WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 3, 14-27. Review Article ISSN 2277–7105

NANOCRYSTALS AS A NOVEL PHARMACEUTICAL APPROACH FOR BIOAVAILABILITY ENHANCEMENT: A COMPREHENSIVE REVIEW

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Article Received on 05 Jan. 2026,
Article Revised on 25 Jan. 2026,
Article Published on 01 Feb. 2026,

https://doi.org/10.5281/zenodo.18426660

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How to cite this Article: *[1]Mr. Ganesh D. Parihar, [2]Mr. Harshal S. Nage, [3]Mr. Mukesh S. Naiknawre, [4]Ms. Anuradha. K. Kendhale, [5]Ms. Sakshi S. Ghuge, [6]Mr. Devanand H. Dongre, [7]Dr. Prafulla R. Tathe (2026). Nanocrystals As A Novel Pharmaceutical Approach For Bioavailability Enhancement: A Comprehensive Review. "World Journal of Pharmaceutical Research, 15(3), 14–27.

ABSTRACT

The majority of new drug molecules discovered through high-throughput screening possess poor aqueous solubility, resulting in low oral bioavailability and limited clinical success. Nearly 40–70% of small-molecule drugs fall into Biopharmaceutics Classification System (BCS) Class II or IV, where solubility and dissolution are the rate-limiting steps in absorption. Nanocrystal technology has emerged as a simple yet powerful strategy to address these issues by reducing drug particles to the nanometer scale, thereby increasing surface area, dissolution velocity, and apparent saturation solubility. Unlike polymeric nanoparticles or lipid carriers, nanocrystals consist almost entirely of the pure active pharmaceutical ingredient stabilized by surfactants or polymers, offering high drug loading and improved performance. This review provides a comprehensive overview of nanocrystals as a drug delivery approach, discussing their theoretical basis, preparation methods, stabilizers, characterization techniques, pharmaceutical

applications, marketed products, regulatory aspects, stability concerns, and future perspectives. Tables and figures are included to aid clarity.

KEYWORDS: Nanocrystals, bioavailability enhancement, nanosuspension, poorly soluble drugs, pharmaceutical technology, drug delivery.

1. INTRODUCTION

The modern drug discovery pipeline is dominated by lipophilic molecules with poor aqueous solubility, largely due to combinatorial chemistry and high-throughput screening approaches (Verma et al., 2021). These molecules frequently suffer from poor absorption and low systemic exposure, limiting their therapeutic potential (Dhaval et al., 2020). Statistics suggest that approximately 40% of currently marketed drugs and up to 70% of new drug candidates are poorly water-soluble (Macedo et al., 2024). The consequence is reduced oral bioavailability, high interpatient variability, and frequent failures in late-stage clinical trials.

Traditional formulation approaches such as salt formation, solid dispersions, and lipid-based systems provide partial solutions but have limitations in terms of stability, scalability, or drug loading (Peltonen et al., 2018). In contrast, nanocrystals offer a promising universal strategy, particularly for BCS Class II drugs, where dissolution rather than permeability is the limiting factor (Gigliobianco et al., 2018). Nanocrystals are defined as pure drug crystals with particle sizes in the nanometer range (usually 100–1000 nm) stabilized by surface-active agents to prevent aggregation (Junghanns & Müller, 2008).

The first nanocrystal product to reach the market was *Rapamune*® (sirolimus), followed by several others such as *Emend*® (aprepitant) and *Megace ES*® (megestrol acetate), demonstrating the clinical viability of this technology (Verma et al., 2021). Today, nanocrystal formulations are explored not only for oral delivery but also for parenteral, ocular, dermal, and pulmonary applications (Ji et al., 2025).

This review provides a detailed exploration of nanocrystals in pharmaceutics, focusing on their theoretical principles, production technologies, stabilization strategies, characterization, clinical applications, marketed products, regulatory requirements, challenges, and future perspectives**.**

2. Physicochemical Principles of Bioavailability Enhancement

2.1 Surface area and dissolution rate

According to the Noyes–Whitney equation, the rate of dissolution (dC/dt) is directly proportional to the surface area (A) of the drug particles:

$$\frac{dC}{dt} = \frac{DA(Cs - C}{h} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{equation number 01}$$

Where *D* is the diffusion coefficient, *Cs* is the saturation solubility, *C* is the concentration at time *t*, and *h* is the diffusion layer thickness. Reducing drug particle size to the nanometer range increases surface area dramatically, thereby accelerating dissolution (Gigliobianco et al., 2018). This effect is particularly beneficial for drugs with dissolution-limited absorption.

2.2 Apparent saturation solubility (Ostwald–Freundlich effect)

Nanocrystals also exhibit enhanced apparent saturation solubility compared to bulk drug. This phenomenon is explained by the Ostwald–Freundlich equation, which describes the dependence of solubility on particle curvature. Smaller particles have higher surface free energy, which leads to elevated solubility (Ding et al., 2024). The result is an increased concentration gradient across the gastrointestinal membrane, further improving absorption.

2.3 Mucoadhesion and gastrointestinal retention

Nanocrystals may also interact with mucins in the gastrointestinal tract, leading to prolonged residence time and sustained local drug supersaturation (Macedo et al., 2024). This phenomenon enhances absorption beyond the classical dissolution effect, especially for drugs with narrow absorption windows.

2.4 Reduced food effects and variability

Many poorly soluble drugs show strong food-dependent absorption. Nanocrystals, by virtue of their high dissolution velocity and solubility, reduce variability associated with fed/fasted states (Peltonen et al., 2018). For instance, aprepitant nanocrystals (*Emend*®) demonstrated consistent bioavailability independent of meal conditions (Verma et al., 2021).

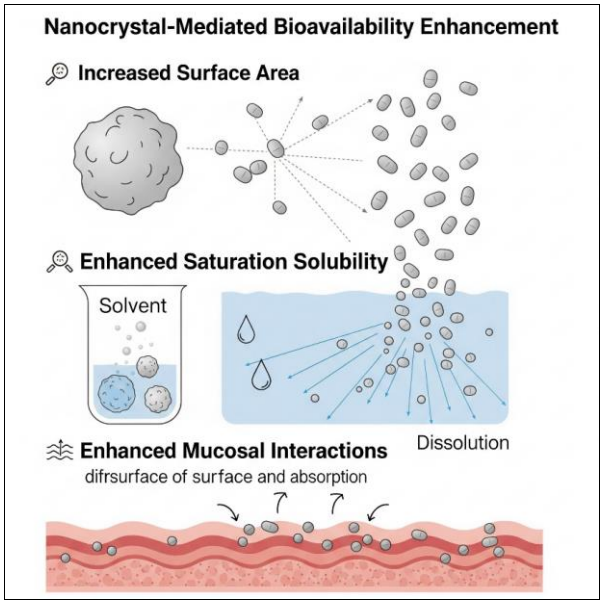

Figure 01: Schematic representation of nanocrystal-mediated bioavailability enhancement showing increased surface area, improved saturation solubility, and enhanced mucosal interactions.

3. Methods of Nanocrystal Production

Nanocrystal production techniques are broadly classified into top-down, bottom-up, and combinative approaches (Junghanns & Müller, 2008; Ran et al., 2022). The choice of method depends on factors such as drug solubility, stability, scalability, and regulatory considerations.

3.1 Top-down approaches

Top-down approaches reduce the size of large drug crystals to the nanometer range using mechanical energy.

3.1.1 Wet media milling

Wet media milling (also called nanomilling or pearl milling) involves dispersing drug crystals in an aqueous stabilizer solution and reducing their size using milling beads. The process is efficient and widely scalable, producing particles with narrow size distribution (Malamatari et al., 2018). However, prolonged milling can generate heat, potentially leading to chemical degradation or polymorphic transformation (Verma et al., 2021).

3.1.2 High-pressure homogenization (HPH)

HPH involves forcing a coarse drug suspension through narrow gaps under pressures up to 2000 bar, generating intense shear forces, cavitation, and turbulence (Junghanns & Müller, 2008). Variants include piston-gap homogenization and microfluidization. HPH is solvent-

free, scalable, and commonly used in commercial nanocrystal production. However, multiple homogenization cycles may be required, and the method may not suit thermolabile drugs (Peltonen et al., 2018).

3.2 Bottom-up approaches

Bottom-up methods rely on nucleation and controlled crystal growth from molecularly dissolved drug solutions.

3.2.1 Antisolvent precipitation

In this technique, the drug is dissolved in a solvent and rapidly mixed with a miscible nonsolvent (antisolvent), leading to supersaturation and nucleation of drug crystals. Stabilizers are added to control growth and prevent aggregation (Mahesh et al., 2014). The method allows control over crystal size but faces challenges in large-scale manufacturing and solvent removal.

3.2.2 Supercritical fluid crystallization

Here, supercritical fluids such as CO_2 are used as antisolvents to induce crystallization. This method avoids toxic solvents and offers precise size control but requires high-pressure equipment and is relatively costly (Ran et al., 2022).

3.3 Combinative approaches

Hybrid techniques combine the advantages of top-down and bottom-up methods. For instance, precipitation followed by high-pressure homogenization reduces energy consumption and improves size uniformity (Ran et al., 2022). Another example is spray-drying followed by nanomilling, which enhances process efficiency.

Table 1: Comparison of Top-down and Bottom-up Approaches for Nanocrystal Production (Junghanns & Müller (2008), Malamatari et al. (2018), Ran et al. (2022)).

Feature	Top-down methods (Wet milling, HPH)	Bottom-up methods (Precipitation, SCF)
Principle	Size reduction of large crystals	Controlled nucleation from solution
Solvent use	Usually aqueous, solvent-free	Requires solvent/antisolvent
Scalability	High, industry-proven	Moderate, scale-up challenging
Energy demand	High (mechanical stress)	Low to moderate
Particle size control	Narrow distribution, but polymorph risk	Precise control possible
Examples	Media milling, HPH	Antisolvent precipitation, SCF crystallization

4. Stabilizers and Surface Engineering

Nanocrystals are thermodynamically unstable and prone to aggregation, Ostwald ripening, and sedimentation. Stabilizers adsorb onto the particle surface to provide steric, electrostatic, or electrosteric repulsion (Malamatari et al., 2018).

4.1 Types of stabilizers

- **Polymers:** Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG) provide steric hindrance.
- **Surfactants:** Polysorbates (Tween 80), sodium dodecyl sulfate (SDS), and poloxamers reduce interfacial tension and provide electrostatic stabilization.
- **Natural stabilizers:** Lecithin and chitosan offer biocompatibility and multifunctional benefits (Lhaglham et al., 2024).

4.2 Surface engineering strategies

Recent innovations involve functionalizing nanocrystal surfaces to enhance performance:

- **PEGylation:** Provides “stealth” properties, reducing opsonization and prolonging circulation time (Tabatabaei et al., 2024).
- **Targeting ligands:** Folic acid, antibodies, or peptides are grafted for site-specific delivery.
- **Mucoadhesive coatings:** Chitosan and thiolated polymers increase gastrointestinal residence and uptake (Macedo et al., 2024).

4.3 Stabilizer selection considerations

The choice of stabilizer depends on:

- Drug–stabilizer compatibility
- Desired route of administration
- Toxicity profile
- Regulatory acceptability (Peltonen et al., 2018)

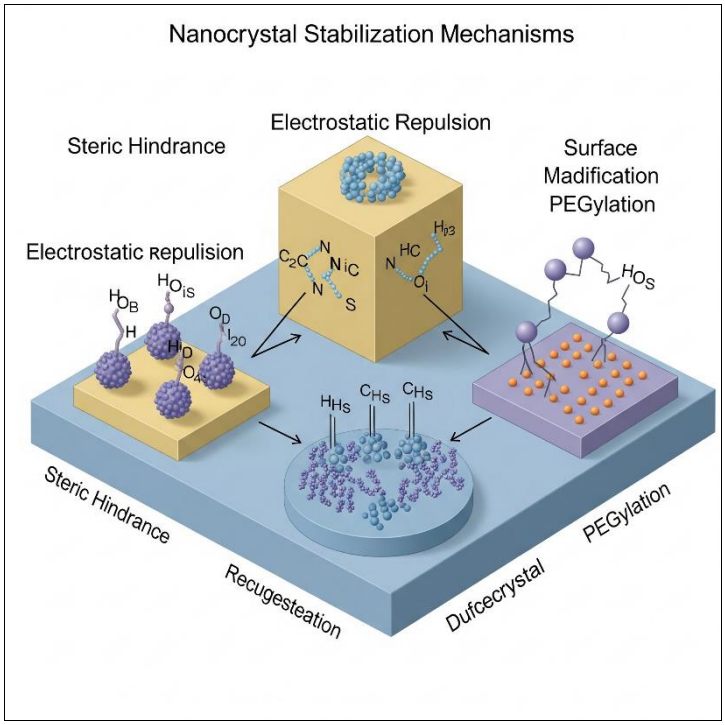

Figure 2: Illustration of nanocrystal stabilization mechanisms – steric hindrance, electrostatic repulsion, and surface modifications such as PEGylation.

5. Characterization of Nanocrystals

The characterization of nanocrystals is essential to ensure their size, crystallinity, stability, and dissolution behavior are well understood, as these directly influence bioavailability (Peltonen et al., 2018). A variety of techniques are employed:

5.1 Particle size and distribution

- **Dynamic light scattering (DLS):** Widely used to measure average particle size and polydispersity index (PDI). Nanocrystals with PDI < 0.3 are generally considered stable and uniform (Gigliobianco et al., 2018).
- **Laser diffraction (LD):** Suitable for detecting wide size ranges, including micro-scale aggregates.

5.2 Morphology and surface properties

- **Scanning electron microscopy (SEM) and transmission electron microscopy (TEM):** Provide detailed images of particle shape, aggregation, and surface texture (Todaro & Santi, 2022).
- **Atomic force microscopy (AFM):** Allows visualization of surface roughness and interaction forces.

5.3 Crystallinity and polymorphism

- **Powder X-ray diffraction (PXRD):** Distinguishes between crystalline and amorphous forms.
- **Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA):** Assess thermal behavior and polymorphic transitions (Peltonen et al., 2018).

5.4 Surface charge and stability

- **Zeta potential analysis:** Indicates electrostatic repulsion; values greater than ±30 mV usually predict colloidal stability (Malamatari et al., 2018).

5.5 Dissolution and solubility studies

- **In vitro dissolution testing:** Simulates gastrointestinal conditions to predict drug release. Special care is taken to minimize sedimentation artifacts (Gigliobianco et al., 2018).
- **Apparent solubility tests:** Compare solubility of nanocrystals with bulk drug to demonstrate the Ostwald–Freundlich effect (Ding et al., 2024).

Table 2: Key Characterization Techniques for Nanocrystals.

Property	Technique	Purpose	Reference
Particle size	DLS, LD	Size distribution, PDI	Gigliobianco et al. (2018)
Morphology	SEM, TEM, AFM	Particle shape, aggregation	Todaro & Santi (2022)
Crystallinity	PXRD, DSC, TGA	Detect polymorphic changes	Peltonen et al. (2018)
Surface charge	Zeta potential	Colloidal stability	Malamatari et al. (2018)
Dissolution	USP dissolution tests	In vitro–in vivo correlation	Ding et al. (2024)

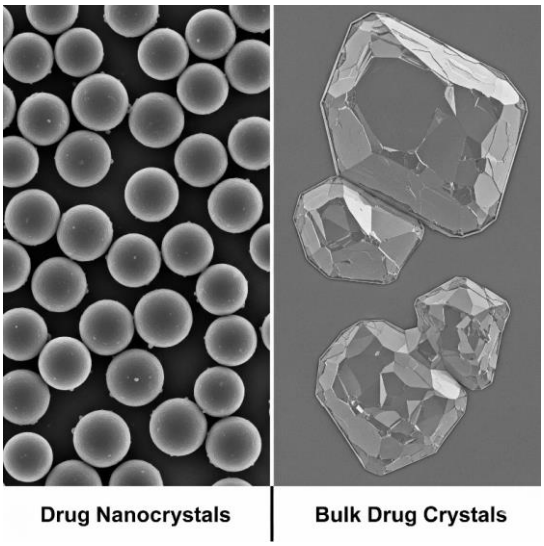

Figure 3: Microscopic images of drug nanocrystals showing uniform spherical morphology compared to irregular bulk drug crystals.

6. Pharmaceutical Applications

Nanocrystals have been widely investigated for diverse drug delivery routes. Their versatility stems from high drug loading, scalability, and enhanced solubility (Junghanns & Müller, 2008).

6.1 Oral delivery

Oral nanocrystal formulations improve dissolution, absorption, and reduce variability related to fed/fasted states (Macedo et al., 2024).

- **Tablets and capsules:** Spray-drying or freeze-drying of nanosuspensions allows conversion into solid dosage forms.
- **Suspensions:** Direct nanosuspensions provide fast onset of action.
- **Examples:** *Rapamune® (sirolimus)* and *Emend® (aprepitant)* achieved enhanced oral bioavailability and patient compliance (Verma et al., 2021).

6.2 Parenteral delivery

Nanocrystal suspensions are suitable for intravenous administration, eliminating the need for harmful cosolvents like Cremophor EL (Junghanns & Müller, 2008). However, strict control of size (<200 nm) is necessary to avoid embolism.

- **Examples:** Intravenous nanosuspensions of itraconazole and paclitaxel have been developed (Peltonen et al., 2018).

6.3 Ocular delivery

Poor solubility limits drug residence in the eye. Nanocrystals increase corneal permeability and sustain release (Ji et al., 2025).

- **Example:** Nanocrystal formulations of dexamethasone improved ocular bioavailability.

6.4 Dermal and transdermal delivery

Nanocrystals enhance solubility of hydrophobic drugs in topical creams and gels, allowing high local drug loading without penetration enhancers (Malamatari et al., 2018).

- **Example:** Diclofenac nanocrystal gels showed faster onset of analgesic action compared to conventional formulations.

6.5 Pulmonary delivery

Nanocrystals as dry powders or nebulized suspensions provide targeted delivery to the lungs with rapid absorption (Ding et al., 2024). This is useful in treating respiratory infections and cancers.

6.6 Central nervous system (CNS) delivery

By improving solubility and permeability, nanocrystals enhance CNS penetration of drugs with limited bioavailability (Tabatabaei et al., 2024). Surface modification with targeting ligands further facilitates blood–brain barrier transport.

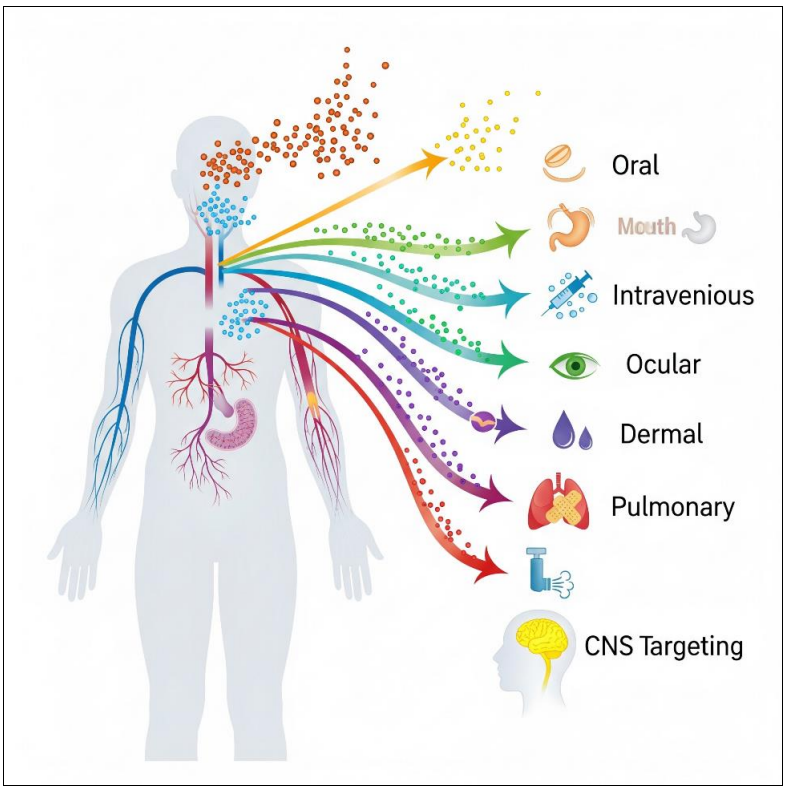

Figure 4: Diagram showing different administration routes of nanocrystals: oral, intravenous, ocular, dermal, pulmonary, and CNS targeting.

7. Marketed Nanocrystal-Based Products

The successful commercialization of nanocrystal formulations has demonstrated their clinical potential and economic value. Several products have received regulatory approval from the US FDA and EMA, paving the way for broader adoption (Verma et al., 2021).

Table 3: Selected Marketed Nanocrystal-Based Drug Products.

Product (Drug)	Therapeutic Area	Company	Dosage Form	Regulatory Status
Rapamune® (Sirolimus)	Immunosuppressant	Wyeth/Pfizer	Oral suspension	FDA approved, 2000
Emend® (Aprepitant)	Antiemetic	Merck	Capsules	FDA approved, 2003
Tricor® (Fenofibrate)	Lipid-lowering	AbbVie	Tablets	FDA approved, 2004
Megace ES® (Megestrol acetate)	Appetite stimulant	Par Pharmaceutical	Oral suspension	FDA approved, 2005
Invega Sustenna® (Paliperidone palmitate)	Antipsychotic	Janssen	Injectable suspension	FDA approved, 2009
Kalydeco® (Ivacaftor)	Cystic fibrosis	Vertex	Tablets	FDA approved, 2012

These examples underscore the versatility of nanocrystal technology across therapeutic domains, from oncology to CNS disorders.

8. Regulatory Considerations

The regulatory landscape for nanocrystals is evolving. Since nanocrystals are composed solely of drug and stabilizers, they are often classified as "simple nanotechnology-based products", unlike more complex nanocarriers such as liposomes or dendrimers (Peltonen et al., 2018).

- **Quality by Design (QbD):** Regulatory agencies encourage the use of QbD in nanocrystal development, focusing on critical quality attributes such as particle size, PDI, zeta potential, and dissolution (Malamatari et al., 2018).
- **Bioequivalence studies:** Comparative pharmacokinetic data with conventional formulations are usually required to establish therapeutic equivalence (Ding et al., 2024).
- **Toxicological evaluation:** Stabilizers and surfactants used in nanosuspensions must be GRAS (Generally Recognized as Safe) certified.

Despite regulatory progress, challenges remain in defining harmonized international guidelines for nanomedicine evaluation.

9. Challenges and Limitations

Despite their promise, nanocrystals face several scientific and practical hurdles:

1. **Physical instability:** Nanocrystals are prone to aggregation, Ostwald ripening, and sedimentation, particularly during long-term storage (Peltonen et al., 2018).

2. **Scalability issues:** Although techniques like wet milling and high-pressure homogenization are scalable, they require specialized equipment and high energy input (Gigliobianco et al., 2018).
3. **Stabilizer selection:** Inappropriate stabilizers may lead to toxicity or inadequate stabilization (Malamatari et al., 2018).
4. **Limited targeting ability:** Compared to lipid-based carriers, nanocrystals rely mainly on passive mechanisms for biodistribution.
5. **Regulatory ambiguity:** Lack of unified international frameworks for nanocrystal products slows down global commercialization.

10. Future Perspectives

Nanocrystals are anticipated to play a transformative role in next-generation drug delivery. Key trends include:

- **Hybrid nanocarriers:** Combining nanocrystals with liposomes, polymeric nanoparticles, or microneedles for enhanced functionality (Tabatabaei et al., 2024).
- **Personalized nanomedicine:** Tailoring nanocrystal formulations for patient-specific pharmacogenomic profiles.
- **Green nanotechnology:** Employing eco-friendly methods such as supercritical fluid technology to minimize energy use and environmental impact (Macedo et al., 2024).
- **Targeted nanocrystals:** Surface modification with ligands (antibodies, peptides) for active targeting in oncology and CNS diseases.
- **Artificial intelligence (AI)-assisted design:** Use of machine learning to predict nanocrystal stability and performance during early formulation stages.

11. CONCLUSION

Nanocrystals have emerged as a powerful and versatile platform for improving the solubility and bioavailability of poorly water-soluble drugs. Their relatively simple composition, scalability, and clinical success have made them a preferred choice over more complex nanocarriers. Numerous marketed formulations including Rapamune®, Emend®, and Tricor® attest to their therapeutic and commercial potential.

However, challenges remain in terms of stability, large-scale manufacturing, and regulatory harmonization. Future innovations involving hybrid systems, AI-driven formulation design, and eco-friendly production are likely to accelerate their global adoption.

Thus, nanocrystals stand as a novel pharmaceutical approach bridging the gap between laboratory innovation and clinical application, offering new hope for patients requiring improved drug therapies.

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