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A Review On Nanocrystals In Drug Delivery

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ABSTRACT

Throughout the last 20 years, several trendy technologies are established within the pharmaceutical analysis and development space. The automation of the drug drug discovery method by technologies like high output screening, combinatorial chemistry and computer aided drug design is resulting in a huge range of drug candidates possessing a very good efficacy. Unfortunately, several of drug candidates are a unit exhibiting poor liquid solubility. The use of drug nanocrystal is an universal formulation approach to extend the therapeutic performance of those medication in any route of administration. Drug nanocrystals are crystals with a size range in the nanometer range, meaning that they are nanoparticles with a crystalline character. This review describes the chemistry properties of drug nanocrystals, production method and potential clinical advantages. Poorly soluble medication are usually difficult drawback in drug formulation. Reducing the particle size of a drug to a nano-scale leads to an increased in surface area-to-volume ratio, increased dissolution velocity and improved in vivo performance of poorly soluble drugs.

Keywords: Nanocrystals, Nanosuspension, Surfactant, Stabilizer, Bioavailability enhancement.

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INTRODUCTION

It's calculable that four-hundredth or additional of active substances being known through combinatorial screening programs a poorly soluble in water (Lipinski, 2001, 2002) [1]. Poor solubility isn't solely a retardant for the formulation development and clinical testing, it's additionally associate obstacle at the terribly starting once screening new compounds, for pharmacological activity. From this, there's as certain want for sensible technological formulation approaches to form such poorly soluble medicine bioavailable. Making such medicine bioavailable means they show sufficiently high absorption when oral administration or they can alternatively be injected intravenously. There is quite an range of formulation approaches for poorly soluble medicine which might be nominal as "specific approaches". These approaches are suitable for molecules having special properties with regard to their chemistry (e.g. solubility in bound organic media) or to the molecular size or conformation (e.g. molecules to be incorporated into the cyclodextrin ring structure) of course it might be a lot of smarter to possess a "universal formulation approach" applicable to any molecule except few exceptions. Such a universal formulation approach to extend the oral bioavailability is micronization, meaning the transfer of drug powder into the size range between typically 1-10 μ m. However, currently a day's several medicine are thus poorly soluble that micronization isn't adequate. The increase in extent, and therefore consequently in dissolution rate, isn't adequate to beat the bioavailability issues of terribly poorly soluble medicine of the biopharmaceutical specification category II. A subsequent next step was to maneuver from micronization to nanonization. Since the start of the 90s, the corporate nanosystems propagated the utilization of nanocrystals (instead of microcrystals) for oral bioavailability sweetening, and additionally to use nanocrystals suspended in water (nanosuspensions) for intravenous or pulmonary drug delivery. For the purpose of this review article, drug nanocrystals may be defined as pure solid particles with a mean diameter <1 μ m and a crystalline character. The platform offers an exceptional opportunity to deliver hydrophobic drugs (Figure 1). Its uniqueness originates from the fact that nanocrystals are composed entirely of 100% drug or the payload thereby eliminating the ancillary role of a carrier.⁷ In addition, surfactants or stabilizers are commonly used to stabilize the crystalline dispersions in liquid media. 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]. Nanocrystal drug formulations have also been shown to be stable in suspensions and are often referred to as nanocrystal colloidal dispersions (NCD's). The dispersions provide a platform for easy scale-up and manufacturing of highly stable and marketable products. Their synthesis and scale-up considerations have been described at length elsewhere [6,7]. Commonly used synthesis techniques include the use of microfluidic based platforms or the milling method, which, among others, is both flexible and tunable[7,8,9]. Taken together, the nanocrystal drug technology has been studied extensively and is well positioned for further exploration in the field of drug delivery.

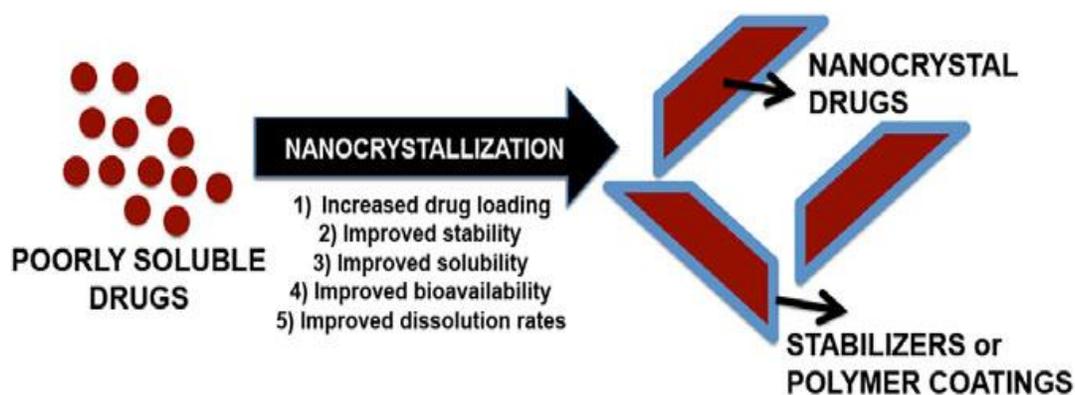


Figure 1: Nanocrystallization of poorly soluble drugs improves physicochemical stability and drug bioavailability

Several hydrophobic drugs have been salvaged via the nanocrystals formulation method. The drugs were successfully developed, and approved by the FDA to treat a variety of indications ranging from dental disorders to cancer in the clinic[10,11-21]. Depending on the malady, the approved formulations can be administered via different routes including oral, dermal, and parenteral. This highlights the versatility of a nanocrystals drug platform. Pharmacokinetic, biodistribution, and bioavailability data for organs involved in delivery routes tested using nanocrystal technology have been addressed at length previously[5,11,12,13,14,15-20]. Specifically, the reviews of Lu et al.2016 and 2017 cut into into the biodistribution pattern of nanocrystal medication within the blood, heart, liver, spleen, lung, kidney, tumor, and thymus (i.e., the organs involved in clearance /circulation and host immune responses)[13,22]. Several articles are printed, discussing the techniques used to synthesize nanocrystal drugs; the kind of stabilizers or surfactants involved; and the methods adopted for

physicochemical and biological characterization[5,19,23,24]. However, a wide translational gap exists between this highly promising platform and its clinical approval. In this review, we discuss the nanocrystal drug technology and its development from a translational perspective. We speak to the paucity of FDA approved products despite the platform's obvious strengths. We discuss the challenges involved in their successful translation to the clinic.

NANOCRYSTAL FOR DRUG DISSOLUTION:

Although often overlooked, crystallinity is a fundamental parameter for drug nanocrystals. It can provide insights into the structure of the final formulation. Assessing crystallinity is critical in verifying the successful integration of stabilizers, surface polymers (chemically conjugated or physically adsorbed), and targeting ligands. Further, nanocrystals with an amorphous crystalline substructure have an increased dissolution rate and are better suited for delivering multiple hydrophobic drugs[21,25,26]. This is better explained using the “spring and parachute” concept adapted to describe dissolution rates of amorphous, crystalline, or co-crystalline drugs. Co-crystalline drugs are often composed of multiple components, including a hydrophobic drug and a stabilizer. Stabilizers are supplementary molecules that once added throughout formulation, will management the nanocrystal size, agglomeration, and its overall biodistribution in vivo[8,10]. Stabilizers are usually 50–500 fold a lot of soluble in water than the drug in its free powder type. When exposed to an aqueous environment, the stabilizer first begins to leach into solution and leaves behind the drug particles. The exaggerated saturation solubility and therefore the accelerated dissolution rate are the foremost necessary differentiating options of drug nanocrystals. In general, the saturation solubility is outlined as a drug-specific constant relying solely on the solvent and therefore the temperature. This definition is just valid for drug particles with a minimum particle size within the micrometer vary. A particle size reduction all the way down to the micro millimeter vary will increase the drug solubility. The solid API dissolution rate is proportional to the area obtainable for dissolution as represented by the Nernst–Brunner/Noyes–Whitney Equation. [27,28,29]

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

Where, dX/dt =dissolution rate, X_d =amount dissolved, A =particle area, D =diffusion constant, V =volume of fluid obtainable 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[30].. For example in the case of a precipitate, the nanocrystal dispersion of 120nm particle size exhibits a 41.5-fold increase in surface area over the standard 5 μm suspension[31]. Furthermore, as described by the Prandtl equation, the diffusion layer thickness (h) will also be decreased thus resulting in an even faster dissolution rate[32]. In addition to the dissolution rate enhancement described above, an increase in the saturation solubility of the nanosized API is also expected [33] , 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_{∞} =saturation solubility of an infinitely large API crystal, γ is the crystal-medium interfacial surface tension, M is the compound molecular weight, r is the particle radius, ρ is the density, R is a gas constant and T is the temperature. Assuming a molecular weight of 500,=1 g/mL and a 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 a lot of vital increase in solubility seems to occur truly 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 [33]. This increase in solubility ends up in an extra 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 rise in surface wetting by the surfactants within the Nanosuspension formulations presumably ends up in an extra sweetening of the dissolution rates compared to micronized suspensions.

Advantages of Nanocrystals

- Applicability to all routes of administration in any dosage form.
- Increased rate of absorption.
- Increased dissolution, bioavailability and solubility.
- Increased drug loading.
- Rapid, simple and cheap formulation development.
- Reduction in dose and fed/fasted variability.
- Increased reliability.
- High stability and rapid effect.

Limitations

- ✓ Limited to only BCS II class drug only.
- ✓ High cost instruments are required for production of drug nanocrystal that increase the cost of dosage form.
- ✓ The formation of nanocrystals and their stability is depend on the molecular structure of the drug, so only certain classes of compound will qualify.

PHYSICAL ANALYTICAL METHODS TO CHARACTERIZE NANOCRYSTAL DRUG PRODUCTS:

Stabilizers that are widely used in nanocrystal drug formulations are presented in Table 1. These are amphiphilic molecules that increase the nanocrystal's surface wettability, and when used at optimal concentrations, do not interfere with the crystal growth. Its successful integration into the final formulation can be confirmed simultaneously with the crystal's substructure using X-Ray spectroscopy methods such as Small-angle X-ray scattering, X-ray diffraction, and X-ray photoelectron spectroscopy. Nanocrystal drug sample preparation for X-Ray spectroscopy analysis often involves freeze-drying. The effects of freeze-drying on the agglomeration of nanocrystals and its subsequent re-dispersibility have been studied and reported previously[34]. Previous studies have probed the effects of NP size, shape, surface morphology, and charge on therapeutic out come.

Table 1: Examples of drug/stabilizer combinations in nanocrystal formulations

Nanocrystal core molecule	Stabilizer	Process
Glibizide	Sodium lauryl sulfate, Polyvinyl pyrrolidone K30, Pluronic F68 and F127, Tween 80, hydroxypropyl methylcellulose	Milling, Antisolvent precipitation
MTKi-327	Pluronic F108, Lipid S75,	Milling,
Beclomethasonedipropionate	Hydrophobin	Antisolvent precipitation
Naproxen	Vitamin E tocopherol polyethylene glycol succinate, Pluronic F127, sodium lauryl sulfate, di(2-ethylhexyl) sulfosuccinate,	Milling,
Paclitaxel	Hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyethylene glycol 400, Pluronic F127 and F68, sodium lauryl sulfate, Tween 20 and 80, transferrin, immunoglobulin G, human serum albumin	Antisolvent precipitation, Sonication
Indomethacin	α -, β -, and γ - cyclodextrans, Pluronic F68, 17R4, and L64, Tetronics 908 and 1107	Emulsion solvent diffusion, milling
Budesonide	Lecithin, Pluronic F68	Milling
Curcumin	Polyvinyl alcohol, polyvinyl pyrrolidone, vitamin E tocopherol polyethylene glycol succinate, sodium lauryl sulfate, Carboxy methyl cellulose sodium	High pressure, homogenization
Nitrendipine	Polyvinyl alcohol	Antisolvent, precipitation, Ultrasonication
Brinzolamide	Tween 80, Pluronic F68 and F127, Hydroxypropyl Methylcellulose	Milling
Fenofibrate	Hydroxypropyl methylcellulose, Soluplus	Milling
Nimodipine	Pluronic F127, Hydroxypropylmethylcellulose	Microprecipitation, high pressure, Homogenization
Loviridine, cinnarizine, griseofulvin, mebendazole, phenyl butazone, phenytoin	Polyvinyl pyrrolidone, polyvinyl alcohol-polyethylene glycol, Pluronic F68, tocopherol polyethylene glycol succinate, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose sodium, polyvinyl alcohol, sodium alginate, tween 80	Milling
Cellulose	Tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide, cetyltrimethylammonium bromide, Hexadecyltrimethylammonium	Miniemulsion polymerization, Pickering emulsions
PH-797804 MAPK inhibitor nanocrystal-polymer particle	Polylactic acid	Miniemulsion polymerization
Gold	Cetyltrimethylammonium bromide, Benzyltrimethylhexadecyl ammonium chloride, hexamethylenetetramine, PVP	Self-assembly, antisolvent precipitation

Table 2: Nanocrystal variants with a varied range of properties including composition, size, and geometry

Type of nanocrystal	Size	Geometry
Iron oxide	11-16nm	Spheres
Copper nanocrystals	2-10nm	Spheres, cylinders, Tetrahedron
Gold nanocrystals	1-4nm	Spheres
Cellulose nanocrystals	141–1,073 nm (length) 12–28 nm (width) 1.12–1.45 nm (pitch)	Rods Ribbons
Hydroxyapatite	10–12 nm (width)	Plate-like crystals
Camptothecin	200–700 nm	Rods Needles
Lutein nanocrystal	429–560 nm 1–3 μ m	Spheres in suspension Spherical capsules
Chitosan/LaF ₃ :Eu ³⁺	13–18 nm	Spheres

It has been shown that these parameters influence phagocytosis, immune responses, endothelial targeting, adhesion under flow, transport mechanisms, and intracellular delivery[35-44]. As an e.g., Mitragotriand co-workers described the differences in internalization rate and the pathways of NPs differing in shape, size, and aspect ratio in mouse peritoneal macrophages [45]. Large particles (>100 nm) are usually internalized via non-specific pathways such as phagocytosis and macropinocytosis. However, nanocrystal drug surfaces can be modified to minimize non-specific uptake and facilitate entry via specific pathways such as receptor-mediated endocytosis. This can be achieved by coating the surface with polymers or surfactants such as PEG, PEG derivatives, polydopamine, and Pluronic F127 or with antibody coatings. Chung et al. showed that coating iron oxide NPs with positively charged multi-arm PEG derivatives could reduce mass aggregates and used to uniquely label mesenchymal stem cells[46]. Jiang et al. showed that a positive charge on iron oxide NPs coated with lipids can deliver nucleic acid payloads to cells[47]. Sonvico et al. showed that dextran coatings on maghemite NPs can achieve comparable disaggregation properties to PEG coatings and can be used to conjugate targeting moieties. It has also been shown that surface modifications can significantly affect the dissolution kinetics of pure drug NPs[48-51]. Stiffness and surface texture are also known impact the in vivo performance of NPs[43].Eliaz et al. and Lorenzetti et al. showed that nanocrystals developed for bone grafting and other bone related therapeutic applications (i.e., joint reconstruction) are particularly sensitive to stiffness (i.e., rigidity), surface texture (i.e., roughness), and hardness. The properties are influenced by bone-forming cells and are components crucial to the successful integration or rejection of these materials[52,53]. These findings highlight the importance of translational aspects of physical forces and properties that impact the biological performance and its clinical relevance. Table 2 summarizes the different sizes and geometries which have had success in preclinical research models. The table highlights the diversity of size domains, morphologies, and type of nanocrystal (i.e., organic/inorganic). The influence of surface charge on the in vivo fate of NPs has been extensively researched and reported. For instance, positively charged iron oxide nanocrystals have been found to induce cytotoxic effects in vitro in a charge-dependent manner. This is believed to result from increased endocytosis due to the strong binding between the positively charged surface on the crystal to the negatively charged glycolipid membrane. The internalized positively charged nanocrystals further interact with the negatively charged organelles and DNA[54].A similar observation was also noted for paclitaxel nanocrystals where a positive charge led to higher cell uptake and cytotoxicity compared to negatively charged particles[48]. On the contrary, negatively charged nanocrystals exhibited significant uptake via clathrin- and caveolae mediated uptake mechanisms[55]. Additionally, excessive positive and negative surface charges on

NPs have been shown to induce higher rates of opsonization and capture by the immune cells in vivo[55]. Finally, a majority of nanocrystal drug products approved for use in the clinic and or in clinical trials are delivered via oral or intravenous administration. Figure 2 depicts the challenges faced by these products to overcome the various biological barriers in vivo and properties that influence its biodistribution and site-specific delivery.

Nanocrystal-Drug Products

Nanocrystals, on account of their high-drug loading efficiency, steady dissolution rates, enhanced structural stability, and extended circulation times, have been a topic of high research and development activity. Several products are already in the market, and a number of other formulations are undergoing clinical trial.

Methods of Drug Nanocrystal Production

Nanocrystals are typically produced using two approaches:(A) Top-down(B) Bottom-up Top-down approaches include methods such as media milling (pearl milling) and high-pressure homogenization. Bottom-up approach, the most common method is precipitation. The importance for improvement of the bioavailability of poorly soluble medication by the assembly of drug nanocrystals is wide accepted. The intensive analysis for brand new technologies semiconductor diode to several alternative approaches for the assembly of drug nanocrystals. Even non pharmaceutical firms, like 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) (Müllerand 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 area unit reduced in size by shear forces and forces of impaction generated by a movement of the edge media. Small edge pearls or larger edge balls area unit used as edge media. The milling pearls are usually made of stainless steel, glass, zirconium oxide, or highly cross-linked polystyrene resin. The drug-crystals are nanosized by a combination of collision with the milling pearls; the milling chamber; and high shear forces. Problem related to the pearl edge technology is that the erosion from

the edge material throughout the edge method. Buchmann et al. [56] reported the formation of glass microparticles when using glass as milling material. In order to scale back the number of impurities caused by associate degree erosion of the edge media, the edge beads were coated with extremely cross-linked cinnamon rosin [57]. A perpetual downside is that the adherence of product to the big inner extent of the edge system. The inner extent is created of the extent of the chamber and of all edge beads along. Even in recirculation systems, this product adherence causes a product loss. Of course, this undesirable drug loss will be a problem in terribly overpriced medication, particularly once terribly tiny quantities of recent chemical entities (NCEs) are unit 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 [58]. This is an example to compare two formulation strategies. The oral resolution shows the principles of cosolvents and surfactants, whereas the tablets shows the nice performance of a particle size reduction technique. Emend® is that the second product incorporating the Nano Crystal technology. It was introduced to the market in 2003 by Merck. Emend® is a capsule containing pellets of nanocrystalline aprepitant, sucrose, microcrystalline cellulose, hypolose, and sodium dodecylsulfate [59].

Precipitation Methods

It is also known as hydrosol technology, and the IP is owned by Sandoz (now Novartis). A poor soluble drug is dissolved in associate degree organic medium, which is water miscible. A running of this resolution into a non solvent, such as water, will cause a precipitation of finely dispersed drug nanocrystals. A problem related to this technology is that the fashioned nanoparticles got to be stable 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 [60]. Another approach to preserve the scale of the precipitated nanocrystals is that the use of chemical compound growth inhibitors, which are preferably soluble in the aqueous phase.

High Pressure Homogenization Methods

The microfluidizer could be a airstream homogenizer of 2 fluid streams collided frontally with high speed (up to 1000m/sec) below pressures up to 4000 bar. There is a turbulent flow, high shear forces, particles collided leading to particle diminution to the nanometer range [61-

63]. The high applied and therefore the high streaming speed of the lipid can even cause cavitation to boot, contributing to size diminution. To preserve the particle size, stabilization with phospholipids or other surfactants and stabilizers is required. A major disadvantage of this method is that the needed production time. In many cases, 50 to 100 time-consuming passes are necessary for a sufficient particle size reduction [64-65].

Nanopure® Technology

In 1999, Muller et al. found that a similar effective particle diminution can also be obtained in nonaqueous or water-reduced media [66]. An elegant technique to get a final formulation directly is that the production of nanocrystals in non-aqueous homogenization media. Drug nanocrystals distributed in liquid polythene glycol (PEG) or oils is directly crammed as drug suspensions into albuminoid or HPMC capsules. The non-aqueous blending technology was established against the teaching that cavitation is that the major diminution force in high blending. Efficient particle diminution could also be obtained in non- aqueous media[67]. For oral administration, the drug nanosuspensions themselves are, in most cases, not the final products. For patient's convenience, the drug nanocrystals thought to be incorporated in ancient dry dose type, e.g. tablets, pellets and capsules. To prepare tablets or pellets, the phase of the nanosuspension has to be removed, i.e.in general, evaporated. Evaporation is quicker and potential underneath milder conditions once mixtures of water with water miscible liquids are used, e.g. water-ethanol. To obtain isotonic nanosuspensions for injection, it's helpful to homogenize in water-glycerol mixtures. By reducing the water content within the phase, the specified energy is reduced for drying steps, such as spray-drying, fluidized bed drying, or upon suspension layering onto sugar spheres. The evaporation processes is performed underneath milder conditions, which is beneficial for temperature-sensitive drugs. The scientific discipline closely held 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 danger that during the period of time 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 nonaqueous media possessing low toxicity, such as Nmethyl-2-pyrrolidinone.

NANOPURE® XP TECHNOLOGY

An advantage of this technology is its scaling up ability and also the chance to provide on massive scale, applying "normal" production conditions. PharmaSol uses in its Nanopure XP technology a pretreatment step with subsequent homogenization to produce particles well below 100 nm (Muller 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.

Table 3: Top-down versus bottom-up approaches for nanocrystal-drug products

	Technique	Merits	Limitations
Top-down approaches	Media milling (MM)	<ol style="list-style-type: none"> 1.Works for drugs that are insoluble in both aqueous and non-aqueous solvent. 2.No organic solvents are used 3.Ease of scale-up 4.Minimal batch to batch variation 5.Narrow size distribution of particles 6. High drug loading efficiency 	<ol style="list-style-type: none"> 1. Costly manufacturing process 2. high energy requirements with long durations for milling 3. could destabilize the drugs due to high shear forces and temperature 4. risks for contamination from the dispersion media 5. unwanted drug loss
	High Pressure Homogenization	Same as MM	<ol style="list-style-type: none"> 1. Particles need to be micronized and form suspensions 2. risk of contamination including Machine debris 3. high energy requirements
Bottom-up approach	Precipitation	<ol style="list-style-type: none"> 1. Simple and less expensive 2. Minimal energy requirements 3. Ease of scale-up 4. Possible non-stop production 	<ol style="list-style-type: none"> 1. Extensive optimization required selecting solvent/antisolvent 2. Possible growth of particles with time 3.Inadequate purification process or removal of toxic solvents

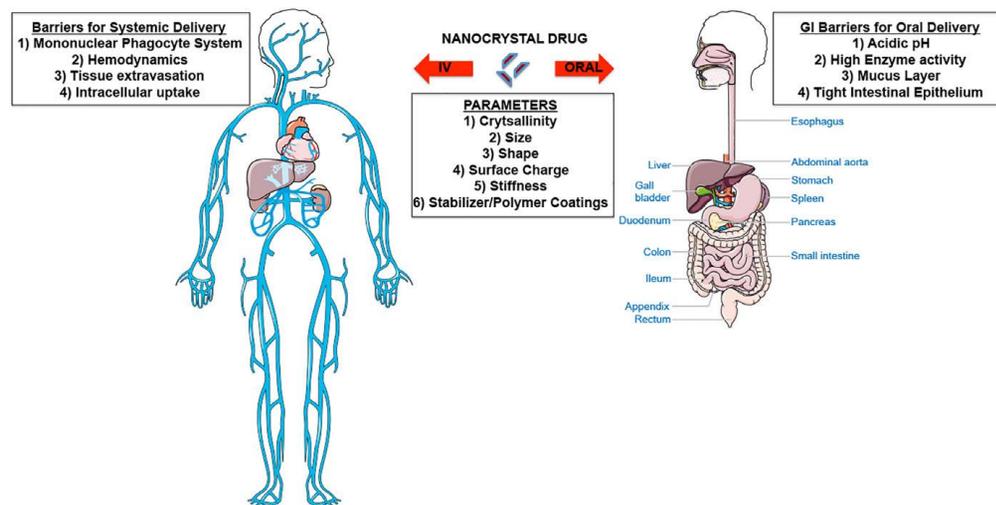


Figure 2. A schematic depicting the in vivo barriers and properties that influence in vivo biodistribution and site-specific delivery of nanocrystal drug products administered orally or intravenously (IV)

DOSAGE FORM DEVELOPMENTS OF NANOCRYSTALS

In order to indicate their blessings *in vivo*, the drug nanocrystals got to be transferred into the correct dose type. Nanosuspensions may be directly used as oral suspensions to beat the difficulties of swallowing tablets by medical specialty 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 those nanosuspensions will improve the solubility of the drug and also the dissolution rate; to boot, suspensions can be applied for reasons of taste-masking. Nanosuspensions may also be used directly for channel drug administration. Although nanosuspensions have shown a ample long stability while not 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 [68]. Without question, both the patients and the marketing experts prefer the oral administration of traditional dosage forms. Hence, to enter the pharmaceutical market with success in most cases drug nanocrystals ought to be developed as ancient product, such as tablets or capsules. A perfect solid dose type ought to 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, non-aggregated suspension. Otherwise, self-agglomeration or aggregation can impair the drug release [69]. Using nanosuspensions as granulation fluid for an extra pill production could be a terribly easy 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.

NANOCRYSTAL DRUG PRODUCTS IN THE MARKET

Since 1995, the FDA has approved ~50 nanodrugs, mostly based on liposomes, polymers, and nanocrystals for various indications [70]. Nano crystallization is an effective way to formulate and develop poorly soluble drugs. The commercial value of this technology is further enhanced by the relatively short span of time to clinical approval. While liposomes took almost 25 years to commercialize, the relative development time for Emend® was just 10 years. Emend's first patent application was filed in 1990 and the product was launched in 2000 [29]. Thus, compared to other nanosized platforms, a large number of nanocrystal drug products have been developed and launched successfully within a limited span [29]. Rapamune®, a poorly soluble immunosuppressant Sirolimus (SRL), was the first marketed nanocrystal drug product,

introduced by Wyeth Pharmaceuticals (Madison, NJ) in the year 2000[15]. Rapamune was formulated using the pearl mill technology method, and its oral bioavailability was found to be 21% higher than SRL in its conventional oral solution form. This was followed by the launch of Emend (Aprepitant), in 2003 by Merck (Winehouse Station, NJ). Aprepitant-a poorly water soluble anti-emetic medication, which can only be absorbed in the upper gastrointestinal tract and has a narrow absorption window. Nanoionization of Aprepitant via the pearl mill technology increased its oral bioavailability by making it more soluble in water. Tricor®, launched by Abbott Laboratories in 2003, was formulated from fenofibrate-a lipophilic medication for Hypercholestremia using the pearlmill technology method. Formulating fenofibrate into nanocrystals increased its adhesiveness to the gut wall and improved its oral bioavailability by 9% independent of fed or fasted state. This made way for a simplified, flexible dosing regimen for patients. Another nanocrystal drug product, derived from fenofibrate is Triglide® which was launched by Skye pharma in 2005. The Triglide nanocrystals were produced using the HPH method and provided benefits similar to Tricor. Triglide achieved an improved bioavailability that was independent of the fed or fasted state with increased adhesiveness to the gut wall. Triglide is currently marketed by ScielePharma Inc. (Atlanta, GA). Another nanocrystal product is Megace ES® and was launched by Par Pharmaceutical Companies, Inc. (Spring Valley, NY) in 2005. Megace ES was formulated into nanocrystals from megestrol acetate-an appetite stimulant using the pearl mill method. This improved its dissolution rate and reduced the single dose volume by four times, thereby improving its oral bioavailability and patient compliance when compared to the highly viscous megestrolacetate oral suspension. Other approved nanocrystal drug products are listed in Table 5 and media milling is the most widely accepted method used to produce a majority of the marketed products.

Table 4: Nanocrystal drug products in the market [15]

Trade name	Company	Drug	Indication	Technology	Route	Approval
Rapamune	Wyeth	Rapamycin	Immunosuppressive	Coprecipitation	Oral	2000
Emend	Merck	Aprepitant	Anti-emetic	Media milling	Oral	2003
Tricor	Abbott	Fenofibrate	Hypercholesterolemia	Media milling	Oral	2004
Triglide	Skye Pharma	Fenofibrate	Hypercholesterolemia	High pressure homogenization	Oral	2005
Megace®ES	Par Pharma	Megestrol acetate	Appetite stimulant	Media milling	Oral	2005
Invega Sustenna®	Johnson & Johnson	Paliperidonepalmitate	Antidepressant	High pressure Homogenization	Parental	2009
Cesamet®	Lilly	Nabilone	Anti-emetic	Coprecipitation	Oral	2009

NANOCRYSTAL DRUG-PRODUCTS IN CLINICAL TRIALS

As seen in Table 4, a majority of nanocrystal drug products are currently approved for oral ingestion and treating diseases other than cancer. The market for oral administration is enormous and, the path to commercialization is easier compared to injectables. Since the product is primarily composed of the drug and can be incorporated with GRAS approved stabilizers and excipients, the regulatory approval process for nanocrystal drug products is easier. Thus considering the feasibility for rapid development and commercialization, there are several nanocrystal drug products currently in clinical trials, as referred to in Table 6. Semapimod® nanocrystals from Cytokine Pharam sciences(CPSI) is a synthetic guanylhydrazone and was found to act an immunomodulator, preventing the production of TNF- α , a pro inflammatory cytokine, involved in inflammation-associated carcinogens is during a Phase I study in cancer patients[71]. CPSI also showed the drug to be effective in treating psoriasis and moderate-to-severe Crohn's disease during a preliminary clinical trial. Another nanocrystal drug currently in clinical trials is PAXCEED™ from Angiotech Pharmaceuticals, Inc[72]. PAXCEED is formulated from paclitaxel and is a cremophorEL-free systemic formulation. This could potentially reduce hypersensitivity in patients treated for cancer or chronic inflammation. Theralux™ from Celmed BioSciences Inc., (Saint-Laurent, QC) is aphotodynamic therapy-based treatment system consisting of thymectacin, which is poorly soluble and has minimal bioavailability [73].

Table 5: Nanocrystal drug products in clinical trials

Trade name	Company	Drug	Indication	Technology	Clinical status
Semapimod	Cytokine Phamasciences	Guanylhydrazone	TNF- α Inhibitor	Self-developed	II
Paxceed®	Angiotech	Paclitaxel	Anti-inflammatory	Unknown	III
Theralux	Celmed	Themectacin	Autoimmune diseases and cancer	Media milling	II
Nucryst®	Nucryst Pharmaceuticals	Silver	Atopic dermatitis	Self-developed	II
Panzem NCD	EntreMed	2-methoxy estradiol	Ovarian cancer	Media milling	II

CHARACTERIZATIONS OF DRUG NCs

To substantiate the successful nanocrystallization of drugs, the as prepared drug NCs should be carefully characterized. Their morphology, crystallinity, particle size, and dissolution rate were considered as important indexes for further applications.

STABILIZERS SELECTION OF DRUG NCS

Before the preparation process of drug NCs, selecting suitable stabilizers is the first step as they play an important role in the growth inhibition and stabilization of NCs. Atomic force microscope (AFM)method was usually utilized to investigate the interaction between polymeric stabilizers and

drug NCs, and observe their morphologies. For example, AFM images displayed that HPMC reacted strongly with the ibuprofen NCs, which suggested its suitability for the preparation and stabilization of ibuprofen nanosuspension[74]. In another case, AFM images indicated that HPMC, due to the chain-like pattern, exhibited higher adsorption on the surface of icariin (ICT)NCs compared with other stabilizers[75].

MORPHOLOGY OBSERVATION OF DRUG NCS

The morphology of drug NCs could be observed by AFM, SEM, and TEM. SEM and TEM methods were selected to characterize the surface morphology and inner structure of drug NCs, respectively. SEM imaging's used to observe morphological structure change of drug NCs during the whole progress including preparation method.[76] drying and storage. Moreover, we can measure the size of drug NCs from AFM, SEM, and TEM images.

CRYSTALLINE STATE OF DRUG NCS

The crystalline state of drug NCs is another crucial factor, which can be identified by differential scanning calorimetry (DSC) and x-ray Diffraction (XRD)[77]. From DSC detection, the melting points of coarse drugs, mixture of stabilizers and drugs, and drug NCs can be confirmed. According to XRD patterns, the characterized peaks of crystals can be identified. By comparison of these characterizations, the crystallization of drug NCs will be confirmed. Polymorphisms also can be confirmed by these two methods, take SN 30191 as an example, DSC thermograms of three solid forms of SN 30191 including form I, form II, and hydrate. Form I and II exhibited melting peak at 178.5 and 172.9_C, respectively. Hydrate form showed two endothermic transitions at 92 and 179.6_C and XRD peaks of form I was more intense and sharp than form II, indicating that form II probably has a more disordered structure. Moreover, at high 2θ angles (20–25_), peaks of form I were more intense than that of form II, indicating a high degree of crystallinity for form I

Size Distribution and Dissolution Rate

The size distribution of drug NCs is commonly detected by DLS, which offers hydrodynamic diameter and particle dispersion index (PDI). The hydrodynamic diameter provides the information of drug NC core, coating materials, and hydration layer. Additionally the size of drug NCs could be measured on SEM, TEM, and AFM images in their drying regime, in this case, the hydration layer is not present. Hence, the hydrodynamic diameter of drug NCs is always larger than the size estimated by SEM, TEM, and AFM images.

CHARACTERIZATION OF NANOCRYSTALS

Table 6: Evaluation parameter

Sr.No	Parameter	Methods
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1	Mean particle size and size distribution	Transmission Electron Microscopy(TEM), Scanning Electron Microscopy (SEM), Environmental Scanning Electron Microscopy (ESEM)
2	Structure and morphology	Light microscopy, Scanning electron microscopy, transmission, Electron microscopy, Field emission scanning electron microscopy, Atomic force microscopy
3	Surface charge	Zeta potential
4	Rheological properties	Viscometer, rheometer
5	Solid state analysis	Powder X-ray diffraction, Differential scanning calorimetry
6	Solubility	UV spectrophotometer
7	Concentration determination	Fluorescence spectroscopy

NANOCRYSTALS BASED FORMULATIONS

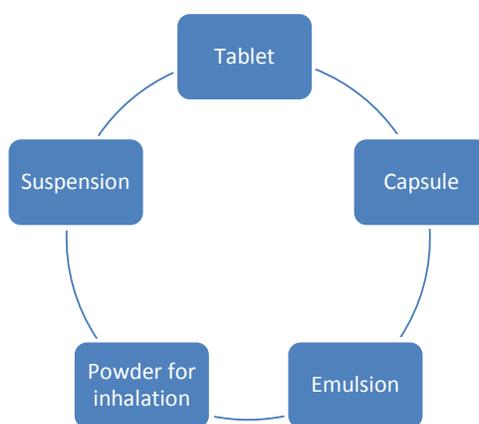


Figure 3: Types of formulation

APPLICATIONS OF DRUG NANOCRYSTALS

Application for Oral Delivery

The oral route is that the most vital 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 $5.1 \pm 1.9\%$ for the conventional suspension to $82.3 \pm 10.1\%$ for the nanosuspensions [78]. 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 are often beneficial, for instance, just in case of analgesics. The analgesic naproxen, formulated as a nanosuspension, has shown a reduced t_{max} but simultaneously approximately three fold increased AUC in comparison to a normal suspension (Naprosyn®) [79]. Besides the faster onset of action, the naproxen nanosuspension has also shown are reduced gastric irritancy. If

absorption windows limit the drug absorption or by food effects, drug nanocrystals have advantages as compared to standard 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 therefore the increased duration, which may positively influence the bioavailability. The mucoadhesiveness can be raised by the use of mucoadhesive polymers in the dispersion medium. 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 [or the lymphatic drug uptake [80]. Muller et al the use of mucoadhesive nanosuspensions as layering dispersions for preparation of multi particulate drug delivery systems was investigated. Nanosuspensions on the opposite hand, enable incorporation of all hydrophobic drugs in well established sustained release technologies. However while doing so, the effect and interaction of dosage form excipients with the nanocrystalline drug must be critically investigated.

Parenteral Administration of Drug Nanocrystals

The parenteral application of poorly soluble drugs, particularly intravenous (IV) administration of practically insoluble compounds, using co-solvents, surfactants, liposomes, or cyclodextrines, 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. To fulfill the distinctly higher regulatory hurdles, the drug nanocrystals need to be produced in an aseptic process. Alternatively, nanosuspensions can be sterilized by autoclaving oral alternatively by gamma irradiation as well as sterile filtration [81]. When a drug is run as a nanosuspension, the rapid dissolution of the nanocrystals will mimic the plasma concentration profile of an answer. Drug nanosuspensions can be formulated with accepted surfactants and polymeric stabilizers for IV injection. In contrast, solutions of poorly soluble drugs require the utilization of co-solvents and/or high surfactant contents (e.g. Chremophor EL in Taxol®), which can cause undesired side effects.

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 non-aqueous media, for example, important corticosteroids such as budesonide or beclomethasone dipropionate. Poorly soluble drugs could

be inhaled as drug nanosuspension. The drug nanosuspension are often nebulized using commercially available nebulizers. Disposition within the lungs are often controlled via the dimensions distribution of the generated aerosol droplets. Compared with microcrystals, the drug is more evenly distributed within the droplets when employing 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 [82].

Drug Nanocrystals for Ophthalmic 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 might be administered as a nanosuspension. The development of such colloidal delivery systems for ophthalmic 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 ophthalmic applications. Stability tests (up to 24 months storage at 4 °C or at room temperature) or freeze-drying were carried out to optimize a suitable pharmaceutical preparation.

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.

Drug Nanocrystals for Targeted Drug Delivery

Nanosuspension can be used for targeted delivery 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 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 [83]. Nanosuspensions afford a means of administering poorly soluble drugs to brain with decreased side effects.

Nanocrystal Drugs: A Carrier Free Therapeutic Platform for Cancer and Other Diseases

By the year 2021, nanocrystal drug products are estimated to account for 60% of the total NP-based drug delivery market[84]. This is valued to be at ~\$82 billion. While nanocrystal technology is attractive due to its ease of formulation, uniform composition, and attractive pharmacoeconomical use, it also has the potential to overcome some of the biggest challenges for drug development. Poor solubility could result in abysmal bioavailability, thereby affecting optimal delivery of the drug. By formulating poorly soluble drugs into nanocrystals, the resulting increase in surface/volume ratio, saturation solubility, and the rate of dissolution can ensure an enhanced bioavailability of most insoluble drugs irrespective of its route of administration. Clinical efficacy of nanocrystal drugs depend on several factors including the size, morphology, surface charge, amount of drug loaded, the type of excipients used, the degree of redispersability, and site-specific targeting. Also, multimodal theranostic nanocrystal drug products would be vital to assess and monitor in vivo bioavailability. Overall, nanocrystals have the potential to open up new frontiers in the field of therapeutics. The ability to reformulate off-patent drugs into novel nanocrystal drug products for clinical use offers a clear competitive edge for companies in the market.

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. 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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