancement, and also to use nanocrystals suspended in water (nanosuspensions) for intravenous or pulmonary drug delivery. Drug nanocrystals can be used for a chemical stabilization of chemically labile drugs. The drug paclitaxel can be preserved from degradation when it is formulated as a nanosuspension [2-3]. The same result was found for the chemically labile drug omeprazole. When formulated as a nanosuspension, the stability was distinctly increased in comparison to the aqueous solution [4]. The increased stability can be explained by a shield effect of the surfactants and the drug protection by a monolayer made of degraded drug molecules which reduce the accessibility for destructive agents [5].

**Definition**

Drug nanocrystals are pure solid drug particles with a mean diameter below 1000 nm. A nanosuspension consists of drug nanocrystals, stabilizing agents such as surfactants and/or polymeric stabilizers, and a liquid dispersion medium. The dispersion media can be water, aqueous solutions, or nonaqueous media. The term .drug nanocrystals. implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals have to be distinguished from polymeric nano particles, which consist of a polymeric matrix and an incorporated drug. Drug nanocrystals do not consist of any matrix material.

**Increasing dissolution rate through nanosization — theoretical aspects**

The increased saturation solubility and the accelerated dissolution velocity are the most important differentiating features of drug nanocrystals. In general, the saturation solubility (cs) is defined as a drug-specific constant depending only on the solvent and the temperature. This definition is only valid for drug particles with a minimum particle size in the micrometer range. A particle size reduction down to the nanometer range can increase the drug solubility. The solid API dissolution rate is proportional to the surface area available for dissolution as described by the Nernst–Brunner/Noyes–Whitney equation [6–8]:

$$\frac{dX}{dt} = \frac{A \cdot D}{h} \left( C_s - \frac{X_d}{V} \right)$$

where $dX/dt$=dissolution rate, $X_d$=amount dissolved, $A$=particle surface area, $D$=diffusion coefficient, $V$=volume of fluid available for dissolution, $C_s$=saturation solubility, $h$=effective boundary layer thickness. Based on this principle, API micronization has been extensively used in the pharmaceutical industry to improve oral bioavailability of drug compounds. It is evident that a further decrease of the particle size down to the sub-micron range will further increase dissolution rate due to the increase of the effective particle surface area [9]. For example in the case of aprepitant, the nanocrystal dispersion of 120-nm particle size exhibits a 41.5-fold increase in surface area over the standard 5 µm suspension [10]. Furthermore, as described by the Prandtl equation, the diffusion layer thickness ($h$) will also be decreased thus resulting in an even faster dissolution rate [11]. In addition to the dissolution rate enhancement described above, an increase in the saturation solubility of the nanosized API is also expected [12], as described by the Freundlich–Ostwald equation:

$$S = S_\infty \exp \left( \frac{2\gamma M}{r \rho RT} \right)$$

where $S$=saturation solubility of the nanosized API, $S_\infty$=saturation solubility of an infinitely large API crystal, $\gamma$ is the crystal-medium interfacial tension, $M$ is the compound molecular weight, $r$ is the particle radius, $\rho$ is the density, $R$ is a gas constant and $T$ is the temperature. Assuming a molecular weight of 500, $\gamma$=1 g/mL and a $\gamma$ value of 15–20 mN m-1 for the crystal-intestinal fluid
interfacial tension, the above equation would predict an approximately 10–15% increase in solubility at a particle size of 100 nm. However a more significant increase in solubility appears to occur in reality e.g. Muller and Peters reported an increase of 50% in the solubility of an insoluble antimicrobial compound when the particle size was reduced from 2.4 µm to 800 or 300 nm [12]. This increase in solubility leads to a further increase in dissolution rate and, as a result, nanosuspensions often achieve significantly higher exposure levels compared to suspensions of micronized API, even when the same surfactants are used. Finally, the increase in surface wetting by the surfactants in the nanosuspension formulations most likely results in a further enhancement of the dissolution rates compared to micronized suspensions.

**Methods for Production of drug Nanocrystals**

Milling, high-pressure homogenization, and precipitation are the main methods employed for the production of drug nanocrystals. The importance for improvement of the bioavailability of poorly soluble drugs by the production of drug nanocrystals is widely accepted. The intensive research for new technologies led to many other approaches for the production of drug nanocrystals. Even non pharmaceutical companies, such as Dow Chemical, are entering the market of poorly soluble drugs with solubility-enhancing technologies. Among other technologies, the following supercritical fluid methods are mentioned for reasons of completeness only. Rapid expansion of supercritical solution (RESS), rapid expansion from supercritical to aqueous solution (RESAS), solution-enhanced dispersion by the supercritical fluids (SEDS), spray freezing into liquid (SFL) evaporative precipitation into aqueous solution (EPAS) and aerosol solvent extraction (ASES) (Müller and Bleich 1996; Lee et al 2005).

**Media milling process**

In order to produce nanocrystalline dispersions by the NanoCrystals® technology, a milling chamber is charged with milling media, dispersion medium (normally water), stabilizer, and the drug. The drug particles are reduced in size by shear forces and forces of impaction generated by a movement of the milling media. Small milling pearls or larger milling balls are used as milling media. With a reduction in the size of grinding media in a media mill, the number of contact points is increased exponentially, resulting in improved grinding and dispersing action (i.e., leading to smaller particles). The pearls or balls consist of ceramics (cerium- or yttrium-stabilized zirconium dioxide), stainless steel, glass, or highly cross-linked polystyrene resin-coated beads. A problem associated with the pearl milling technology is the erosion from the milling material during the milling process. Buchmann et al. [13] reported the formation of glass microparticles when using glass as milling material. In order to reduce the quantity of impurities caused by an erosion of the milling media, the milling beads were coated with highly cross-linked polystyrene resin [14]. A perpetual problem is the adherence of product to the large inner surface area of the milling system. The inner surface area is made up of the surface area of the chamber and of all milling beads together. Even in recirculation systems, this product adherence causes a product loss. Of course, this undesirable drug loss can be an issue in very expensive drugs, especially when very small quantities of new chemical entities (NCEs) are processed. Various marketed formulations are developed using this technology such as-In 2000 Rapamune was launched by Wyeth as the first product containing sirolimus NanoCrystals. The coated Rapamune tablets are more convenient and show a 27% increased bioavailability compared to the Rapamune® solution [15]. This is an example to compare two formulation strategies. The oral solution shows the principles of cosolvents and surfactants, whereas the tablets shows the nice performance of a particle size reduction technique. Emend® is the second product incorporating the NanoCrystal technology. It was introduced to the market in 2003 by Merck. Emend® is a capsule containing pellets of nanocrystalline aprepitant, sucrose, microcrystalline cellulose, hyprollose, and sodium dodecylsulfate [16]. The third product is TriCor, a nanocrystalline fenofibrate tablet marketed in 2004 by Abott. Megaace ES, an oral suspension containing megestrol acetate for the treatment of HIV-associated anorexia and cachexia, was launched as a fourth product late in the middle of the year 2005.

**Precipitation Methods**

It is also known as hydrosol technology, and the IP is
owned by Sandoz (now Novartis). A poor water-soluble drug is dissolved in an organic medium, which is water-miscible. A pouring of this solution into a non solvent, such as water, will cause a precipitation of finely dispersed drug nanocrystals. A problem associated with this technology is that the formed nanoparticles need to be stabilized to avoid growth in micrometer crystals. In addition, the drug needs to be soluble at least in one solvent, this creates problems for the newly synthesized or discovered drugs, being poorly soluble in water and simultaneously in organic media. Lyophilization is recommended to preserve the particle size [17]. Another approach to preserve the size of the precipitated nanocrystals is the use of polymeric growth inhibitors, which are preferably soluble in the aqueous phase. The increased viscosity of the aqueous phase can reduce particle growing. But this technology has not been applied to a product to date.

**Homogenization methods**

**Microfluidizer Technology (IDD-P™ technology)**

The microfluidizer is a jet stream homogenizer of two fluid streams collided frontally with high velocity (up to 1000 m/sec) under pressures up to 4000 bar. There is a turbulent flow, high shear forces, particles collided leading to particle diminution to the nanometer range [18-20]. The high pressure applied and the high streaming velocity of the lipid can also lead to cavitation additionally, contributing to size diminution. To preserve the particle size, stabilization with phospholipids or other surfactants and stabilizers is required. A major disadvantage of this process is the required production time. In many cases, 50 to 100 time-consuming passes are necessary for a sufficient particle size reduction [21-22]. SkyePharma Canada, Inc. (previously RTP, Inc.) applies this principle for its IDD-P™ technology to produce submicron particles of poorly soluble drugs [23].

**Piston-gap homogenization in water (Dissocubes®)**

Drug nanocrystals can also be produced by high-pressure homogenization using piston gap homogenizers. Depending on the homogenization temperature and the dispersion media, there is a difference between the Dissocubes® technology and the Nanopure® technology. Dispersion medium of the suspensions was water. A piston in a large bore cylinder creates pressure up to 2000 bar. The suspension is pressed through a very narrow ring gap. The gap width is typically in the range of 3-15 micrometer at pressures between 1500-150 bar. There is a high streaming velocity in the gap according to the Bernoulli equation [24]. Due to the reduction in diameter from the large bore cylinder (e.g. 3 cm) to the homogenization gap, the dynamic pressure (streaming velocity) increases and simultaneously decreases the static pressure on the liquid. The liquid starts boiling, and gas bubbles occur which subsequently implode, when the suspension leaves the gap and is again under normal pressure (cavitation). Gas bubble formation and implosion lead to shock waves which cause particle diminution. The patent describes cavitation as the reason for the achieved size diminution [25-26]. Piston-gap homogenizers which can be used for the production of nanosuspensions are e.g. from the companies APV Gaulin, Avestin or Niro Soavi. The technology was acquired by SkyePharma PLC at the end of the 90s and employed in its formulation development [27-29]. The use of water as dispersion medium is associated with some disadvantages. Hydrolysis of water-sensitive drugs can occur, as well as problems during drying steps. In cases of thermolabile drugs or drugs possessing a low melting point, a complete water removal requires relatively expensive techniques, such as lyophilization. For these reasons, the Dissocubes® technology is particularly suitable if the resulting nanosuspension is directly used without modifications, such as drying steps. Many different drugs have been processed by high-pressure homogenization to produce DissoCubes. Up to now each drug investigated could be converted into a nanosuspension. Examples include RMKP22, carbamazepin (unpublished data), bupravaquone, aphidicolin, cyclosporine, paclitaxel, RMBB98, azodicarbonamide, and prednisolone [28].

**Nanopure® Technology**

In 1999, Müller et al. found that a similar effective particle diminution can also be obtained in nonaqueous or water-reduced media [30]. An elegant method to obtain a final formulation directly is the production of nanocrystals in non-aqueous homogenization media. Drug nanocrystals dispersed in liquid polyethylene glycol (PEG) or oils can be directly filled as drug suspensions
into gelatine or HPMC capsules. The non-aqueous homogenization technology was established against the teaching that cavitation is the major diminution force in high pressure homogenization. Efficient particle diminution could also be obtained in non-aqueous media [31-37]. For oral administration, the drug nanosuspensions themselves are, in most cases, not the final products. For patient's convenience, the drug nanocrystals should be incorporated in traditional dry dosage form, e.g. tablets, pellets and capsules. To prepare tablets or pellets, the dispersion medium of the nanosuspension needs to be removed, i.e. in general, evaporated. Evaporation is faster and possible under milder conditions when mixtures of water with water miscible liquids are used, e.g. water-ethanol. To obtain isotonic nanosuspensions for intravenous injection, it is beneficial to homogenize in water-glycerol mixtures. By reducing the water content in the dispersion medium, the required energy is minimized for drying steps, such as spray-drying, fluidized bed drying, or upon suspension layering onto sugar spheres. The evaporation processes can be performed under milder conditions when mixtures of water with water miscible liquids are used, e.g. water-ethanol. To obtain isotonic nanosuspensions for intravenous injection, it is beneficial to homogenize in water-glycerol mixtures. By reducing the water content in the dispersion medium, the required energy is minimized for drying

steps, such as spray-drying, fluidized bed drying, or upon suspension layering onto sugar spheres. The evaporation processes can be performed under milder conditions, which is beneficial for temperature-sensitive drugs. The IP owned by Pharmasol covers, therefore, water-free dispersion media (e.g. PEG, oils) and also water mixtures.

Combination Technologies

Nanoedge® Technology (Microprecipitation™ and High Shear Forces (NANOEDGE™)

The Nanoedge technology by the company Baxter covers a combination of precipitation and subsequent application of high energy shear forces, preferentially high pressure homogenization with piston-gap homogenizers. As mentioned above the precipitated particles have a tendency to grow. According to the patent by Kipp et al, treatment of a precipitated suspension with energy (e.g. high shear forces) avoids particle growth in precipitated suspensions (= annealing process). The relative complex patent description can be summarized in a particle size by precipitation. Precipitated particles can be amorphous or partially amorphous. This implies the risk that during the shelf life of a product, the amorphous particles can recrystallize, leading subsequently to a reduction in oral bioavailability or a change in pharmacokinetics after intravenous injection. The annealing process by Baxter converts amorphous or partially amorphous particles to completely crystalline material. NANOEDGE® process is particularly suitable for drugs that are soluble in non-aqueous media possessing low toxicity, such as N-methyl-2-pyrrolidinone.

Nanopure® XP technology

An advantage of this technology is its scaling up ability and the possibility to produce on large scale, applying "normal" production conditions. PharmaSol uses in its Nanopure XP technology a pre-treatment step with subsequent homogenization to produce particles well below 100 nm (Müller and Moeschwitzer 2005). Drug nanocrystals with a size of about 50 nm and below are distinctly smaller than the wavelength of the visible light, and so the nanosuspensions are translucent.

Other Techniques for the Production of Drug Nanocrystals

Rapid expansion from a liquefied-gas solution (RESS)

The RESS process uses the high solvating power of supercritical fluids. After loading the supercritical fluid with the solute, an extremely fast phase change from the supercritical to the gas like state takes place during the expansion in the supersonic free jet. This phase change leads to high supersaturation and subsequently to particle formation. Since the solvent is a dilute gas after expansion, the RESS process offers a solvent free final product. The improvement of the bioavailability of the RESS-produced griseofulvin has been verified by dissolution experiments according to the Stricker model. The dissolution rate of griseofulvin produced by RESS is about 2-fold higher than the common micronized material [38]. Modelling results suggest that it should be possible to form particles smaller than 50 nm in diameter. This process was used by Young et al. to prepare nanoparticles of cyclosporine in the size range of 500–700 nm. Tween-80 solution was used as a surfactant to prevent flocculation and agglomeration of nanoparticles. Researchers reported that the cyclosporine particles formed by this process could be stabilized for drug concentrations as high as 6.2 and 37.5 mg/ml in 1.0 and 5% (w/w) Tween-80 solutions [39]. RESS process was combined with high-pressure homogenization by Pace et al. to prepare a physically stable nanosuspension. In this process, the poorly soluble drugs and surface
modifier were first dissolved in a liquefied, compressed gas solvent, which was subsequently expanded into an aqueous solution containing surfactant. The suspension so formed was further subjected to a high-pressure homogenization process to produce a stable nanosuspension [40].

**Spray Freezing into Liquid (SFL) technology**

In this process, developed at the University of Texas at Austin (Austin, TX) and commercialized by Dow Chemical Company (Midland, MI). This is a particle engineering technology that utilizes a feed solution containing an Active Pharmaceutical Excipient (API) and dissolution enhancing excipient(s) which is atomized directly into a cryogenic liquid, such as nitrogen. The resulting dried powder is composed of discrete microparticles where the API is molecularly dispersed with a polymer in a matrix. Highly potent danazol nanoparticles contained in larger structured aggregates were produced by the SFL process. The SFL powders exhibited significantly enhanced dissolution rates. The micronized bulk danazol exhibited a slow dissolution rate; only 30% of the danazol was dissolved in 2 min. Nonetheless, 95% of the danazol was dissolved in only 2 min for the SFL highly potent powders. In a recent study, SFL danazol/PVP K-15 powders with high surface areas and high glass transition temperatures remained amorphous and exhibited rapid dissolution rates after 6 months in storage [41]. The EPAS process also was developed by the University of Texas at Austin and commercialized by Dow Chemical Company. In the Evaporative Precipitation into Aqueous Solution (EPAS) technology, the API precipitates due to evaporation of the organic solvent from the feed solution near or above the boiling point upon contact with a heated aqueous solution. The immediate evaporation of the feed solvent causes rapid saturation of the aqueous solution, supersaturation, nucleation and precipitation of the dissolved API with dissolution enhancing excipients. Danazol (2%) and stabilizer (0-1%; povidone K15, poloxamer 407) were dissolved in dichloromethane, pumped via an HPLC pump through a preheating coil and sprayed through a fine nozzle (127 micron inner diameter crimped tubing with and without an ultrasonic horn) into a heated receiving vessel containing 0-2% stabilizer (e.g. povidone K-15, deoxycholic acid) dissolved in water at 80°C. The solution spray produced a fine jet of very small, rapidly evaporating droplets causing precipitation of the danazol through either nozzle. Significantly increased dissolution rates (> 90% dissolved in 10 minutes), high surface areas (> 40 m2/g) and low crystallinities were found for all EPAS processed danazol formulations investigated, when compared to the bulk danazol or physical mixture [42].

**Dosage form developments of Nanocrystals**

In order to show their advantages in vivo, the drug nanocrystals need to be transferred into the right dosage form. Nanosuspensions can be directly used as oral suspensions to overcome the difficulties of swallowing tablets by pediatric or geriatric patients. One example is Megace® (Bristol Meyers Squibb), an oral suspension of megestrol acetate, used for the treatment of HIV-associated anorexia and cachexia. The application of these nanosuspensions can improve the solubility of the drug and the dissolution rate; additionally, suspensions can be applied for reasons of taste-masking. Nanosuspensions can also be used directly for parenteral drug administration. Although nanosuspensions have shown a sufficient long-term stability without Ostwald ripening, for intravenous products a lyophilization step is recommended in order to avoid aggregation or caking of settled drug nanocrystals. The lyophilized product can be easily reconstituted before use by adding isotonic water, aqueous glucose solution, or other reconstitution media [43-44]. Without question, both the patients and the marketing experts prefer the oral administration of traditional dosage forms. Hence, to enter the pharmaceutical market successfully in most cases drug nanocrystals have to be formulated as traditional products, such as tablets or capsules. A perfect solid dosage form should preserve the in vivo performance of drug nanocrystals. When reaching the target part of the GI tract, the dosage form should release the drug nanocrystals as a fine, nonaggregated suspension. Otherwise, self-agglomeration or aggregation can impair the drug release [45]. Using nanosuspensions as granulation fluid for a further tablet production is a very simple approach. The nanosuspension is admixed to binders and other excipients, and the granules are finely compressed to tablets. This dosage form is limited in the maximum achievable drug content. A maximum drug
content of about 50% or less is suggested in order to ensure a complete disintegration into a finely dispersed suspension [46]. Nanosuspensions can also be used for the production of matrix pellets or as layering dispersions in a fluidized bed process. After the pellet preparation, the cores can be coated with several polymers in order to modify the release profile of the final formulation [47-49]. A very smart formulation approach is the Nanopure® technology. Nanocrystals produced in non-aqueous media, such as liquid PEG or oils (e.g., Miglyol), can be directly filled into gelatine or HPMC capsules. The production of drug nanocrystals in melted PEGs is a new strategy for the production of final dosage forms containing drug nanocrystals. After performing the high-pressure homogenization in melted PEG at about 60°C, the mixture can be solidified. The resulting matrix, fixing the drug nanocrystals in separated state, can be compressed to tablets or directly filled into capsules [50].

Spray-drying of the nanosuspensions is another cost-effective approach to transfer nanosuspensions into dry products. The drug nanocrystals can directly be produced by high-pressure homogenization in aqueous solutions of water-soluble matrix materials, for example, polymers [polyvinylpyrrolidone, polyvinyl alcohol or long-chained PEG, sugars (saccharose, lactose) or sugar alcohols (mannitol, sorbitol)]. Afterwards, the resulting nanosuspension can be spray-dried under appropriate conditions. The dry powder, composed of drug nanocrystals embedded in a watersoluble matrix, can be filled in hard gelatine capsules for oral administration [51]. Another attractive approach using the spray-drying principle is described as direct compress technology [52]. Lactose and other matrix-forming materials, such as micronized polymer powders or lipids, are admixed to the prior-produced nanosuspension. The resulting suspension is transferred into a drug–matrix–compound by spray-drying. Subsequently, the free-flowable powder can be used for direct compression of fast dissolving or prolonged release tablets. Alternatively, the powder can also be filled into hard gelatine capsules.

Potential clinical advantages of Nanocrystals

Application for Oral Delivery

The oral route is the most important and preferred route of administration. The formulation of drug nanocrystals can impressively improve the bioavailability of perorally administered poorly soluble drugs. In 1995, Liversidge and Cundy reported an increase in bioavailability for the drug Danazol from 5.1 ± 1.9% for the conventional suspension to 82.3 ± 10.1% for the nanosuspension [53]. The increased dissolution velocity and saturation solubility lead to fast and complete drug dissolution, an important prerequisite for drug absorption. Whenever a rapid onset of a poorly soluble drug is desired, the formulation of drug nanocrystals can be beneficial, for example, in case of analgesics. The analgesic naproxen, formulated as a nanosuspension, has shown a reduced tmax but simultaneously approximately threefold increased AUC in comparison to a normal suspension (Naprosyn®) [54]. Besides the faster onset of action, the naproxen nanosuspension has also shown a reduced gastric irritancy [55-56]. If absorption windows limit the drug absorption or by food effects, drug nanocrystals have advantages in comparison to conventional suspensions. Wu et al. have reported reduced fed-fasted ratio and an improved bioavailability for nanocrystalline aprepitant (MK-0869), the active ingredient in Emend®, in beagle dogs.

Another important advantage of drug nanocrystals is their adhesiveness and the increased residence time, which can positively influence the bioavailability. The mucoadhesiveness can be raised by the use of mucoadhesive polymers in the dispersion medium [57-58]. Additionally the utilized mucoadhesive polymers can prevent the drug from degradation. The reduced particle size can be also exploited for improved drug targeting, as reported for inflammatory tissues [59] or the lymphatic drug uptake [60]. Muller et al. the use of mucoadhesive nanosuspensions as layering dispersions for preparation of multiparticulate drug delivery systems was investigated. Nanosuspensions on the other hand, enable incorporation of all hydrophobic drugs in well-established sustained release technologies. However whole doing so, the effect and interaction of dosage form excipients with the nanocrystalline drug must be critically investigated. Drug nanosuspensions can be incorporated into dosage forms, such as tablets, capsules, and fast melts by means of standard manufacturing technologies. A ketoprofen nanosuspension has been successfully incorporated into pellets to release drug over a period of 24 hrs [61]. O.kayser prepared bupravaquone mucoadhesive
nanosuspensions, a potential drug delivery system for poorly soluble drugs has been investigated to overcome bioavailability problems caused by the pathophysiological diarrhoeic situation in patients suffering from cryptosporidiosis. Cryptosporidium parvum identified as the main pathogen causing severe diarrhoea in immune suppressant HIV patients has attracted much interest. Adapting drug delivery systems to the situation of Cryptosporidium parvum infections in man allows increased retention times with a prolonged action at reduced elimination in the gastrointestinal tract.

In this communication, in vivo data are presented to document the efficiency of bupravaquone formulated as mucoadhesive polymers to improve its activity against C. Parvum [62].

Parenteral Administration of Drug Nanocrystals

The parenteral application of poorly soluble drugs, particularly intravenous (IV) administration of practically insoluble compounds, using cosolvents, surfactants, liposomes, or cyclohexetrines, is often associated with large injection volumes or toxic side effects. Carrier-free nanosuspensions enable potential higher loading capacity compared to other parenteral application systems. Using nanosuspensions, the application volume can be distinctly reduced compared to solutions [63]. To fulfil the distinctly higher regulatory hurdles, the drug nanocrystals need to be produced in an aseptic process. Alternatively, nanosuspensions can be sterilized by autoclaving or alternatively by gamma irradiation as well as sterile filtration [64-65]. When a drug is administered as a nanosuspension, the rapid dissolution of the nanocrystals will mimic the plasma concentration profile of a solution. Drug nanosuspensions can be formulated with accepted surfactants and polymeric stabilizers for IV injection. In contrast, solutions of poorly soluble drugs require the use of cosolvents and/or high surfactant contents (e.g., Chremophor EL in Taxol®), which can cause undesired side effects [66].

Comparing a clofazimine nanosuspension with a liposomal formulation, both are similarly effective in the treatment of artificially induced Mycobacterium avium infections. The targeting to the reticuloendothelial system, the lung, liver, and spleen was comparable to the liposomal formulation [67]. Furthermore, a special targeting can be achieved by a surface modification using the concept of differential protein adsorption. A surface modification of drug nanocrystals with the surfactant Tween 80 leads to a preferential adsorption of apolipoprotein E. This protein adsorption enables a targeted delivery of drugnanocrystals to efficacy in the treatment of Toxoplasmosis [68]. Administration of nanosuspensions into body cavities is also of great interest, e.g. to increase the tolerability of the drug, to achieve a local treatment or to have a depot with slow release (e.g. into the blood). It could be shown that intraperitoneal administration of a nanosuspension was well tolerated, whereas administration of a macroemulsion leads to irritancy [azodicarbonamide (ADA), unpublished data]. Intraperitoneal administration can be used for local treatment or to obtain a depot with prolonged release into the blood. Interesting therapeutic targets include local inflammations, e.g. in joints. For instance, arthritic joint inflammations are caused by secretion products of activated macrophages. An interesting approach is therefore the administration of a corticoid nanosuspension directly into the joint capsule. The drug particles will be phagocytosed, the drug dissolves and reduces the hyperactivity of the macrophages. This concept is not new, being adopted by the company Boots in the 80s in an attempt to incorporate the corticoid prednisolone into polymeric nanoparticles made from PLA-GA-copolymer [69]. Moschwitzer & co workers developed intravenously injectable and chemically stable aqueous omeprazole formulations using nanosuspension technology. The researchers stated that even after 1 month of production, no discoloration or recognizable drug loss was observed when nanosuspensions were formulated at 0ºc. As a result, it can be proven that the production of nanosuspension by high pressure homogenization is suitable for preventing degradation of labile drugs [70].

Drug Nanocrystals for Pulmonary Drug Delivery

Delivery of water-insoluble drugs to the respiratory tract is very important for the local or systemic treatment of diseases. Many important drugs for pulmonary delivery show poor solubility simultaneously in water and nonaqueous media, for example, important corticosteroids such as budesonide or beclomethasone dipropionate. Poorly soluble drugs could be inhaled as drug nanosuspension. The drug nanosuspension can be
nebulized using commercially available nebulizers. Disposition in the lungs can be controlled via the size distribution of the generated aerosol droplets. Compared with microcrystals, the drug is more evenly distributed in the droplets when using a nanosuspension. The number of crystals are higher, consequently, the possibility that one or more drug crystals are present in each droplet is higher. Besides this, drug nanocrystals show an increased mucoadhesiveness, leading to a prolonged residence time at the mucosal surface of the lung [71]. Claudia Jacobs et al prepared budesonide nanosuspension by High-pressure homogenization. It was possible to obtain a long-term stable budesonide nanosuspension. Mean particle size of this nanosuspension was about 500-600 nm, analyzed by photon correlation spectroscopy. Analysis by laser diffraction showed that the diameters 95% and 99% were below 3 m. Budesonide nanosuspension showed a long-term stability; no aggregates and particle growth occurred over the examined period of 1 year [72]. Hernandez-Trejo and coworkers stated that the poorly soluble drug bupravaquone is proposed for an alternative treatment of lung infection (pneumonia), which is caused by pneumocystis carinii. Physically stable nanosuspensions were formulated to deliver bupravaquone at the site of lung infection using nebulization [73].

**Drug Nanocrystals for opthalmic Drug Delivery:**
It could be shown that nanoparticles possess a prolonged retention time in the eye, most likely due to their adhesive properties. From this, poorly soluble drugs could be administered as a nanosuspension. The development of such colloidal delivery systems for opthalmic use aims at dropable dosage forms with a high drug loading and a long-lasting drug action. The nanosuspensions were prepared by a modification of the quasi-emulsion solvent diffusion technique using variable formulation parameters (drug-to-polymer ratio, total drug and polymer amount, stirring speed). Nanosuspensions had mean sizes around 100 nm and a positive charge (zeta-potential of +40/+60 mV), this makes them suitable for opthalmic applications. Stability tests (up to 24 months storage at 4 degrees C or at room temperature) or freeze-drying were carried out to optimize a suitable pharmaceutical preparation. In vitro dissolution tests indicated a controlled release profile of IBU from nanoparticles. In vivo efficacy was assessed on the rabbit eye after induction of an ocular trauma (paracentesis). An inhibition of the miotic response to the surgical trauma was achieved, comparable to a control aqueous eye-drop formulation, even though a lower concentration of free drug in the conjunctival sac was reached from the nanoparticle system. Drug levels in the aqueous humour were also higher after application of the nanosuspensions; moreover, IBU-loaded nanosuspensions did not show toxicity on ocular tissues [74].

**Drug Nanocrystals for Dermal Drug Delivery:**
Dermal nanosuspensions are mainly of interest if conventional formulation approaches fail. The use of drug nanocrystals leads to an increased concentration gradient between the formulation and the skin. The increased saturation solubility leads to supersaturated formulations, enhancing the drug absorption through the skin. This effect can further be enhanced by the use of positively charged polymers as stabilizers for the drug nanocrystals. The opposite charge leads to an increased affinity of the drug nanocrystals to the negatively charged stratum corneum (unpublished data).

**Drug Nanocrystals for targeted Drug Delivery**
Nanosuspension can be used for targeted deliver as their surface properties & changing of the stabilizer can easily alter in vivo behaviour. Their versatility and ease of scale up and commercial production enables the development of commercially viable nanosuspensions for targeted drug delivery. The natural targeting process could pose obstacles when macrophages are not the desired targets. Hence, in order to bypass the phagocytic uptake of drugs, its surface potential needs to be altered. Kayser developed the formulation of aphidicolin as a nanosuspension to improve the drug targeting effect against Leishmania-infected macrophages. He stated that aphidicolin was highly active at a concentration in the microgram range [75]. Nanosuspensions afford a means of administrating poorly soluble drugs to brain with decreased side effects. Significant efficiency has been associated with microparticulate busulfan in mice administered intrathecally. Another example is successful targeting of the peptide Dalargin to the brain by employing surface modified polyisobutyl cyanoacrylate nanoparticles [76].
Conclusion
Poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds and leads to employment of novel formulation technologies. The use of drug nanocrystals is a universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. Almost any drug can be reduced in size to the nanometer range. Owing to their great formulation versatility drug nanocrystals are no longer only the last chance rescue for a few drugs. Many insoluble drug candidates are in clinical trials formulated as drug nanocrystals (at present about 10). Currently, attention is turned to improving the diminution performance to produce drug nanocrystals well below 100 nm, also in cases of very hard drugs. First approaches were already successful. New technologies are in development to produce final dosage forms with higher drug loadings, better redispersability at their site of action, and an improved drug targeting.

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