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Advancements in Pharmaceutical Nanocrystals: A Comprehensive Review

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Abstract Poorly soluble small compounds pose challenges in drug formulation due to low solubility, bioavailability, and therapeutic efficacy. These compounds often struggle to effectively target the disease due to their limited solubility. A large particle size further complicates reaching the desired site of action in the body. Reducing particle size through micronization or nanonization can enhance the efficacy of these active substances. Various methods, such as precipitation, milling, and high-pressure homogenization, are used to create nanocrystals, which can be delivered via multiple routes, with oral administration being preferred for safety and patient compliance. Nanonization is a key process in improving bioavailability, transforming micronized particles into nanoparticles under 1000 nm.

Keywords Nanocrystal; Bottom-up; Top-down; Poor solubility; Bioavailability

1. Introduction

Approximately 40% of drugs in development face solubility issues, and 60% of new pharmaceuticals exhibit poor water solubility (1). This low solubility hampers the development of highly potent pharmacological formulations, especially for biopharmaceutical class 2 (BCS) drugs, which suffer from poor oral bioavailability and unpredictable absorption (1). To address this challenge, Butler and Dressman introduced the Developability Classification System (DCS), which differentiates between dissolution rate-limited (Class IIa) and solubility-limited (Class IIb) compounds (2). For Class IIb and IV drugs, the intrinsic solubility is too low for adequate absorption, making complexation or solid-state modifications preferable to nanocrystals (3).

Nanocrystals, which are pure drug nanoparticles without a matrix and stabilized by a surface agent, typically range in size from 200 to 500 nm. They have been shown to enhance solubility and bioavailability (4). Since their introduction in the early 1990s, nanocrystals have been explored for various drug delivery methods, including tablet, ophthalmic, cutaneous, and buccal applications (5). Despite their promise, the production of nanocrystals can lead to challenges such as aggregation and crystallinity variations over time, affecting their stability (5).

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Although nanocrystals improve solubility, their small size presents analytical difficulties, particularly with low concentrations and high chemical stability (6).

To overcome drug insolubility, two primary strategies are commonly employed: modifying the morphology of the raw drug (increasing surface area or porosity) and altering the physicochemical properties of active pharmaceutical ingredients (APIs) through polymorphic forms, cocrystals, or solid dispersions (7). For DCS IIa drugs, reducing particle size is the most effective strategy, as the second approach requires extensive screening efforts (7).

Nanocrystals are advantageous for targeted drug delivery because they can carry up to 100% of the drug without the need for a carrier molecule, typically achieving 50-90% drug content with low dosages (8). The encapsulating excipients help reduce toxic effects and improve stability (5). Nanocrystals, produced through top-down and bottom-up methods, avoid the physical instability problems common with other nanocarriers and can be scaled up for commercial production (5). Several commercial products demonstrate the effectiveness of nanocrystals in improving drug delivery (6).

2. Preparation of Nanocrystals

Most drugs are developed using their stable crystalline form, but this can lead to issues like poor solubility and bioavailability. Amorphous forms of drugs can be created without altering their chemical composition, but they often lack stability for production and storage (9). Nanocrystals, which fall between the crystalline and amorphous phases, offer improved dissolution due to their increased surface area and energy. However, traditional crystallization methods are unsuitable for their preparation, and their smaller size makes stabilization, filtering, and characterization more complex (5).

There are two main techniques for preparing nanocrystals: (5)

1. Top-down
2. Bottom-up

Top-Down Technology:

Top-down technology primarily involves wet bead milling and high-pressure homogenization, both of which are suitable for industrial use. In this method, drug particles are reduced by shear forces and collisions, leading to the fragmentation of crystals and formation of secondary nucleation sites (6). The rate of formation is not dependent on supersaturation. This technology is commonly used for preparing anticancer drugs since it doesn't require organic solvents and can be easily scaled for production. Overall, top-down technology is ideal for insoluble drugs and is widely applied in commercial nanocrystal production (10).

Wet Bead Milling:

Wet bead milling reduces drug particles into nanoparticles using high-intensity mechanical force, stabilizers, and water. The particle size depends on the milling bead size (typically 0.1–20 nm), drug properties, and process settings (8). It's particularly useful for thermally unstable drugs (7) and provides uniform products. However, stabilizers and several cycles are needed, and contamination from grinding beads and poor physical stability due to agglomeration can occur (11). Funahashi et al. found that melting ice beads during milling avoids contamination. Successful industrial applications include pentoxifylline (Verelan ®PM), fenofibrate (Tricor®), and Naprelan® (7).

Media Milling:

Media milling uses a recirculating chamber, coolant, and milling medium to grind particles to the nanoscale (12). Common milling media include glass pearls, zircon oxide, and polystyrene derivatives. The slurry is agitated to create high energy forces that reduce particle size. Continuous milling produces smaller, more uniform particles. However, temperature rise can affect particle stability, so coolants are used to manage this. Developed by Liversidge, this method is widely used in commercial products by Elan Pharma.

High-Pressure Homogenization (HPH):

HPH involves shearing, colliding, and cavitating drug particles in a homogenization chamber. There are variations like microfluidization, IDD-PTM, Dissocubes ®, and Nanopure®, each suited for different media (14). Although effective, it requires costly equipment and can adversely affect particle stability and crystal structure (13). Drugs like paliperidone (Invega Sustenna), fenofibrate (Triglide®), and Luteolin use HPH (14).

Laser Ablation:

Laser ablation uses laser light to create nanoparticles by focusing on a solid target. The process involves stirring suspensions of microparticles into nanoparticles. The laser's power, scanning speed, and suspension properties affect particle size. This method, despite its advantages, can alter crystal structure with

excessive power. Drugs like paclitaxel and curcumin have been processed this way (15).

Ultrasound:

Ultrasound breaks drug particles into smaller sizes using acoustic waves. It enhances nucleation by creating cavitation in the solution, promoting rapid dispersion (16). Ultrasound is easy to operate and often combined with other methods to improve reproducibility. The intensity of treatment and other factors determine the final nanocrystal size (17).

Bottom-Up Technique:

Bottom-up technology focuses on precipitation and evaporation to form nanocrystals from supersaturated drug solutions. While it offers more control over particle size than top-down methods, scalability is challenging due to poor reproducibility and potential use of organic solvents (18).

Spray Techniques:

Spray drying is cost-effective for industrial use, forming drug nanosuspensions. The drug is embedded in a water-soluble matrix like polymers or sugars, preventing aggregation and stabilizing the nanocrystals. It is used to make powders for tablets, capsules, or injectables (19).

Liquid Antisolvent Precipitation:

In this process, a drug solution is combined with an aqueous antisolvent, causing nanocrystals to form. While simple and affordable, it may lead to aggregation, and using organic solvents can leave residues. Drugs like hydrochlorothiazide have been processed this way (20).

Precipitation Assisted by Acid-Base Method:

This eco-friendly method uses weak acid and base solutions to create nanocrystals without organic solvents. It's suitable for drugs whose solubility depends on pH (21).

High Gravity Controlled Precipitation (HGCP):

HGCP improves the size and homogeneity of nanocrystals by enhancing the gravity-controlled precipitation process (22). However, its scalability is limited due to potential oversaturation during mixing. Drugs like salbutamol sulfate have been produced in labs using this method.

Supercritical Fluid Method:

Supercritical fluids like CO2 dissolve drugs, which then precipitate into nanocrystals. Techniques like RESS and SAS are used to control particle size. This method is limited to drugs soluble in supercritical fluids and is more expensive. Apigenin was processed with SAS (23).

Emulsion Polymerization Method:

This method creates an O/W emulsion, dispersing the drug in organic solvents. After emulsification, the solvent is evaporated, leaving drug nanocrystals in the matrix. It is suitable for laboratory-scale operations but challenging for large-scale production (24).

Combinative Technology:

By combining top-down and bottom-up methods, combinative technologies avoid the drawbacks of each technique alone. For example, the NANOEDGE® method reduces micron-sized particles before high-pressure homogenization, improving particle size reduction (25). Other methods like SmartCrystals ® and CT combine various techniques to enhance nanocrystal production.

Nanoedge Technology:

Nanoedge technology integrates precipitation and high-pressure homogenization to reduce particle size and avoid issues like uneven distribution and aggregation. This approach improves physical stability and is often combined with methods like ultrasound or microfluidization (26).

H42 and H96 Technology:

H42 and H96 combine spray drying, freeze drying, and high-pressure homogenization (HPH) to create drug nanocrystals. The insoluble drug and stabilizer are first uniformly distributed in a stabilizer skeleton, then redispersed in water using HPH. This method reduces particle agglomeration and improves processing efficiency, making it suitable for large-scale production. Poloxamer 188 was used as a stabilizer in preparing hydrocortisone acetate powder by H42, resulting in stable, homogeneous nanosuspensions. Yu applied the H96 method to create nano-amorphous drugs like naproxen and meloxicam (27).

H69 Technology:

H69 combines high-pressure homogenization with a microprecipitation step using organic solvents to reduce particle size. The drug is dissolved in a suitable solvent and mixed with an aqueous nonsolvent. As the nonsolvent is added, drug precipitation occurs,

and particles are immediately subjected to cavitation, collision, and shear forces in the homogenizer's high-energy zone (28).

CT Technology:

CT integrates top-down and bottom-up methods. Commonly used wet bead milling techniques include rotor-stators and mills. For example, a combination of rotor-stator HPH and high-speed shear technology is used to create stable suspensions, followed by high-pressure homogenization. Wadhawan et al. used HPH with hydroxypropyl cellulose-LF to produce acyclovir nanocrystals with improved solubility and smaller particle sizes (29). Martina et al. tested different methods, finding that the combination of bead milling (BM) and HPH produced nanocrystals with the smallest particle size and faster dissolution rates.

3. Scale-up Techniques and Issues

Scaling up in pharmaceutical manufacturing refers to moving from small-scale lab production to large-scale industrial production. It is not simply a ratio of small to large-scale production rates but requires careful design, as no single technique can predict product performance across scales (30). Achieving successful scale-up relies on ensuring similarity between the lab, pilot, and production stages (31).

Scaling up nanocrystal technologies presents several challenges. As production volumes increase from 1-100 ml at the lab scale to tonnes at the industrial scale, maintaining consistency becomes difficult. It's hard to replicate the efficiency and characteristics of lab-scale equipment on a large scale. This is why the HPH process, commonly used for parenteral emulsions like Lipofundin, is preferred for producing commercial nanocrystals, as both lab and commercial homogenizers have similar geometries (32).

Literature shows that commercial equipment requires fewer homogenization cycles and lower pressures compared to lab-scale equipment. This is likely due to better control of production parameters such as temperature and fewer fluctuations in conditions. Commercial equipment also uses automated systems, ensuring uniformity in batches. Some commercial homogenizers use multiple valves with varying pressures to support the process, and various improved homogenizers are now in development to enhance nanocrystal production (33).

4. Marketed formulation

Rapamycin, used for antifungal purposes, is stabilized with D-a-tocopherylpolyethylene glycol succinate in tablet form, and ball milling technology is used in its manufacturing.

Fusidic acid, an antibacterial, is stabilized with PVA 4-88 in cream form, with modified nanoprecipitation technology employed during production.

Luliconazole, for fungal infections, is stabilized with Vitamin E TPGS and HPMC in hydrogel form, manufactured using modified nanoprecipitation technology.

Apremilast, used for psoriasis, is stabilized with Poloxamer 407 in hydrogel form, and wet media milling technology is utilized in its production.

Naproxen, an anti-inflammatory, is stabilized with Vitamin E tocopherol, polyethylene glycol succinate, Pluronic F127, sodium lauryl sulfate, and di(2-ethylhexyl) sulfosuccinate in tablet form, and milling technology is used in its manufacture.

Table 1. Marketed formulation

Generic	Indication	Trade Name	Manufacturer
Rapamycin	Immunosuppressive	Rapamune	Wyeth
Megestrol	Anti-anorexic	Magace ES	Par Pharmaceutical Companies
Fenofibrate	Hypercholesterolemia	Triglide	Sciele Pharma Inc.
Nabilone	Anti-emetic	Cesamet	Lilly
Diltiazem	Anti-angina	Herbesser	Mitsubishi Tanabe Pharma
Silver	Anti-microbial	SILCRYST	Nucryst Pharmaceuticals
Fenofibrate	Hypercholesterolemia	Triglide	Sciele Pharma Inc.
Griseofulvin	Anti-fungal	Gris-peg	Novartis
Theophylline	Bronchial dilation	Theodur	Mitsubishi Tanabe Pharma

Table 2. The nanocrystal-based formulation developed for topical delivery (34)

Sr.no	Drug	Stabilizer Used	Dosage Form	Manufacturing Technology	Application
1	Rapamycin	D-a-tocopherylpolyethyleneglycol succinate	Tablet	Ball milling	Antifungal
2	Fusidic acid	PVA 4-88	Cream	Modified nanoprecipitation	Antibacterial
3	Luliconazole	Vit.E TPGS and HPMC	Hydrogel	Modified nanoprecipitation	Fungal infection
4	Apremilast	Poloxamer 407	Nanosuspension, nanogel, cream	Wet media milling	Psoriasis
5	Naproxen	Vitamin E tocopherol Polyethyleneglycol succinate, Pluronic F127, sodium lauryl sulfate, di(2-ethylhexyl)sulfosuccinate	Tablet	Milling	Anti-inflammatory
6	Curcumin	Polyvinylalcohol, polyvinylpyrrolidone, vitamin E tocopherol polyethylene glycol succinate, sodium lauryl sulfate, Carboxymethyl cellulose sodium	Gel	High pressure homogenization	Anti-inflammatory
7	Beclomethasone propionate	Hydrophobin	Nanosuspension	Antisolvent precipitation	Antifungal
8	Paclitaxel	Hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyethylene glycol 400, Pluronics F127 and F68, sodium lauryl sulfate, Tween 20 and 80, transferrin, immunoglobulin G, human serum albumin	Injection	Antisolvent precipitation, sonication	Anticancer
9	Azelaic acid	Polysorbate 60	Hydrogel	Wet media milling	Acne rosacea

5. Application of Nanocrystals in Drug Delivery Systems

5.1 Oral Delivery:

Oral administration remains the preferred method, particularly for drugs with poor solubility. Nanocrystal technology enhances solubility in digestive fluids, leading to improved bioavailability and controlled release. This method reduces the need for prodrugs or salt forms and increases drug loading, leading to better therapeutic outcomes (35). Elan Drug Technologies has successfully launched drugs using this technology (36,37).

5.2 Ocular Drug Administration:

Nanocrystals show promise in ocular drug delivery, improving corneal permeability and bioavailability, though no commercial products are yet available. The potential advantages include enhanced drug release, better tolerability, and improved treatment of eye conditions (37,38).

5.3 Dermal Drug Delivery:

Nanocrystals enhance transdermal drug delivery by improving membrane penetration and local administration. They boost solubility and bioadhesion, facilitating absorption while reducing side effects (39,40,41). Studies like those by Pireddu et al. (42) and Sung et al. (43) show improved anti-inflammatory effects and skin penetration compared to traditional formulations. Curcumin and resveratrol nanosuspensions also show enhanced skin absorption (44,45).

5.4 Parenteral Drug Delivery:

For poorly soluble drugs, nanocrystal technology improves parenteral delivery by optimizing drug loading, enhancing dissolution rates, and preventing macrophage uptake. It also replaces organic solvents with aqueous ones and improves sterilization and safety (46,47).

5.5 Pulmonary Drug Delivery:

Nanocrystals are advantageous for pulmonary drug delivery systems due to the lung's large surface area and high vascularization. Optimizing particle size (10–100 nm) is crucial for efficient deposition and preventing macrophage clearance (48,49). Studies like Rui et al. (50) and others on baicalein nanocrystals show promising results for sustained pulmonary delivery with good pharmacokinetic profiles (51–54).

5.6 Targeted Drug Delivery:

Nanocrystals enable precise drug targeting by manipulating particle size and surface properties. For instance, aphidicolin nanosuspensions have been effective against leishmania-infected macrophages, and nanoparticles have shown success in targeting brain tissues or tumors. These formulations are also being explored for localized skin treatments and targeted therapies (55,56).

6. Characterization Techniques

6.1 Solid-State Properties:

Nanocrystals may adopt different solid-state forms depending on production conditions. Aqueous environments often favor more stable hydrate forms, which are less soluble. Stability studies should account for potential triggers for hydrate formation. Common techniques for solid-state characterization include X-ray Powder Diffraction (XRD), differential scanning calorimetry (DSC), and vibrational spectroscopy (infrared and Raman) (58).

6.2 Particle Size:

Particle size influences the effectiveness, dissolution rate, and stability of nanocrystals. Techniques like dynamic light scattering (DLS) and photon correlation spectroscopy (PCS) measure particles between 3 nm and 3 μm. These methods help determine size distribution, mean size, and stability, with a polydispersity index (PI) indicating the uniformity of particle size. Laser diffractometry (LD) can also measure particles ranging from 10 nm to 8 μm (59).

6.3 Zeta Potential:

Zeta potential measures the surface charge of particles, which impacts the stability of nanosuspensions. A high zeta potential (±30 mV) indicates stable suspensions due to electrostatic repulsion, while low values suggest aggregation. Stability is influenced by factors like surfactants, solution chemistry, and particle surface charge (60).

6.4 Particle Shape and Morphology:

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to observe nanocrystal size and shape. SEM examines surface morphology, while TEM provides high-resolution images of internal structure. X-ray diffraction (XRD) analyzes particle size using reflection broadening (59).

6.5 FT-IR Studies:

Fourier Transform Infrared (FT-IR) spectroscopy evaluates the chemical properties of nanocrystals and their interactions with excipients. For example, curcumin nanocrystals' FT-IR studies confirmed that milling and spray drying did not alter its chemical structure (63,64).

6.6 Particle Surface Charge:

Surface charge affects the physical stability of nanosuspensions. Zeta potential is used to measure this charge, indicating the likelihood of aggregation. The Helmholtz-Smoluchowski equation helps calculate zeta potential, with values above ±30 mV suggesting stability. A higher zeta potential indicates strong electrostatic repulsion and stable suspension (65,66).

6.7 Thermal Analysis:

Differential scanning calorimetry (DSC) is commonly used to study the thermal behavior of nanocrystals. Other techniques like thermogravimetric analysis (TGA) and Differential Thermal Analysis (DTA) provide complementary thermal insights.

6.8 Raman Spectroscopy:

Raman spectroscopy is used to study phase transitions, crystal structure, and defects in nanocrystals. It helps analyze structural properties and compatibility with excipients, and is widely used in pharmaceutical research for formulation characterization.

6.9 Rheological Properties:

Rheological properties, such as shear thinning

behavior, are observed in suspensions of nanocrystals. At certain concentrations and shear rates, nanocrystals align into nematic structures, which can influence flow behavior and material characteristics. Larger aspect ratio nanocrystals maintain alignment for longer periods after shear (67,68).

7. Physical Properties of Nanocrystals

Around 70% of new drug candidates are hydrophobic, and traditional micronization doesn't work effectively for these compounds (69). Therefore, reducing particle size to the nanoscale is essential to enhance bioavailability, with nanocrystals offering a promising solution (70). Depending on their production method, nanocrystals can either replace or complement existing solid-state preparation techniques discussed earlier.

Impact of Particle Size on Solubility:

The dissolution pressure of nanocrystals can be calculated using the Kelvin equation [Eq. (1)], which shows that as particle size decreases, the curvature increases, leading to higher dissolving pressure (Pr). This effect becomes significant when particle size reaches the nanoscale.

$$\ln(Pr/P\infty)=(4\gamma M/d_{np}RT\rho) \quad \text{.....(1)}$$

Where γ is surface tension, Pr and P∞ represent the pressures of a nanocrystal and an indestructible nanocrystal, respectively, R is the gas constant, T is temperature, ρ is particle density, M is molecular mass, and d_np is the particle diameter.

The Ostwald-Friendlich equation [Eq. (2)] highlights the relationship between particle radius and saturation solubility. As the particle radius decreases, saturation solubility increases.

$$\log(Cs/C\alpha)=4\sigma V/(2{,}303\times RT\rho d_{np}) \quad \text{.....(2)}$$

Where Cs is the saturation solubility, σ is interfacial tension, V is the nanocrystal's molar volume, R is the gas constant, T is temperature, ρ is particle density, and d_np is particle diameter. A higher saturation solubility leads to a stronger concentration gradient, which facilitates drug diffusion through membranes and into circulation.

Effect of Particle Size on Dissolution Rate:

The dissolution rate can be calculated using the Noyes-Whitney equation [Eq. (3)]:

$$dm/dt=s(D/d)(Cs-Cp) \quad \text{.....(3)}$$

Here, dm/dt represents the dissolution rate, S is surface area, D is the diffusion coefficient, d is the hydrodynamic boundary layer thickness, Cs is the saturation solubility, and Cp is the concentration surrounding the particle. As particle size decreases, the diffusional distance (d) reduces, improving dissolution.

The Prandtl equation [Eq. (4)] further explains how nanoparticle size influences the diffusion distance within the hydrodynamic boundary layer (71).

Bisrat and Nyström utilized the Prandtl boundary layer equation to examine how the hydrodynamic boundary layer thickness (h) affects particle dissolution rate. Their study found that reducing the

Table 3. Characterization Parameters and Methods for Nanosuspension Analysis

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

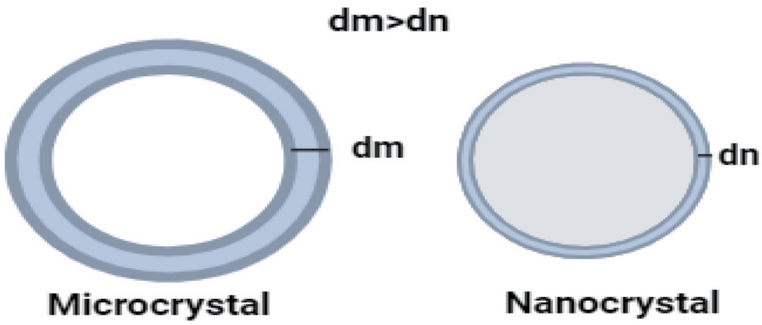

Fig 1: Comparison of the diffusional distance d for micro- (dm) and nanocrystals(dn).

size of solid dispersions in solution decreased the particle surface area in the flow direction, along with a reduction in the liquid flow velocity near nanoparticles (71,72).

$$h=c(L/V)^{1/2} \qquad (4)$$

Where L is the particle surface dimension in the flow direction, V is the liquid velocity near the particle, and h is the thickness of the boundary layer.

Liversidge and Cundy showed that nanocrystallization improves the saturation and bioavailability of danazol (73). They administered three formulations—danazol microcrystal suspension (10 μm), danazol-hydroxypropyl-b-cyclodextrin (HPB) complex, and danazol nanocrystals (169 nm) from wet milling—to fasted beagle dogs. The bioavailability was 82.3 ± 10.1% for nanocrystals, 106 ± 12.3% for the nanocrystal-HPB complex, and only 5.1 ± 1.9% for microcrystals, demonstrating better absorption for nanocrystals (73).

Hecq and colleagues used dialysis bag techniques to compare the dissolution rate of UCB-35440-3 nanocrystals (600 nm) and microcrystals. Nanocrystals showed a marked improvement in solubilization, with over 95% of the drug becoming soluble after one hour, compared to only 30% for microcrystals, which did not fully dissolve for 12 hours (74). Similar results were obtained for fenofibrate nanocrystals (75).

Nanocrystalline materials must be characterized at both atomic and nanometer scales to understand the interaction between structure and properties. Key microstructural aspects include grain size, distribution, and morphology; grain boundaries and interphase interfaces; intragrain defects; composition across grains and interfaces; and trapped species after processing. For layered nanostructures, the thickness and coherence of interfaces, along with defect forms, are also important.

Various experimental methods are used to analyze nanocrystalline materials. Direct methods include transmission electron microscopy (TEM), scanning tunneling microscopy (STM), field-ion microscopy (FIM), and X-ray and neutron diffraction. Indirect techniques such as nuclear spectroscopy, X-ray absorption fine structure, positron lifetime spectroscopy, and magnetic resonance have also been applied. Advanced tools like differential scanning calorimetry and mass spectroscopy aid in understanding these materials.

Traditional techniques like TEM, X-ray, and neutron diffraction are essential for characterizing nanocrystalline materials at the nanoscale. However, improved instrumentation is needed for better chemical mapping on fine scales, with atom-probe FIM and STM providing the best resolution currently (74).

High-resolution TEM studies of nanocrystalline metals show they consist of small crystallites with different crystallographic orientations separated by grain boundaries. These studies reveal that grain boundaries are mostly flat but exhibit local faceting. Despite observations of porosity in nanocrystalline metals, no dislocations have been found, though facets and crystal pairings are visible (72).

These findings suggest a two-component microstructure: long-range atomic organization in grains and a random component at the grain boundaries. The structure of nanocrystalline metals is similar to coarser polycrystals, as seen in studies of palladium (73).

When analyzing high-resolution TEM data, the influence of impurities must be considered, as electron microscopic analysis is conducted under non-UHV conditions. Additionally, the stability and morphology of nanostructures may be impacted by the high-energy electron beam. As TEM requires thin samples, the 3-D crystal structure is reduced to a 2-D layout, which may alter the forces between crystals and the boundary structure (74).

Despite the energy stored in grain boundaries, high-resolution TEM studies suggest that atoms at these boundaries tend to rearrange into low-energy configurations. To further understand the

boundary structure, FIM and STM data are essential. Nanocrystalline metals also absorb significant contaminants during production, and this must be considered when assessing their properties.

8. Current Status and Recent Advances

Nanomedicine faces significant challenges before it can progress to clinical trials. Key obstacles include designing nanopharmaceuticals that are suitable for large-scale production under Good Manufacturing Practice (GMP) standards, as well as ensuring the development of high-quality control assays. These factors often limit the transition from laboratory research to commercialization. Success depends on several stages, ranging from preformulation (lab scale) to full-scale commercialization, with crucial factors such as stability, effectiveness, and market acceptance. Additionally, formulation methods must be within predefined parameters and be easily repeatable for consistent quality and scalability.

Translating nanomedicine from lab to industrial scale is difficult. Formulations must be scalable and reliable at all stages—lab, pilot, and industrial levels. Developments in scale-up technology and Quality by Design (QbD) have accelerated nanomedicine commercialization (75).

Recent advances in formulation research have led to the development of various nanoformulations, including liposomes, solid lipid nanoparticles, and micelles, which are now undergoing preclinical and clinical trials. However, the development of these nanomedicines continues. Fifteen drugs, utilizing nanocrystals for different administration methods, are in commercial investigation. The primary methods for producing nanocrystals are top-down and bottom-up approaches. A study using Nano Spray Dryer B-90 technology revealed variations in particle sizes for steroid medications like fluorometholone and dexamethasone, which ranged from 620 to 856 nm, depending on mesh size.

Nanoparticles can be crystalline or amorphous, depending on the production process and materials used. The production process must achieve consistent polydispersity index and size. Methods such as emulsions, salting-out, and nanoprecipitation were found to affect particle size distributions. For example, salting-out resulted in particle sizes between 715 nm and 147-245 nm.

In scaling up the production of nanocapsules, Colombo et al. applied emulsification-diffusion at a pilot scale, scaling the experimental batch from 60 mL to 2 L. Their findings showed that increasing impeller duration and speed reduced emulsion size slightly (76).

Low-energy techniques for nanoparticle creation from micro/nanoemulsions face scaling issues and require significant surfactant quantities. High-energy methods like ultrasonication and microfiltration, which manage nanoparticle properties and reproducibility, are being explored. Microfiltration, particularly, offers advantages such as low energy, shorter production time, and cost reduction, making it viable for large-scale applications. Gdowski et al. demonstrated the potential of microfiltration for maintaining batch-to-batch homogeneity in nanolipomer formulations.

Additionally, advanced methods like BONAPARTE, which uses arc and spark discharges for scaling up nanoparticles, show promise. This technology is efficient and cost-effective, enabling high-volume production (77).

Supercritical solvent methods are also under investigation for scaling nanocarrier production. Jung et al. used a supercritical anti-solvent technique to produce nanoparticles at three scales (0.5 L, 4 L, and 50 L), with consistent particle size distribution and yield. In another study, Pham et al. scaled up liposome and niosome production from laboratory to pilot scale, ensuring reproducible particle size and entrapment efficiency.

Recent technologies like PRINT and hydrogel templates have been developed for creating nanocarriers, especially for ocular delivery. PRINT technology allows for precise control over particle size, shape, and modulus, which is vital for therapeutic applications. Hydrogel templates have also been used to create ultra-thin lenses with controlled drug loading (78).

Technological advancements in microfluidics, high-pressure homogenizing, and PRINT, along with improved regulatory standards, offer hope for the commercialization of ophthalmic nanomedicines.

9. Products Based on Drug Nanocrystals in Market/Clinical Phases

To date, 50 nanopharmaceuticals, including liposomes, nanocrystals, and polymer-based formulations, have received FDA approval for clinical use. These are also being investigated in clinical trials for various therapeutic purposes. Nanocrystallization effectively enhances the dissolution rate and solubility of poorly soluble drugs, contributing to its rapid clinical acceptance and commercialization (79).

While liposome commercialization took about 25 years, Emend® was developed in roughly 10 years. Its patent was filed in 1990, and it received approval in 2000. This faster development highlights the success of nanocrystal-based products compared to other nanoformulations.

Rapamune®, an immunosuppressant, was the first nanocrystal-based drug, introduced in 2000 by Wyeth Pharmaceuticals. It used the pearl mill process and showed 21% higher oral bioavailability compared to its traditional form. Emend®, introduced by Merck in 2003, was another early nanocrystal drug. It was created from a poorly soluble antiemetic, enhancing its bioavailability through nanocrystallization (80).

In 2003, Abbott Lab launched Tricor®, a fenofibrate-based treatment for hypercholesteremia, using the pearl mill process. This formulation improved oral bioavailability by 9%, regardless of whether the patient was in a fed or fasted state. In 2005, Triglide®, another nanocrystal-based drug, was developed by Skye Pharma using high-pressure homogenization (HPH). Triglide showed enhanced bioavailability and better adhesion in the gastrointestinal tract, similar to Tricor, and is marketed by Sciele Pharma Inc. (80).

10. Nanocrystal-based formulation has patents has been done this is mentioned below (80)

Sr. No.	Title	Application date	Patent No. / Application No.	Status of patent
1	Atazanavir Nanocrystal Formulation	09/09/2020	393527	Granted
2	Method of synthesis of atomically precise metal cluster-cellulose nanocrystal composite for diffusion-controlled simultaneously sensing and scavenging of heavy metal ions in water	19/09/2016	367409	Granted
3	Cellulose nanocrystal template iron oxyhydroxide-based adsorbent for arsenic removal from water and a device thereof	12/08/2016	343818	Granted
4	"Redox doping of semiconductors by colloidal nanocrystal dopants"	15/07/2014	328951	Granted
5	Nanocrystal titanium alloy and the production method for the same	21/03/2012	345625	Granted
6	Novel gold-platinum-based bimetallic nanocrystal suspensions, electrochemical manufacturing processes therefore and uses for the same	21/10/2013	311966	Granted
7	Nanocrystal nano-emulsion	14/07/2021	299583	Granted
8	Nanocrystal-sized cerium zirconium-aluminium oxide material and method of making the same	23/04/2021	202147034077	Published (under Examination for grant)
9	Solubility enhancement and bioavailability improvement of rosuvastatin calcium using nanocrystal-based hydrogel	30/06/2021	202121002129	Published (under Examination for grant)
10	Biological self-assembled nanocrystal injection having a lymphatic targeting function and preparation method thereof	01/10/2019	201947045083	Published (under Examination for grant)

11. Future Prospects

Nanocrystal drug products are expected to represent 50% of all nano-based drug delivery technologies by 2021, with the market estimated to reach $82 billion. The simplicity of manufacturing, homogeneous composition, and pharmacoeconomic benefits make nanocrystal technology highly promising. It also

addresses major challenges in drug development, such as poor solubility, which can limit bioavailability and drug circulation. By increasing the surface area, solubility, and dissolution rate, nanocrystals can improve bioavailability.

The therapeutic potential of nanocrystals is influenced by factors like drug load, particle size, surface area, shape, and targeted delivery. Several drug-loaded nanocrystals have been approved for oral use to treat various conditions. Nanocrystals typically measure over 200 nm in size, but those in the 100-200 nm range may be cleared rapidly by the bloodstream and undergo macrophage-mediated phagocytosis. To avoid renal clearance and mononuclear phagocytic system involvement, it is recommended to engineer crystal products below 100 nm (89). Understanding their behavior in cells and tumors is also crucial.

The advantages of nanocrystals, such as better physical stability, higher drug loading, and easier manufacturing, make them attractive for delivering poorly soluble drugs. Nanocrystals offer a universal strategy to enhance therapeutic effectiveness across various administration routes. Research has focused on developing advanced methods for nanocrystal production, with numerous pharmaceutical companies filing patents for this technology, resulting in a diverse range of available solutions.

12. Conclusion

Effective approaches to enhance dissolution rate, solubility, permeability, and oral bioavailability of poorly soluble drugs include solid dispersions, co-solvency, and particle size reduction to the sub-micron level. Nanocrystal technology meets these requirements and provides a superior delivery system with fewer side effects compared to traditional methods. This review summarizes various characteristics, characterization techniques, and pharmaceutical applications in drug delivery systems. However, additional clinical trials are needed for nanocrystals to be approved as treatments for various diseases.

Conflict of interest

The writer attests that there is not a conflict between their interests in the article's content.

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