



Pharmaceutical nanocrystals: A review of formulation approaches and drug delivery applications

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Abstract

Roughly a third to a half of all newly discovered drug candidates run into the same wall during early Development: they simply will not dissolve in water fast enough, or in high enough amounts, to reach the Bloodstream in a therapeutically useful way. Pharmaceutical scientists have tried almost everything to get around this problem salt formation, co-solvents, cyclodextrin complexation, lipid carriers, amorphous solid Dispersions and each of these has its place. But one approach has quietly become the workhorse solution for a surprisingly large number of marketed products: shrinking the drug crystal itself down to a size between roughly ten and a thousand nanometres, without diluting it in any carrier. This is the nanocrystal, or “Nano suspension,” Approach, and it has moved from a laboratory curiosity in the early 1990s to a technology that underpins several Billion-dollar drug products and a growing list of applications well beyond the oral route.

Keywords: Nanocrystals, nano suspension, poorly water-soluble drugs, bioavailability enhancement, media milling, high-pressure homogenization

Introduction

Anyone who has spent time in early-stage drug discovery has heard some version of the same complaint from a formulation scientist: “the compound works beautifully in the test tube, but we can’t get enough of it into the animal.” This is not a rare complaint. Estimates vary depending on how a research group counts its candidates, but somewhere between one-third and one-half of newly synthesized drug molecules, and by some counts up to 90% of compounds currently in discovery pipelines, are poorly soluble in water ^[1]. Under the Biopharmaceutics Classification System, these fall largely into Class II (low solubility, high permeability) and Class IV (low solubility, low permeability) the two categories that give formulators the most grief, because no amount of clever excipient design can push a drug across the gut wall if the drug never dissolves in the first place.

The irony is that combinatorial chemistry and high-throughput screening, both of which were supposed to accelerate drug discovery, made this problem measurably worse. Modern screening libraries are enriched with larger, more lipophilic, more crystalline molecules than the drugs of forty years ago, simply because lipophilicity tends to improve binding affinity at a target receptor. A molecule that binds its target beautifully is often, almost by construction, a molecule that hates water. Formulators have therefore spent decades building a toolbox of workarounds: salt forms, particle size reduction by conventional ionization, solid dispersions, cyclodextrin inclusion complexes, self-emulsifying lipid systems, and amorphous formulations that trade thermodynamic stability for kinetic solubility. Each of these has genuine strengths, and each has a failure mode. Salts are not possible for every molecule, cyclodextrin have a finite loading capacity, amorphous forms can recrystallize on the shelf, and lipid systems struggle with very high-melting, poorly lipid-soluble actives.

Nanocrystal technology takes a conceptually different route. Rather than dissolving the drug into something else, or changing its chemical form, it simply makes the solid particles of the drug itself very small typically under one micrometre, and often in the 100–500 nm range while leaving the crystal lattice, and therefore the chemical identity of the drug, essentially untouched. Because the particle is composed almost entirely of active pharmaceutical ingredient, with only a thin stabilizing layer of surfactant or polymer on its surface, nanocrystals are sometimes described as a “carrier-free” nanoparticle system, in contrast to liposomes, polymeric nanoparticles, or lipid nanoparticles, all of which dilute the drug inside a matrix of non-drug material ^[2]. This distinction matters practically: drug loading in a nanocrystal formulation can approach 100%, which is difficult to achieve with almost any encapsulated delivery system and becomes particularly important for drugs that must be dosed in the tens or hundreds of milligrams. What makes the small particle size useful is not a new discovery. Two relationships that pharmacy students encounter early in their training the Noyes–Whitney equation describing dissolution rate, and the Ostwald–Freundlich (and closely related Kelvin) equation describing how curvature affects apparent solubility together explain why shrinking a crystal changes its behaviour in the body. For it is enough to say that going from a typical micronized drug powder (several microns in diameter) down into the nanometre range produces such a large jump in surface area that dissolution becomes dramatically faster, and, for the very smallest particles, the apparent solubility itself edges upward. The practical consequence has been a string of approved medicines an immunosuppressant, an antiemetic, a lipid-lowering agent, an antipsychotic depot injection, among others whose clinical usefulness depended on solving exactly this solubility bottleneck ^[3].

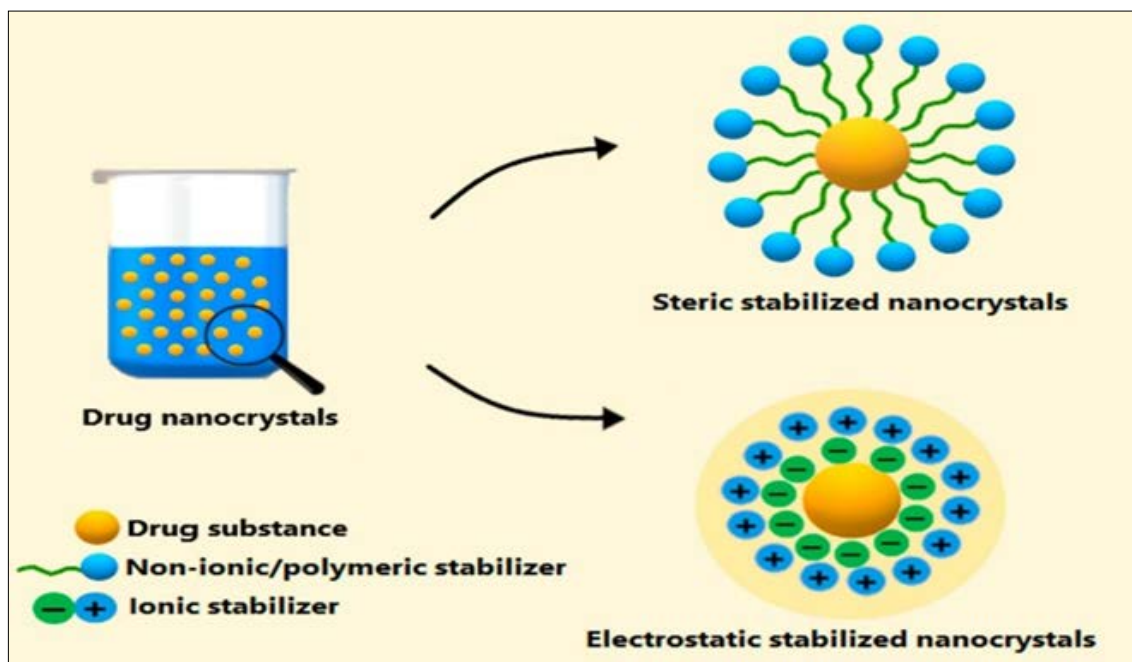


Fig 1: drug nano crystals

Historical Evolution of Nanocrystal Technology

It is tempting to think of nanotechnology in pharmaceuticals as a twenty-first-century development, but the roots of drug nanocrystals actually reach back to the early 1990s, growing out of work on parenteral

fat emulsions and, separately, out of milling technology borrowed from the paint and pigment industries. Below we trace the major milestones, not as a dry list of dates, but as a story of how an idea moved from patent filings to hospital pharmacies

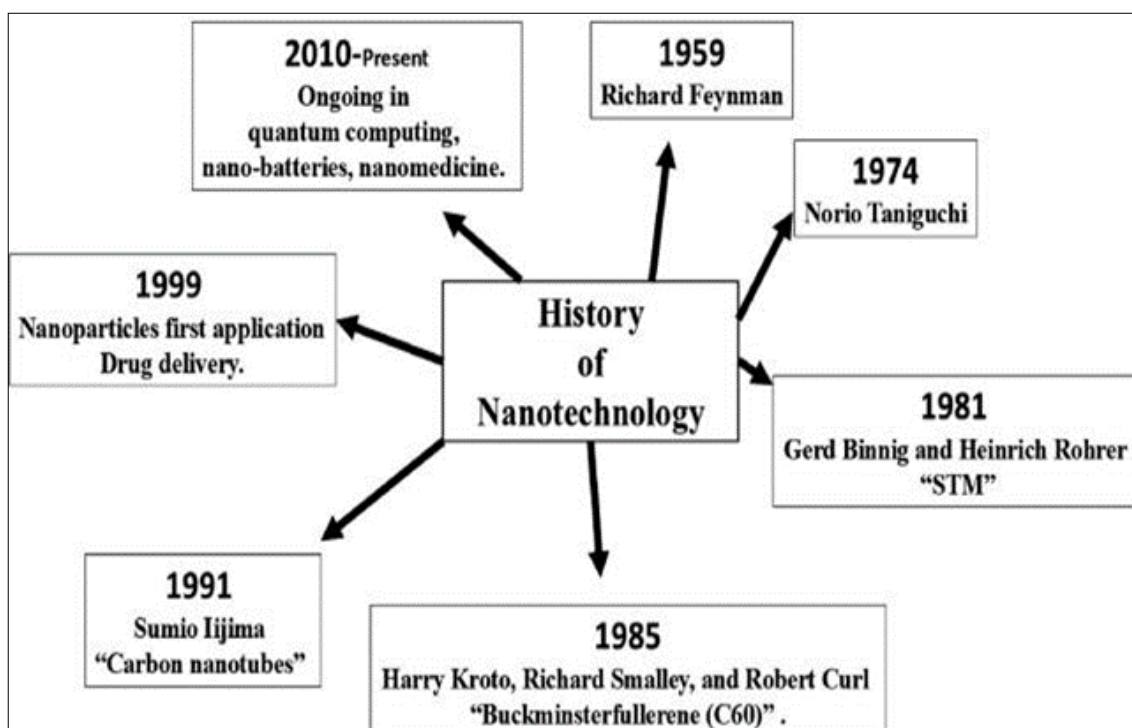


Fig 2: Historical Evolution of Nanocrystal Technology

1. The early patents and the industrial milling connection

The conceptual seed for nanocrystal technology is often traced to patents filed by Douglas Haynes in the early 1990s describing phospholipid-coated microcrystals for injectable delivery of water-insoluble drugs [4]. Around the same period, formulation scientists working with poorly soluble parenteral actives were borrowing wet-Milling technology

that had long been used in the paint, ceramics, and pigment industries to reduce particle size in slurries. Pearl or bead mills vessels filled with small, hard grinding media that collide with suspended particles and gradually fracture them turned out to be well suited to pharmaceutical suspensions once appropriately validated for the much stricter purity requirements of a drug product [5]. In parallel, high-pressure homogenization, a technology already used to prepare stable

oil-in-water emulsions and liposomes, was adapted by Rainer H. Müller's group in Berlin to fracture drug crystals through cavitation forces generated as a suspension is forced through a narrow homogenization gap at high pressure ^[6]

2. Diversification beyond the oral and parenteral routes

Through the 2000s and into the 2010s, academic and industrial groups increasingly explored whether the same Size-reduction logic could be applied beyond tablets and injections. Pulmonary Nano suspensions for nebulized or inhaled delivery were investigated for drugs such as budesonide, where nanonization improved the Uniformity and depth of lung deposition compared with coarser suspensions ^[7]. Dermal and cosmetic applications followed, driven largely by Cornelia Keck and Rainer Müller's work showing that nanocrystals applied to skin can act as a kind of local depot, dissolving slowly within hair follicles and skin folds to sustain a saturated concentration gradient that drives passive diffusion into deeper skin layers ^[8]. Ocular Nano suspensions, ophthalmic gels, and even nanocrystal-based vaccine adjuvant research emerged over the Following decade, and by the early 2020s, several groups had begun exploring surface -functionalized or "targeted" nanocrystals designed to accumulate preferentially in tumour tissue, extending the technology from A solubility fix into something closer to an active drug delivery and targeting platform ^[9].

3. Where things stand today

By most industry estimates, the nanocrystal drug product market is now worth tens of billions of dollars globally, the majority of it still concentrated in oral products, largely because ultrafine nanocrystals suitable for parenteral or pulmonary administration remain harder and more expensive to manufacture reliably at scale. Regulatory experience has matured alongside the science: agencies including the US FDA and the EMA now have reasonably well-established expectations for the chemistry, manufacturing, and controls (CMC) package required for a nanocrystal new drug application, discussed further in Section 15. What began as a somewhat opportunistic use of industrial milling equipment has become, three decades later, a mainstream formulation strategy taught in pharmaceuticals courses worldwide.

What Exactly Is a Drug Nanocrystal?

Before going further, it is worth being precise about terminology, because "nanoparticle," "nanocrystal," and "nan suspension" get used loosely, sometimes interchangeably, in casual conversation and even in some published papers. A drug nanocrystal is a solid particle of pure, crystalline (or sometimes partially amorphous) active pharmaceutical ingredient, generally with a mean diameter somewhere between about 10 nanometres and 1000 nanometres (1 micrometre), stabilized against aggregation by a thin coating of surfactant, polymer, or both, adsorbed on its surface ^[10]. Unlike a liposome, polymeric nanoparticle, or lipid nanoparticle, which are structurally organized around a carrier material that dilutes the drug payload, a nanocrystal is essentially "all drug." Drug loading can therefore reach close to 100% by weight, with the stabilizer typically contributing only a few percent of the total mass. When these particles are suspended in an

aqueous (or occasionally non-aqueous) liquid medium, the resulting liquid formulation is called a Nano suspension. A Nano suspension can be administered as-is (for example, as an oral liquid or an injectable suspension), or it can be further processed by spray drying, freeze drying, or granulation into a solid intermediate that is then compressed into tablets, filled into capsules, or reconstituted before use. It is worth remembering that "Nano suspension" describes the liquid dispersion, while "nanocrystal" strictly refers to the individual solid particles suspended within it; in practice, the two terms are frequently used as shorthand for each other in the literature, and we follow that convention loosely in this review while trying to be explicit where the distinction matters.

1. Size range and why it matters

The practically useful size window for nanocrystals sits below roughly 1 μm , with most marketed and Investigational products falling somewhere between 100 and 500 nm, depending on the route of administration and the desired dissolution profile. Intravenous nanosuspensions generally require the tightest control, because particles above roughly 5–7 μm risk causing capillary blockage, so IV nanocrystal formulations are Usually milled down toward the lower end of the range and rigorously filtered and characterized before use ^[11]. Oral formulations have somewhat more latitude, since gastrointestinal transit and absorption are less sensitive to the exact particle size once the suspension is well below a few hundred nanometres, though smaller is still generally better for dissolution rate.

The Physical Chemistry Behind the Technology

The entire rationale for nanocrystal technology rests on two relationships that are more than a century old. Neither was developed with pharmaceuticals in mind the Noyes–Whitney equation dates to a 1897 paper on the rate at which solids dissolve, refined by Nernst and Brunner in the early 1900s into what is often called the Nernst–Brunner form, and the Ostwald–Freundlich relationship (closely related to the Kelvin equation from colloid science) describes how the curvature of a very small particle's surface raises its apparent, or "kinetic," solubility relative to a large flat crystal of the same material ^[12].

1. Dissolution rate: the Noyes–Whitney / Nernst–Brunner equation

The classical form of the equation states that the rate of dissolution, dC/dt , is proportional to the surface area of the dissolving solid, the concentration gradient across a thin stagnant diffusion layer surrounding each Particle, and the diffusion coefficient of the dissolved drug, and inversely proportional to the thickness of that

$$\text{Diffusion layer: } dC/dt = (A \cdot D \cdot (C_s - C_t)) / (V \cdot h)$$

where A is the surface area of the solid particles exposed to the dissolution medium, D is the diffusion coefficient of the drug in solution, C_s is the saturation solubility of the drug at the particle surface, C_t is the bulk drug concentration at time t, V is the volume of The variable that nanocrystal technology attacks directly is A. Reducing a particle's diameter by a factor of ten increases its surface-area-to-volume ratio by roughly the same factor, and because a given mass of drug is now distributed across vastly more,

vastly smaller particles, the total surface area available for dissolution climbs steeply. There is a secondary effect too: very small particles have a thinner effective diffusion layer (h decreases as particle radius decreases, following the Prandtl boundary-layer relationship), which further accelerates dissolution beyond what the surface-area term alone would predict. dissolution medium, and h is the thickness of the diffusion boundary layer^[13]. The variable that nanocrystal technology attacks directly is A. Reducing a particle's Diameter by a factor of ten increases its surface-area-to-volume ratio by roughly the same factor, and because a Given mass of drug is now distributed across vastly more, vastly smaller particles, the total surface area Available for dissolution climbs steeply. There is a secondary effect too: very small particles have a thinner Effective diffusion layer (h decreases as particle radius decreases, following the Prandtl boundary-layer Relationship), which further accelerates dissolution beyond what the surface-area term alone would predict.^[14]

2. Apparent solubility: the Ostwald–Freundlich equation

The second relationship is subtler and, in recent years, has been the subject of some healthy scientific debate about how large an effect it really produces in practice.

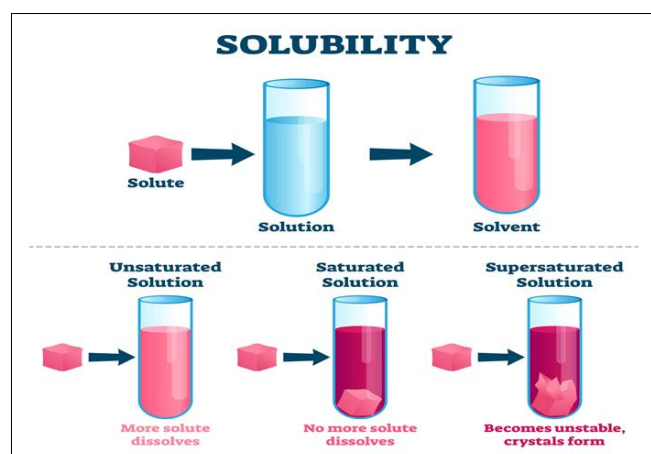


Fig 3: The Solubility

The Ostwald–Freundlich equation predicts that the Saturation solubility of a solid rises as particle radius shrinks, because smaller particles have a higher Proportion of surface molecules with excess free energy relative to molecules in the bulk crystal interior:

$$\ln(C_s/C_\infty) = (2\sigma V_m) / (rRT)$$

Is the solubility of a particle of radius r, C_∞ is the solubility of an infinitely large (bulk) crystal of the Same material, σ is the interfacial energy between the solid and the liquid, V_m is the molar volume of the solid, R is the universal gas constant, and T is absolute temperature. In plain language: as r gets smaller, the Exponent grows, and C_s rises above C_∞ . The effect is negligible for particles above roughly 1 μm and only becomes noticeable once particles drop well below 500 nm, which is precisely the range nanocrystal Manufacturing targets. It is worth being candid about the magnitude of this effect, because early nanocrystal literature sometimes overstated it. More recent numerical modelling work combining experimental solubility measurements with

the Ostwald–Freundlich and Nernst–Brunner equations found that the increase in apparent solubility for well-Characterized nanocrystal systems is generally modest — on the order of 15–20% for particles around 150 nm and becomes clinically meaningful mainly for the very finest particle populations, in the tens of nanometres. The broader consensus in the field today is that the dissolution-rate improvement (Noyes–Whitney) is Usually the dominant mechanism behind the bioavailability gains seen with nanocrystal products, with the Solubility increase (Ostwald–Freundlich) playing a secondary, supporting role rather than being the primary Driver^[15].

Manufacturing Technologies Bottom-Up Technology

Nanocrystals can be produced either by a top-down approach, where larger particles are reduced to the nanoscale, or by a bottom-up precipitation technique, in which dissolved molecules assemble to form crystals^[16]. Hydrosol technology, developed by List and Sucker, represents one of the earliest applications of the precipitation approach for producing drug nanocrystals. The technology was patented by Novartis, formerly known as Sandoz. In the nanoprecipitation process, drug molecules are initially dissolved in a suitable organic solvent, such as acetone, tetrahydrofuran, or N-methyl-2-pyrrolidone. The solution is then allowed to reach a supersaturated state, promoting the formation of initial nuclei. Subsequently, an antisolvent containing suitable stabilizers, such as polyvinylpyrrolidone (PVP), Tween 80, Poloxamer 188, polyvinyl chloride, hydroxypropyl methylcellulose (HPMC), or hydroxypropyl cellulose (HPC), is introduced. This leads to rapid nucleation and precipitation of the drug, resulting in the formation and growth of crystalline or semi-crystalline drug nanocrystals^[17]. The precipitation technique is suitable only for drugs that exhibit adequate solubility in at least one solvent, provided that the solvent is miscible with the selected antisolvent. Another important consideration is to ensure that the residual solvents are reduced to levels that comply with acceptable limits in the final formulation. For successful application of the bottom-up approach, the manufacturing conditions must be carefully controlled to prevent the newly formed nanocrystals from undergoing recrystallization and increasing to the micro meter size range^[18].

Manufacturing Technologies Top-Down Technology

High-pressure homogenization and media milling are widely used top-down techniques for preparing drug nanocrystals. In high-pressure homogenization, particle size is reduced by propelling a drug suspension at very high velocity through a narrow gap, usually around 25 μm in width.^[19] Media milling reduces the size of drug particles suspended in a liquid through mechanical attrition using milling agents, such as beads or balls, manufactured from materials including ceramics, cerium-based compounds, yttria-stabilized zirconia, stainless steel, glass, and highly cross-linked polystyrene resin^[20]. A significant drawback of wet milling is the potential for particles or residues from the milling equipment to enter the formulation and contaminate the final product^[21]. During the milling process, the movement of the grinding media produces shear forces that break down the drug particles and reduce their size. However, wear and tear of the milling material can introduce process-related impurities into the formulation,

which is a major concern because these contaminants may be insoluble in the dispersion medium. Therefore, detecting and controlling such contaminants throughout manufacturing is an important consideration in the development of nanocrystal-based products. Other critical process parameters include the temperature of the product, the chiller temperature, and the milling duration needed to obtain the desired particle size. Furthermore, the reproducibility of the milling process cannot be determined solely by the number of milling cycles, as factors such as the geometry of the milling media, the aspect ratio of the active pharmaceutical ingredient (API), and the viscosity of the dispersion can also influence the characteristics of the final product.^[22]

1. Media Milling

In this process, the milling chamber is loaded with grinding media such as beads or rods, along with the drug, a dispersion medium (usually water), and a suitable stabilizer. The drug particles undergo size reduction due to the shear forces produced by the movement of the milling media. Increasing the effective surface area of the grinding media provides a greater number of particle-contact sites, thereby improving the grinding and dispersion efficiency and facilitating more effective reduction in particle size^[23].

2. High-Pressure Homogenization Method

In high-pressure homogenization, the drug is first dispersed in a surfactant-containing solution and then subjected to extremely high pressure as it is forced through a narrow orifice by a piston. The pressure may reach up to 4000 bar, although pressures of approximately 1500–2000 bar are commonly employed. Based on Bernoulli's principle, the velocity of a liquid increases considerably when it moves from a wider passage into a much narrower opening, resulting in a substantial reduction in static pressure. This sudden pressure decrease can lower the liquid's boiling point, causing vapour bubbles to develop within the homogenization orifice. When the suspension leaves the narrow opening and enters a region of larger diameter, the bubbles rapidly collapse, producing the phenomenon known as cavitation. The intense energy generated during bubble collapse contributes to the disruption and reduction of drug particles. The final particle size is influenced by several processing parameters, particularly the applied homogenization pressure, the number of homogenization cycles, and the physical hardness of the drug.

3. Micro fluidizer Technology

Micro fluidization is based on the jet-stream principle, where the drug suspension is propelled at high velocity through a specially designed homogenization chamber with either a "Z" or "Y" configuration. In the "Z"-type chamber, the flow direction changes several times, causing the suspended particles to collide with one another and generating intense shear forces that facilitate particle size reduction. In contrast, the "Y"-type chamber divides the suspension into two separate streams, which are subsequently directed toward each other and collide head-on, producing the forces required for particle disruption.^[24]

Method of Preparations of Nanocrystals

Top-down techniques, including media milling and high-pressure homogenization, are commonly employed to transform larger drug micro particles into nanoscale

crystals. In media milling, a drug suspension is mixed with suitable milling beads or media and subjected to prolonged mechanical grinding until the desired particle size is achieved. High-pressure homogenization reduces particle dimensions by exposing the drug particles to intense shear, impact, and cavitation forces within a piston-gap homogenizer. Similarly, microfluidic homogenization utilizes high-velocity fluid flow through narrow micro channels to facilitate the reduction of drug particle size^[25]. Bottom-up techniques involve the formation of drug nanocrystals from molecules that are initially dissolved in a suitable medium. Common methods include antisolvent precipitation, supercritical fluid precipitation, hot-melt extrusion, spray drying, spray-freeze drying, and ultra sonication. To maintain the physical stability of the resulting nanocrystals during formulation and storage, stabilizing agents such as cellulose derivatives, polysaccharides, polymers, and surfactants can adsorb onto the crystal surface and prevent particle aggregation^[26]. Nanocrystals can enhance topical and transdermal drug delivery by increasing drug partitioning into the skin, forming an occlusive layer on the skin surface, and improving drug saturation within the stratum corneum. These effects promote greater drug accumulation in the deeper skin layers, thereby enhancing both localized therapeutic activity and systemic drug absorption.

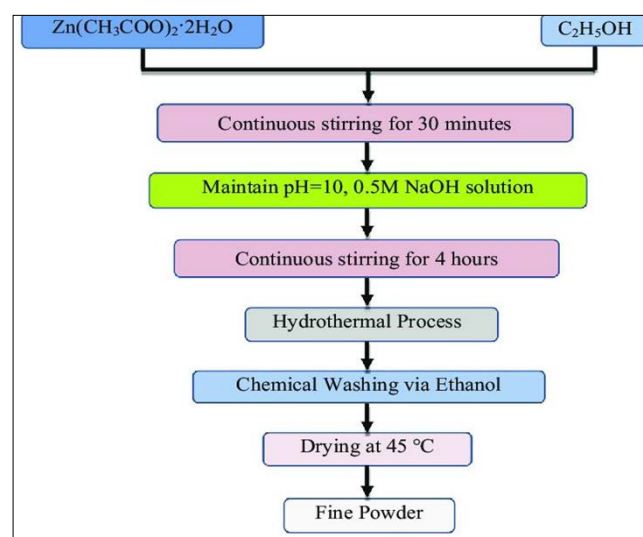


Fig 4: synthesis of nanoparticles

Stabilizers and excipients in nanocrystal design

Nanocrystal-based drug delivery systems offer considerable potential for improving the dissolution and bioavailability of poorly water-soluble drugs. Nevertheless, their formulation can be challenging because of physicochemical instability, including particle aggregation, crystal growth, and possible phase transitions. The incorporation of suitable excipients and stabilizing agents is therefore essential for controlling particle size, maintaining colloidal stability, promoting effective redispersion following drying, and optimizing *in vivo* performance. The following sections discuss the mechanisms of action, selection principles, safety aspects, and pharmacokinetic implications of major stabilizer categories, including surfactants, polymers, and cryoprotective agents (CPAs). To minimize redundancy with previously discussed material, the emphasis is placed on their functional roles and the key considerations relevant to formulation development and clinical translation.

1. Role of stabilizers in nanocrystal systems

Nanocrystals consist primarily of pure drug particles and therefore require suitable stabilizing agents during formulation and storage to minimize particle aggregation and crystal growth. These stabilizers are essential for maintaining colloidal stability while also improving the apparent solubility and dissolution behavior of poorly water-soluble drugs. Surfactants such as Tween 80, sodium lauryl sulfate (SLS), and poloxamer 188 can stabilize nanocrystals by providing electrostatic or steric repulsion between particles. Polymers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and poloxamer 407 offer steric protection and facilitate the re-dispersion of dried nanocrystals, supporting consistent drug delivery. During freeze-drying, cryoprotective agents including mannitol and trehalose help protect the nanoparticles against thermal and mechanical stresses, thereby maintaining their physical stability and drug integrity^[27].

Despite their benefits, individual stabilizers may have certain limitations that must be considered during formulation. Tween 80 can enhance drug wettability and particle dispersion, but its potential to cause hypersensitivity reactions may restrict its suitability for injectable products. Sodium lauryl sulfate (SLS) can improve drug dissolution; however, at elevated concentrations, it may cause mucosal irritation and affect cell membrane integrity. Poloxamers such as poloxamer 188 (P188) and poloxamer 407 (P407) are useful for maintaining the stability of nanocrystals intended for intravenous administration, although high levels may be associated with infusion-related reactions, making careful control of concentration and impurities necessary. HPMC and PVP are generally considered well tolerated, but their use in excessive quantities can increase formulation viscosity and consequently interfere with

injection or reconstitution. Therefore, selecting the appropriate stabilizer and optimizing its concentration are essential for achieving the desired stability, safety, and performance of nanocrystal-based pharmaceutical formulations.

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Drug delivery systems and route of administration

One of the more appealing features of nanocrystal technology is its versatility across delivery routes. This section works through the major administration pathways in turn.

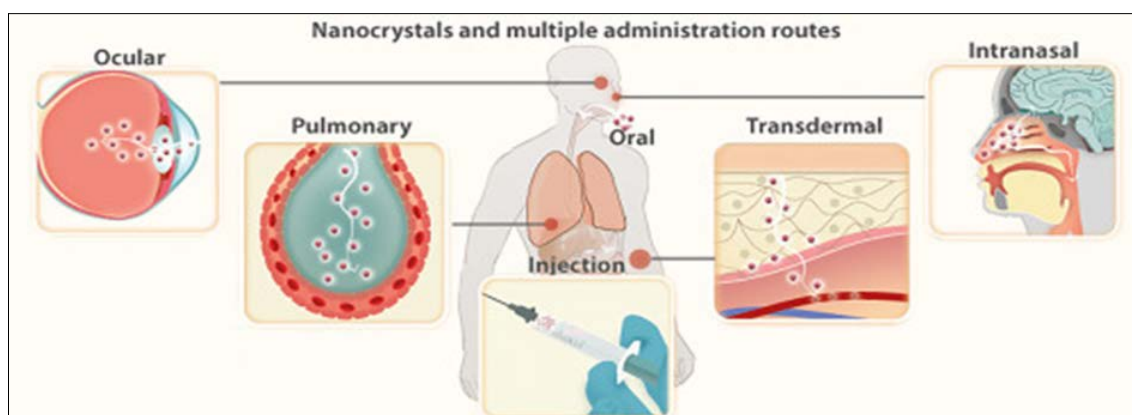


Fig 5: route of administration of nanoparticles

1. Oral delivery

Oral delivery represents the predominant application of nanocrystal technology, accounting for the majority of marketed formulations, current research efforts, and the overall commercial potential of these systems. Nanocrystals can improve oral drug absorption primarily by accelerating drug dissolution in the gastrointestinal tract, while also providing a moderate increase in apparent solubility. This enhanced dissolution increases the concentration of dissolved drug available for absorption through the intestinal epithelium during the relatively short gastrointestinal transit period. Such an effect is particularly beneficial for drugs such as aprepitant, which are absorbed

mainly within the upper gastrointestinal tract and therefore have a limited absorption window. In addition to improving bioavailability, studies have indicated that oral nanocrystal formulations may lessen variations in drug absorption between fed and fasting conditions. Reducing this food-related variability can simplify dosing requirements and promote more consistent drug exposure among patients^[29].

2. Parenteral (intravenous and intramuscular) delivery

Intravenous nanosuspensions provide an effective approach for delivering poorly water-soluble drugs that cannot be prepared as conventional solutions, thereby reducing the need for co-solvents or high levels of surfactants that may

cause adverse reactions or irritation at the injection site. Since intravenous delivery avoids hepatic first-pass metabolism and introduces the formulation directly into the bloodstream, strict control of particle size is essential. The particles are generally maintained well below the approximately 5–7 μm range to minimize the possibility of capillary blockage, while stringent sterility and endotoxin controls are also required. In contrast, intramuscular and subcutaneous nanosuspensions can be designed as long-acting depots by using relatively larger particles with slower dissolution rates. For example, paliperidone palmitate utilizes this approach to provide sustained drug release over several weeks, which can be particularly beneficial in chronic psychiatric conditions where maintaining adherence to daily oral medication may be difficult ^[30].

3. Pulmonary delivery

Inhalable nanosuspensions are generally administered through nebulization, which generates aerosol droplets containing numerous drug nanocrystals. The small particle size of the drug within these droplets can promote faster dissolution after deposition in the lung fluids, potentially enhancing both pulmonary and systemic drug absorption. Initial studies using budesonide nanosuspensions established the feasibility of developing pharmaceutically suitable and physically stable formulations for nebulized pulmonary delivery. Subsequent research on inhaled nanoparticle systems has further investigated the influence of factors such as particle size, aerodynamic characteristics, and formulation composition on pulmonary deposition, as well as their role in determining the relative extent of local versus systemic drug exposure ^[31].

4. ocular delivery

Untreated ocular infections may lead to severe complications and, in some cases, life-threatening outcomes. A substantial proportion of these infections is associated with bacterial pathogens such as *Staphylococcus aureus*. Developed an ion-paired moxifloxacin nanocrystal formulation designed to improve ocular drug delivery compared with conventional eye drops that require multiple administrations per day. The ion-pairing approach enhanced the drug's solubility and prolonged its residence within ocular tissues, thereby supporting improved antimicrobial activity. The formulation also demonstrated effective corneal penetration and sustained drug release. In animal studies, administration of a single dose of the nanocrystal formulation produced a reduction in bacterial burden while maintaining prolonged drug availability, suggesting its potential to reduce the need for frequent dosing in the management of bacterial ocular infections ^[32].

5. Dermal and transdermal delivery

Following topical application, nanocrystals can preferentially localize in the grooves of the skin and within hair follicles, with the latter serving as both an alternative route for drug penetration and a localized drug reservoir. Their gradual dissolution at the skin surface and follicular openings maintains a high local drug concentration, creating a concentration gradient that promotes passive diffusion into deeper skin layers over an extended period. This sustained delivery behavior has been demonstrated with caffeine nanocrystals, where variations in nanocrystal size were

found to affect the rate and extent of drug absorption through the skin *in vivo*.^[33] . This drug-delivery approach has received considerable attention in dermatology, with increasing research investigating topical nanocrystal formulations for various skin-related disorders, such as fungal infections, inflammatory diseases, and localized pain or inflammation. Although promising findings have been reported and several cosmetic products containing nanocrystals are commercially available, prescription-based dermal pharmaceutical products using this technology have not yet received regulatory approval. This limited clinical translation may be associated with ongoing difficulties in maintaining formulation stability, achieving reliable large-scale manufacturing, and establishing clear clinical benefits that can be specifically linked to the use of nanocrystals ^[34].

Characterization of Nanocrystals for Drug Delivery

1. Size Distribution and Particle Size

Nanocrystal size and polydispersity index are important factors influencing drug penetration through the skin. Particle size can be evaluated using techniques such as dynamic light scattering (DLS), laser diffraction (LD), and nanoparticle tracking analysis (NTA). Since each technique has certain limitations, multiple methods are often used together; DLS may be unreliable for highly polydisperse samples, whereas LD has reduced accuracy when measuring particles smaller than approximately 1 μm in diameter ^[35].

2. Surface Charge (Zeta Potential)

The surface charge of nanocrystals plays a significant role in determining the physical stability of their dispersion. Zeta potential is assessed by applying an electric field to a particle-containing dispersion and measuring the resulting particle movement. Higher positive or negative zeta potential values generally indicate stronger electrostatic repulsion and improved dispersion stability. Electrophoretic light scattering is commonly employed for zeta potential determination ^[36].

3. Morphology

The morphology of particles, including their shape and surface characteristics, can be examined using imaging methods such as atomic force microscopy (AFM), transmission electron microscopy (TEM), and scanning electron microscopy (SEM). Cryogenic TEM (cryo-TEM) is particularly useful for visualizing samples in their frozen-hydrated state ^[37].

4. Crystallinity

X-ray diffraction (XRD) is used to determine the crystalline structure of a material and assess its chemical integrity. Differential scanning calorimetry (DSC) provides valuable information about thermal behaviour, including melting transitions, recrystallization processes, and other solid-state properties ^[38].

5. Drug Release (*in vitro*)

The release profile of a nanocrystal formulation provides important information about initial burst release, prolonged drug release, and improvements in dissolution compared with the conventional drug formulation. *In vitro* drug release studies are commonly performed using dialysis membranes or Franz diffusion cells ^[39].

Combination and Emerging Hybrid Technologies

Top-down and bottom-up nanocrystal production techniques offer different advantages, which has led to the development of hybrid approaches that employ both methods consecutively. In a typical process, precipitation is initially used to generate a relatively small-particle suspension, although the resulting particles may still exhibit size variation and partial amorphous characteristics. This intermediate product is then subjected to a mechanical size-reduction process, such as high-pressure homogenization, to obtain a more uniform particle-size distribution, enhance crystallinity, and improve the physical stability of the formulation. Nanoedge® technology developed by Baxter Healthcare represents an example of this combined approach, in which controlled precipitation is followed by high-pressure homogenization to further optimize particle size and morphology. Similar strategies, often referred to as combination technologies, may use a preliminary precipitation step to modify or partially amorphize highly crystalline and difficult-to-process drug particles. This treatment can facilitate the subsequent milling or homogenization stage, reducing the energy and processing time required compared with directly processing the original crystalline material. Such sequential techniques are particularly useful for drug substances that are difficult to reduce to nanoscale dimensions or are sensitive to heat generated during mechanical processing^[40].

Clinical translation and marketed products

Drug nanocrystals have emerged as an important approach in pharmaceutical formulation and drug delivery, particularly for enhancing the therapeutic performance and bioavailability of poorly water-soluble drugs. Over the last two decades, several nanocrystal-based formulations have progressed successfully from preclinical research through clinical development and regulatory approval, with a number of products reaching the commercial market. This progress demonstrates the growing clinical potential of nanocrystal technology. This section focuses on the clinical translation of drug nanocrystals by discussing FDA-approved products available in the United States, highlighting promising formulations currently undergoing clinical evaluation, and outlining the major challenges that must be addressed to facilitate their successful commercialization.

1. Clinical pipeline and investigational formulations

Beyond the limited number of nanocrystal formulations that have already received FDA approval, numerous investigational products are currently advancing through clinical development. These emerging formulations show considerable therapeutic potential across several fields, including oncology, infectious diseases, neurological disorders, and cardiovascular conditions. At present, more than 20 nanocrystal-based therapeutic candidates are being evaluated in clinical trials at different stages worldwide, demonstrating the increasing clinical interest in this drug delivery strategy. These candidates cover diverse therapeutic applications and range from early-stage clinical investigations to advanced development programs approaching regulatory submission^[41].

A notable advancement in nanocrystal-based drug delivery is the development of injectable formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) for

managing acute and postoperative pain. These formulations, which are currently being investigated in Phase II clinical trials, have demonstrated a more rapid therapeutic effect and reduced gastrointestinal irritation compared with conventional oral dosage forms. Their enhanced dissolution characteristics and improved bioavailability highlight the potential of nanocrystal technology for applications in emergency medicine and perioperative pain management.

Nanocrystal suspensions are also being investigated for the delivery of poorly water-soluble antifungal drugs used against systemic fungal infections. Compared with lipid-based and cyclodextrin-containing formulations, which may be associated with toxicity and formulation-related limitations, nanosized preparations can offer improved pharmacokinetic behavior and enhanced distribution into tissues. Preclinical investigations and early human studies have reported these advantages, along with a potential reduction in hepatotoxicity, supporting further clinical development of nanocrystal-based antifungal therapies.^[42]

2. FDA-approved nanocrystal drugs

FDA-approved pharmaceutical products incorporating nanonization technology provide evidence of the clinical utility and reliability of drug nanocrystals for improving pharmacokinetic performance. An important early example is Rapamune (sirolimus), originally developed by Wyeth, which was subsequently acquired by Pfizer, for the prevention of organ rejection in kidney transplant recipients. Sirolimus is classified as a Biopharmaceutics Classification System (BCS) Class II drug and has limited aqueous solubility. Formulating sirolimus as a nanocrystal increased its dissolution and oral bioavailability, representing an important milestone that contributed to the subsequent development of other nanocrystal-based drug products^[43]. Following the approval of Rapamune, the FDA authorized two additional nanocrystal-based formulations, namely Emend (aprepitant) and Tricor (fenofibrate). Aprepitant, marketed as Emend® for the prevention of chemotherapy-induced nausea and vomiting, presented formulation challenges because of its low aqueous solubility and variable absorption. Converting aprepitant into a nanocrystal dispersion reduced the particle size and increased the available surface area, thereby enhancing the dissolution rate and promoting more consistent plasma drug concentrations^[44].

3. Regulatory pathways and safety assessment

The clinical and commercial development of nanocrystal formulations can be complicated by rigorous regulatory requirements. Since dedicated regulatory guidelines specifically addressing drug nanocrystals are not yet widely established, regulatory authorities typically assess these formulations under frameworks applicable to modified-release products or nanosuspensions. Consequently, comprehensive characterization of critical quality attributes, including particle size and size distribution, polydispersity index (PDI), zeta potential, drug content uniformity, and excipient safety, is essential for regulatory submissions. In addition, thorough evaluation of microbiological sterility, chemical and physical stability, and compatibility under intended storage conditions is necessary to establish product quality and support regulatory approval^[45]. Long-term stability, particularly during accelerated storage studies, remains an important consideration in the regulatory

evaluation of drug nanocrystals. Without adequate stabilization, nanocrystals may undergo aggregation or crystal growth through ripening, which can alter their dissolution behavior and potentially influence therapeutic performance. Surfactants are commonly incorporated to minimize particle aggregation; however, their presence may introduce additional safety considerations. Certain surfactants, including sodium dodecyl sulfate and poloxamer 188, may cause immune-mediated or hypersensitivity reactions in susceptible individuals. Therefore, formulations containing such excipients require comprehensive preclinical and clinical toxicological assessments to characterize their safety and establish an appropriate therapeutic margin [46].

4. Biopharmaceutical considerations

Nanocrystal technology provides important biopharmaceutical benefits, especially for poorly water-soluble drug candidates belonging to BCS Class II and Class IV. In these drug classes, limited aqueous solubility can be a major factor restricting effective oral absorption. Reducing the drug particles to the nanoscale markedly increases their specific surface area, thereby facilitating greater interaction with gastrointestinal fluids. According to the Noyes–Whitney principle, this increased surface area promotes faster drug dissolution, which can subsequently improve the dissolution performance and oral absorption of the drug [47]. The enhanced dissolution and absorption associated with nanocrystal formulations can result in faster drug uptake, reduced pharmacokinetic variability, and improved systemic bioavailability. A thorough biopharmaceutical evaluation is an essential component of nanocrystal development and should extend beyond the assessment of solubility and permeability. It should also consider the interactions of the formulation with biological systems, including plasma protein binding, tissue distribution, and metabolic processes. Since these factors can significantly influence both therapeutic efficacy and potential toxicity, their systematic evaluation during the early stages of development is important for selecting promising candidates for further clinical investigation [48].

Advantages and Properties of Drug Nanocrystals

- Nanocrystals exhibit inherent mucoadhesive properties that enable them to interact with biological mucosal surfaces, including the gastrointestinal tract. Following administration, nanocrystals either remain dispersed in the suspension or are released from the solid dosage form and adhere to the gastrointestinal mucus layer through hydrogen bonding and van der Waals interactions. Their prolonged residence at the mucosal surface maintains a higher concentration gradient across the gastrointestinal tract, thereby enhancing drug absorption and ultimately improving its bioavailability [49].
- Nanocrystals can be produced through two main methods: the top-down approach, which involves reducing larger particles to the nanoscale, and the bottom-up approach, in which crystals are formed by precipitating molecules from a dissolved state.
- Suitable for various routes of administration and different dosage forms.
- Enhances the rate at which the drug is absorbed.

- Improves drug dissolution, solubility, and overall bioavailability.
- Allows a greater amount of drug to be incorporated into the formulation.
- Enables formulation development that is rapid, straightforward, and cost-effective.
- Helps reduce the required drug dose and minimizes variations caused by fed or fasting conditions.
- Provides consistent and dependable drug performance [50].



Fig 6: advantages of drug nanocrystals

Conclusion

Nanocrystal technology occupies an unusual position in pharmaceutical science: it is, at its core, a fairly simple idea make the drug particle small enough, and it dissolves fast enough to matter clinically resting on physical chemistry that pharmacy students learn in their first years of study. And yet turning that simple idea into a reliable, scalable, regulator-approved product has taken more than three decades of iterative engineering, from the earliest phospholipid-coated microcrystal patents through the first marketed products in the early 2000s, and on to the sophisticated targeted and multi-route platforms now under active investigation.

What has made the technology durable, rather than a passing formulation fashion, is its genuine versatility. Few other single formulation strategies can plausibly be applied to oral tablets, sterile injectable suspensions, long-acting intramuscular depots, inhaled aerosols, ophthalmic drops, and topical creams, all using essentially the same underlying particle-engineering principle. That versatility has been earned, not assumed each route has required its own body of formulation science, its own characterization standards, and in most cases, its own hard-won manufacturing know-how.

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