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"Recent Advances In Nanocrystal-Based Formulations For Poorly Soluble Compounds"

[1]Harshita Bairagi, [2] Nimita Manocha, [3] Mr., Darshan Jamindar, [4] Nadeem A. Farooqui
[1]Student, [2] Principle & Guide, [3]Co-Guide, [4]Head of Department
Department of Pharmaceutics, *Indore Institute of Pharmacy*, *Indore, (M.P.), India*

Abstract: One of the primary causes for inconsistent exposure and less than ideal oral absorption of small molecule treatments is still poor aqueous solubility. Pure crystalline active pharmaceutical ingredient (API) colloidal dispersions stabilized by polymers or surfactants, known as drug nanocrystals, have become a flexible platform for increasing dissolution rate, apparent solubility (through the Kelvin effect), and, eventually, bioavailability. Improvements over the past five years include long-acting parenteral nanosuspensions, scalable continuous manufacturing, hybrid bottom-up/top-down processes, shape and polymorph control, better solidification techniques for tablets, capsules, and or dispersible dosage forms, and in silico tools that speed up formulation design. This study summarizes the latest developments in quality-by-design (QbD), characterization, materials, processes, and translational pharmacokinetics. It also identifies potential future paths, such as AI-guided excipient selection, green production, and precision long-acting treatments.

Index Terms **-** Poorly soluble drugs, drug nanocrystals, nanosuspensions, high-pressure homogenization, continuous manufacturing

1. INTRODUCTION

Based on Classes II and IV of the Biopharmaceutics Classification System, a significant portion of novel chemical entities (NCEs) have poor water solubility. Bioavailability for these chemicals is frequently restricted by dissolution at the absorptive surface rather than permeability. Particle size reduction to the sub-micron range enhances the saturation solubility at the particle–liquid interface (Kelvin/Gibbs–Thomson) and surface area (Noyes–Whitney), which promotes greater concentration gradients and quicker dissolution. The API stays crystalline in nanocrystals, usually >90% w/w of the dispersed phase, with a low carrier load, in contrast to amorphous solid dispersions and lipid systems. High drug loading, wide excipient compatibility, and suitability for a variety of routes (oral, dermal/ocular, pulmonary, and parenteral long-acting) are among the benefits [1]. Key technological developments in the areas of processing, stability, characterization, manufacturing science, and translational aspects (≈2020–2025) are the main emphasis of this review. The present review aims to provide a comprehensive overview of recent progress in nanocrystal-based formulations as a strategy to address the challenges of poor aqueous solubility. While nanocrystal technology has been studied for over two decades, the last five years have witnessed significant innovations in manufacturing, formulation design, and translational application.

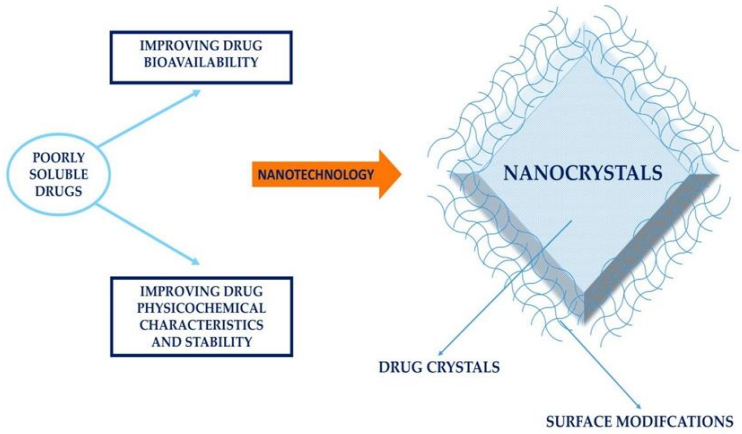

Figure No. 1 Nanocrystals of Poorly Soluble Drugs

2. Fundamentals Of Drug Nanocrystals

Drug nanocrystals are submicron-sized, crystalline particles of pure drug substance with sizes typically ranging from 100 to 1000 nm. They are stabilized in an aqueous or non-aqueous medium by surfactants or polymers to prevent aggregation. When dispersed in liquid media, the system is known as a nanosuspension, which can be further processed into dry powders or solid dosage forms [2].

Key attributes include:

Particle size: Nanocrystals typically measure below 1 µm, providing large surface area for dissolution.

Drug loading: Nearly 100% drug content, unlike other carriers.

Solid state: Crystalline in nature, though polymorph transitions can occur.

Stabilization: Requires polymers/surfactants to prevent aggregation and Ostwald ripening [4].

Dissolution enhancement mechanisms.

1. Noyes–Whitney: surface area ↑ → dissolution rate ↑.

2. Ostwald–Freundlich/Kelvin: curvature at nanoscale increases saturation solubility.

3. Boundary layer effects: shorter diffusion path; improved wetting via surfactants.

Solid-state considerations. Crystal habit, polymorph, and crystallinity influence stability and dissolution. Uncontrolled processing may induce partial amorphization or metastable forms; development programs should define acceptable ranges and monitor via XRPD/DSC [3] [4].

Mechanistic Advantages

Enhanced dissolution rate: Explained by the Noyes–Whitney equation, smaller particles dissolve faster

Increased saturation solubility: Due to the Kelvin/Gibbs–Thomson effect, nanocrystals achieve higher apparent solubility.

Supersaturation potential: Nanocrystals can generate transient supersaturation, enhancing absorption if precipitation is inhibited [5] [7].

Improved absorption and bioavailability: Particularly for BCS Class II and IV drugs.

Stabilization Mechanisms and Formulation Design

Nanocrystals are thermodynamically unstable due to their high surface energy. Stabilizers prevent aggregation and growth via:

Electrostatic stabilization: Ionic surfactants (e.g., sodium dodecyl sulfate) impart charge, increasing zeta potential and repulsion.

Steric stabilization: Non-ionic polymers (e.g., HPMC, PVP, poloxamers) adsorb on surfaces, forming a protective layer.

Electro steric stabilization: Combination of both mechanisms for enhanced stability [10][11].

Critical Quality Attributes (Cqas)

1. Particle size distribution (PSD): D10/D50/D90, polydispersity index (PDI).

2. Surface charge: Zeta potential for predicting suspension stability.

3. Crystallinity: Characterized by PXRD, DSC, and Raman spectroscopy.

4. Stabilizer adsorption: Influences redispersibility and dissolution.

5. Dissolution behavior: Evaluated in biorelevant media to predict in vivo performance [6].

Limitations and Challenges

1. Risk of Ostwald ripening and particle aggregation.
2. Potential polymorphic transitions during processing/storage.
3. Limited physical stability in suspension, requiring solidification strategies.
4. Scale-up challenges in maintaining consistent CQAs [9].

3. PRODUCTION TECHNOLOGIES

1. Top-Down Approaches

Wet media milling: Bead milling breaks coarse crystals into nanometer sizes using polymer/surfactant stabilizers. Pros: scalable, robust, low solvent use. Cons: possible contamination from beads, heat generation, long processing times for hard crystals [10].

High-pressure homogenization (HPH): Cavitation and shear reduce particle size across multiple cycles. Variants include piston-gap and micro fluidization. Pros sterile processing feasible, narrow PDI with optimization. Cons: energy intensive potential polymorphic transitions [11].

2. Bottom-Up Approaches

Antisolvent precipitation: Rapid mixing of a drug solution with a nonsolvent leads to nucleation-dominated formation of nanocrystals; requires effective stabilizers and controlled mixing (e.g., confined impinging jets, microfluidics) [12].

Controlled crystallization from supersaturated systems: Techniques such as pH-shift crystallization or temperature quench to trigger uniform nuclei.

Spray-freezing into liquid / cryo-precipitation: Ultra-rapid quenching suppresses growth; often paired with lyophilization.

Supercritical-fluid (SCF) routes: SAS/SEDS/RESS variants for low residual solvents and habit control—useful for heat-labile APIs or tight solvent limits. Hybrid bottom-up ↔ top-down: Precipitate to 500–2,000 nm then short WSMM/HPH to tighten PSD/lock polymorph → lower energy, fewer defects, better reproducibility [13] [14] [15].

3. Continuous Manufacturing (CM) and PAT End-to-end trains:

feeders → precipitation skid or mill/homogenizer → hold/aging → inline solvent exchange → spray-dryer/lyo → blender/tableting.

PAT toolkit (inline/at-line): PSD (laser diffraction, FBRM), visualization (PVM), solids/viscosity (densitometry, torsional (NIR/Raman/ATR-FTIR), plus T/P/flow sensors. rheometry), chemistry/crystallinity

Control strategies: model-predictive control with soft sensors for PSD; feedback on energy input, bead load, stabilizer feed; digital twins of milling/precipitation kinetics and RTD to keep CQAs steady in long runs.

Quality elements: RTRT concepts for PSD/crystallinity; traceable solvent exchange and residual-solvent clearance; inline bioburden/endotoxin monitoring for parenteral [16][17] [18].

4. CHARACTERIZATION & ANALYTICAL TOOL

Particle size & PDI: Dynamic light scattering (Z-average), laser diffraction, and nanoparticle tracking analysis for number-based distributions.

Zeta potential & rheology: Stability indices and syringeability for parenterals.

Solid-state: XRPD, DSC, modulated DSC, Raman/FTIR, and hot-stage microscopy to monitor polymorph transformations.

Surface properties: Specific surface area (BET), contact angle/wettability.

Dissolution/apparent solubility: Non-sink methods (µDISS, flow-through cells) and biorelevant media; supersaturation/precipitation profiling.

Stability studies: Size growth, sedimentation/redispersion, osmolality, pH, microbial limits (where applicable) [19] [20] [21].

In Vitro–In Vivo Performance

Nanocrystals can improve oral bioavailability by accelerating dissolution at the absorption site and sustaining supersaturation with stabilizers serving as precipitation inhibitors. Food effects may diminish compared to conventional formulations but remain drug-specific. For parenteral depots, apparent half-life is governed by dissolution from the injection site rather than classical clearance; particle size and surface chemistry are major levers. Early IVIVC is aided by nonlinear mixed-effects modeling and PBPK frameworks incorporating dissolution-limited absorption or depot erosion [23].

Advanced Strategies

Mucoadhesive coatings: Chitosan or thiolate polymers enhance residence in GI/ocular mucosa.

PEGylation and stealthing: Reduces opsonization for systemic circulation (when applicable).

Ligand targeting: Folate, transferrin, RGD, or antibodies facilitate tissue/cell targeting; ensure homogeneous, stable conjugation.

Hybrid architectures: Nanocrystal-in-liposome (NCL), nanocrystal-in-hydrogel,or polymer-stabilized co-crystal nanocomposites combine high loading with controlled release [24][25][26].

Table No. 1 Formulation Design and Strategies

Sr.No.	Strategy	Description	Examples/Applications
1.	Stabilizer Selection	Choice of polymers/surfactants to prevent aggregation, control surface charge, and ensure dispersibility.	HPMC, PVP, poloxamers, sodium dodecyl sulfate in oral nanosuspensions.
2.	Solidification Technique	Converting nanosuspensions into solid dosage forms for improved, stability and portability.	Spray-drying, freeze-drying, fluid-bed coating for tablets/capsules.
3.	Long-acting Parenteral Formulations	Nanosuspensions designed for sustained release after injection.	Injectable nanosuspensions of antipsychotics (e.g., paliperidone palmitate).
4.	Oral Delivery Systems	Enhancing dissolution and bioavailability of poorly soluble drugs in the GI tract.	Orodispersible of films, fast-dissolving tablets containing nanocrystals.
5.	Topical/Ophthalmic Delivery	Local delivery to improve solubility, penetration, residence time.	Nanocrystal eye drops (e.g., dexamethasone), dermal gels.

5. MANUFACTURING, REGULATORY, AND QBD

Nanocrystal eye drops (e.g., The application of Quality-by-Design (QbD) principles has become increasingly important in the development of nanocrystal-based formulations. QbD emphasizes a systematic, risk-based, and science-driven approach to pharmaceutical development, ensuring consistent product quality, safety, and efficacy. For drug nanocrystals, QbD provides a framework to define critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs) that influence the performance of the final product [27].

Key QbD Elements in Nanocrystal Development:

QTPP & CQAs: Define target dose strength, route, redispersion time, particle size, PDI, zeta potential, crystallinity, residual solvents, and microbial limits.

Risk assessment: Map CPPs such as homogenization pressure/cycles, milling speed/bead load, solvent ratio, temperature, and addition rate.

PAT & control strategy: Inline/atline DLS or laser diffraction, focused beam reflectance (FBRM), and Raman for polymorph tracking; statistical process control for cycle-to-cycle consistency.

Continuous processing: Plug-flow precipitators, continuous HPH loops, and continuous spray-drying reduce variability and footprint.

Tech transfer & scale: Geometric and dynamic similarity (energy density), excipient grades, and cleaning validation (bead residue, endotoxin for parenterals) [27] [28].

Regulatory Landscape Nanocrystal-based products have gained regulatory acceptance, with several FDA- and EMA approved formulations on the market (e.g., Rapamune® [sirolimus], Emend® [aprepitant],

Tricor® [fenofibrate]). Regulatory agencies emphasize thorough characterization of nanocrystals, stability studies, and demonstration of in vivo–in vitro correlation (IVIVC) [28].

ICH Q8–Q11 guidelines provide the overarching framework for QbD implementation in pharmaceutical development.

Regulatory focus areas include:

1. Particle size distribution and stability over shelf life.
2. Impact of polymorphism and solid-state transformations.
3. Safety and toxicity of stabilizers used at nanoscale levels.
4. Bioequivalence requirements for generic nanocrystal formulations.

6. FUTURE PERSPECTIVE & AI INTEGRATION

Nanocrystal-based formulations have already demonstrated significant clinical and commercial success in improving the solubility and bioavailability of poorly soluble drugs. However, their full potential is yet to be realized. Future developments are likely to focus on expanding therapeutic applications, enhancing stability, and integrating digital technologies such as artificial intelligence (AI) to streamline formulation design [30].

Emerging applications include pulmonary, ocular, and dermal nanocrystals, which could enable localized treatment with improved efficacy and reduced systemic toxicity. Long-acting injectable nanosuspensions, particularly for chronic diseases like HIV, malaria, and psychiatric disorders, are also poised to transform patient adherence and therapeutic outcomes. Meanwhile, oncology research is exploring targeted nanocrystals with surface modifications, offering the possibility of precision drug delivery.

Despite these advances, challenges such as long-term physical stability, scale-up reproducibility, and regulatory hurdles remain. To overcome these barriers, future work will focus on rational stabilizer design, hybrid stabilization strategies, and sustainable manufacturing approaches such as continuous processing and green chemistry [29].

AI integration is expected to be a game changer in nanocrystal development. Machine learning algorithms can predict solubility, stability, and optimal process parameters, thereby reducing experimental workload. AI-based tools can also accelerate excipient screening, support in vitro–in vivo correlation modeling, and even enable personalized nanocrystal medicines tailored to patient-specific needs. By uncovering hidden relationships in large datasets, AI provides a more efficient, data-driven pathway to formulation success.

Looking ahead, the convergence of nanocrystal technology with AI-guided formulation, hybrid delivery systems, and precision medicine will define the next era of drug delivery. Such innovations promise not only to overcome solubility challenges but also to deliver safer, more effective, and patient-centric therapies [30].

7. CONCLUSION

Formulations based on nanocrystals have become a potent way to address one of the most enduring problems in pharmaceutical development: the low bioavailability and poor solubility of many medicinal substances. Nanocrystals improve absorption, solubility, and therapeutic efficacy by shrinking medication particles to the nanometer range. Understanding their stabilizing mechanisms, improving formulation design, and scaling up production methods have all advanced significantly over the last 20 years, resulting in successful translation into marketable goods. Considering these successes, significant obstacles including long-term stability, standardized regulations, and large-scale reproducibility still call for creative solutions. Future research will concentrate on innovative therapeutic uses, such as topical, pulmonary, ophthalmic, and long-acting parenteral administration, as well as sustainable manufacturing techniques and sophisticated stabilization techniques. By enabling predictive modeling, improving process parameters, and supporting personalized medicine techniques, the integration of artificial intelligence (AI) holds the potential to further accelerate progress. It is anticipated that nanocrystal technology will be crucial in forming next generation medication delivery systems as it develops further with digital and hybrid delivery advances. In the end, nanocrystal formulations provide a revolutionary platform for poorly soluble medications, serving as a link between molecular innovation and patient-centered therapies. 7.

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