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Review Article

Nanocrystalline Suspensions for Improved Dissolution Characteristics: A Critical Review of Formulation Strategies and Performance

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ABSTRACT

Poor aqueous solubility affects an estimated 40% of marketed drugs and nearly 90% of molecules currently in the discovery pipeline, making dissolution-rate enhancement one of the most persistent challenges in oral formulation development. Nanocrystalline suspensions (nanosuspensions) — carrier-free, stabilizer-coated nanosized drug particles dispersed in an aqueous or non-aqueous vehicle — address this problem directly by exploiting the Noyes-Whitney relationship between particle surface area and dissolution velocity, while additionally increasing saturation solubility via the Ostwald-Freundlich effect at sub-micron particle sizes. This review synthesizes the pharmaceutical literature on nanocrystal formulation via top-down (media milling, high-pressure homogenization) and bottom-up (precipitation) methods and their combinations, examines stabilizer selection and its role in preventing Ostwald ripening and aggregation, and surveys recent (2022–2025) extensions of the technology including nano-co-crystal hybrids and nanocomposite drying strategies for converting nanosuspensions into solid dosage forms. Persistent gaps are identified in long-term physical stability data, scale-up reproducibility, and the availability of formal in vitro-in vivo correlation for nanocrystal-based oral products.

INTRODUCTION

The proportion of new chemical entities exhibiting poor aqueous solubility has risen steadily with the growth of combinatorial chemistry and structure-based drug design, with poor water solubility now implicated as a leading cause of new drug development failure. Particle size reduction to the

nanometre scale is among the most direct and formulation-agnostic strategies available for addressing this problem: reducing particle size increases the surface-area-to-volume ratio available for dissolution and, below approximately one micrometre, begins to increase saturation solubility itself via curvature-dependent (Ostwald-Freundlich) effects. Nanocrystalline suspensions

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— sometimes termed nanosuspensions — are colloidal dispersions of pure, carrier-free drug nanocrystals stabilized against aggregation and Ostwald ripening by a thin surfactant or polymer coating, distinguishing them from polymeric or lipid nanoparticle carrier systems in which the drug is dissolved or dispersed within a matrix rather than existing as discrete crystalline particles.

This distinction is pharmaceutically significant: because nanocrystals are close to 100% drug by mass (limited only by the thin stabilizer coating), they offer very high drug loading relative to carrier-based nanoparticle systems, making them particularly suited to poorly soluble, high-dose drugs where carrier-based systems would require impractically large dose volumes.

2. Mechanistic Basis and Relevance

The dissolution-rate enhancement achieved by nanocrystals is governed by the Noyes-Whitney equation, in which dissolution velocity (dx/dt) is directly proportional to particle surface area (A) and the saturation solubility gradient ($C_s - C_t$) across the diffusion boundary layer, and inversely proportional to the diffusional distance (h). Nanosizing increases A directly and, via the Prandtl boundary-layer relationship, also reduces the effective diffusional distance h , compounding the dissolution-rate benefit. Below a particle size threshold generally cited around 1–2 micrometres, the Ostwald-Freundlich relationship additionally predicts a measurable increase in saturation solubility (C_s) itself as a function of increasing surface curvature — meaning nanocrystals can enhance both the rate and, to a smaller degree, the extent of dissolution relative to micronized material. Beyond oral bioavailability, nanocrystal formulations have been reported across intravenous, subcutaneous, intramuscular, ocular, pulmonary, and topical routes, and are compatible with downstream processing into fast-melting

tablets, capsules, or lyophilized sterile products, giving the technology platform-level versatility beyond any single dosage form.

3. Formulation Approaches: Literature Review

Top-down methods — which reduce pre-formed drug crystals to nanoscale size via high-energy input — remain the dominant commercial approach, principally media/stirred-ball milling and high-pressure homogenization, alongside proprietary combination technologies (Nano-Edge, SmartCrystal, and precipitation-lyophilization-homogenization, PLH) that combine precipitation with a secondary size-reduction step to improve efficiency and reduce residual crystallinity defects (JETNR, 2024).

A combined co-crystal/nanocrystal ('nano-co-crystal') strategy was demonstrated by Huang, Staufenbiel and Bodmeier (2022), who prepared itraconazole-succinic acid nano-co-crystals achieving a kinetic solubility 51.5-fold higher than raw itraconazole and 6.6-fold higher than the microscale co-crystal alone, directly demonstrating a synergistic combination of crystal-engineering (co-crystal) and particle-size-reduction (nanocrystal) strategies within a single formulation approach (Pharm Res, 2022. doi:10.1007/s11095-022-03243-9).

A review of engineered nanocrystals for poorly soluble drug delivery catalogued the comparative advantages of nanocrystals over microcrystals — enhanced saturation solubility and dissolution velocity, increased bioadhesiveness supporting improved membrane absorption, and superior physical stability against aggregation and Ostwald ripening relative to microsuspensions — alongside the breadth of administration routes (oral, parenteral, ocular, pulmonary, dermal) compatible with nanocrystal technology (Int J Pharm Sci, 2024).

Nanocomposite-based approaches for converting nanosuspensions into stable solid dosage forms



were reviewed with specific attention to drying-process selection (spray-drying, lyophilization) and dispersant class, framed explicitly around the Noyes-Whitney basis for the dissolution-rate benefit and noting that elimination of food effects and support for safe dose escalation are additional benefits reported for nanoparticle-based drug delivery beyond dissolution enhancement alone (PMC6160929).

Broader solubility-enhancement reviews position nanocrystal technology alongside amorphous solid dispersions, polymeric and lipid-based carriers, and mesoporous silica carriers as one of several high-efficacy strategies now available for poorly water-soluble drugs, noting that conventional approaches (particle-size reduction by simple micronization, pH adjustment, salt formation, co-solvency, surfactant solubilization, cyclodextrin complexation) each carry physicochemical stability or capacity limitations that nanocrystal and other advanced nanotechnology-based approaches are intended to address (Primera Scientific, 2025–2026).

4. Identified Gaps and Novelty Statement

Three gaps recur across the nanocrystal literature surveyed. First, while short-term dissolution and saturation-solubility data are consistently reported, long-term physical stability data — specifically resistance to Ostwald ripening and aggregation over pharmaceutically relevant shelf-life durations — is less consistently reported, and stabilizer selection remains largely empirical rather than rationally predicted. Second, scale-up reproducibility from laboratory-scale milling or homogenization to pilot and commercial scale is addressed in only a minority of the primary literature, despite being a recognized translational bottleneck for nanocrystal products. Third, formal in vitro-in vivo correlation data connecting nanocrystal dissolution profiles to oral bioavailability outcomes remains comparatively

sparse relative to the volume of in vitro dissolution-enhancement papers published, mirroring a gap identified in other dissolution-enhancement technology reviews.

5. CONCLUSION

Nanocrystalline suspensions remain a mechanistically well-established and formulation-versatile strategy for addressing the dissolution-rate-limited bioavailability of poorly water-soluble drugs, with a strong theoretical basis in the Noyes-Whitney and Ostwald-Freundlich relationships and a growing toolkit of top-down, bottom-up, and hybrid (nano-co-crystal) preparation methods. The literature reviewed here confirms consistent dissolution and saturation-solubility benefits across drug classes and administration routes, but reveals continuing gaps in long-term stability characterization, scale-up reproducibility, and formal bioavailability confirmation via in vitro-in vivo correlation. Addressing these translational gaps, rather than further in vitro proof-of-concept work, represents the principal opportunity for advancing nanocrystal technology toward broader clinical and commercial application.

Conflict of Interest

The authors declare no conflict of interest.

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