



Predictive Modeling of Pharmaceutical Nanocrystals from 2017 to 2026 Across Particle Engineering, Physical Stability, Dissolution, and Oral Performance

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ABSTRACT

Pharmaceutical nanocrystal development increasingly relies on computational, mechanistic, statistical, and data-driven approaches to anticipate formulation behavior instead of depending solely on iterative experimentation. However, prediction targets differ substantially across particle engineering, stabilization, physical stability, dissolution, and oral performance, which makes apparently similar modeling studies difficult to compare directly. This evidence-mapping review examined peer-reviewed pharmaceutical nanocrystal and closely bounded nanosuspension modeling literature published from 2017 through 2026. Eligible evidence was charted by prediction target, material and process context, model family, experimental scale, validation design, uncertainty source, and intended formulation decision. The verified DOI-level screening inventory comprised 52 eligible candidate articles, of which 15 were excluded after evidence-fit assessment and 37 were included. The resulting map indicates an uneven predictive landscape. Modeling is comparatively mature where controllable process or formulation inputs can be linked to particle-size distributions, stabilizer behavior, or physical-stability endpoints, whereas evidence becomes less continuous across dissolution, supersaturation, permeation, and organism-level oral performance. Machine-learning, mechanistic, population-balance, Quality-by-Design, molecular, and biopharmaceutic models therefore represent distinct predictive logics rather than interchangeable approaches. A proposed stage-and-validation framework distinguishes what a model predicts from how far that prediction has been experimentally tested. Pharmaceutical nanocrystal modeling is becoming more predictive, but the available evidence does not yet support a unified end-to-end predictive framework. Translation requires endpoint-specific validation, explicit applicability boundaries, and separation of predictive accuracy from mechanistic or biopharmaceutic validity.

Key Words: *Pharmaceutical nanocrystals, Predictive modeling, Nanosuspensions, Machine learning, Dissolution, Oral bioavailability*

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INTRODUCTION

Drug nanocrystals address poor aqueous solubility primarily through reduction of crystalline drug particles to

the submicron domain, increasing surface-area-dependent dissolution while leaving oral performance dependent on formulation composition, gastrointestinal conditions, precipitation behavior, permeability, and disposition. Oral

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nanocrystal performance therefore cannot be reduced to particle size alone [1]. Recent development literature similarly depicts nanocrystals as a formulation platform whose performance depends on how particle engineering is connected to stabilization, downstream processing, dosage-form conversion, and bioavailability-oriented behavior [2].

Prediction has entered this development space through several routes. Direct machine learning has been applied to drug-nanocrystal formulation data to predict formulation outcomes from encoded material and formulation variables [3]. In parallel, wet-media milling exposes coupled effects of drug properties, stabilizer composition, equipment configuration, energy input, and operating conditions that are suitable for structured process modeling [4]. The fundamental nanocrystal rationale additionally links particle size and surface area to dissolution and formulation behavior while recognizing substantial drug- and system-specific dependence [5].

This review therefore treats predictive modeling as broader than machine learning. It includes data-driven, empirical, semi-mechanistic, population-balance, molecular, Quality-by-Design, and biopharmaceutic approaches when they anticipate a defined pharmaceutical endpoint. The central question is not whether a model is computationally sophisticated, but what it predicts, under which conditions, and what evidence validates that prediction.

Evidence-Mapping Questions and Classification Scheme

The review was designed to map predictive evidence across successive but non-equivalent development problems: particle-size control, stabilizer and interfacial behavior, processing, physical stability, dissolution and supersaturation, solid-state change, and oral performance. Three questions governed evidence charting. First, which pharmaceutical endpoint was actually predicted? Second, what information and model class generated that prediction? Third, how closely did validation approach the formulation decision for which the prediction might eventually be used?

A manuscript-derived classification was developed after evidence charting. It separates prediction target, development stage, model family, material or API space, experimental scale, validation level, and known transferability boundary. This organization is proposed for the present evidence map rather than presented as an established ontology. Internal model performance, mechanistic consistency, cross-condition transfer, biorelevant agreement, and in-vivo correspondence are therefore treated as different validation achievements.

The verified evidence-selection process is shown in **Figure 1**. The figure deliberately distinguishes auditable DOI-level screening counts from upstream retrieval information that could not be reconstructed reliably, preventing apparent reporting precision from exceeding the available search record.

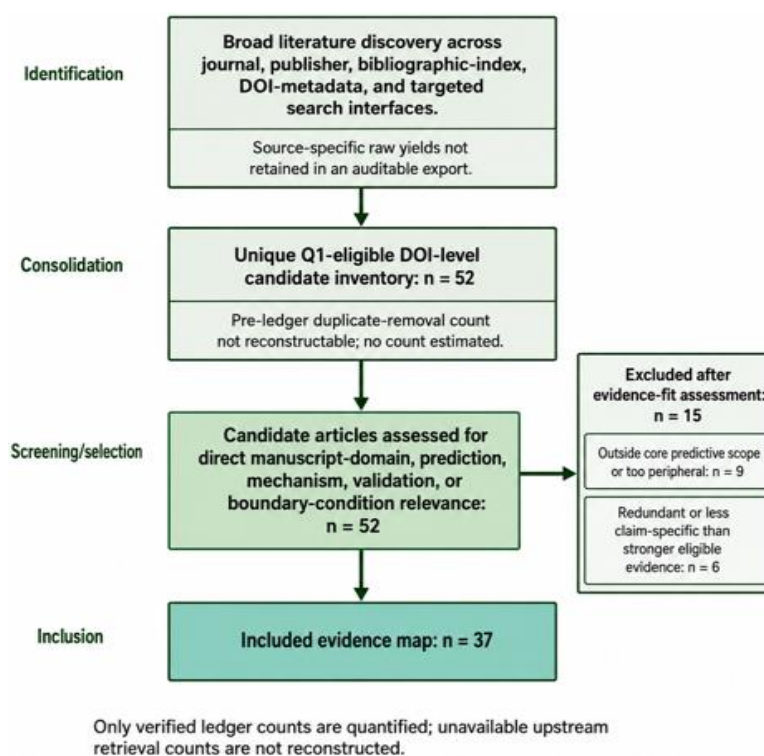


Figure 1. Verified evidence-selection flow from DOI-level consolidation to the pharmaceutical nanocrystal evidence map

The complementary accounting and reporting boundaries are summarized in **Table 1**.

Table 1. Verified search-selection accounting and reporting boundaries of the evidence map

Review stage	Verified result	Selection logic	Reporting boundary
Literature discovery	Broad multi-interface search	Nanocrystal prediction, processing, stability, dissolution, oral performance, validation	Raw source-specific yields not auditable
DOI-level consolidation	52 unique candidates	Eligible journal, year, DOI, Q1 status, direct claim relevance	Pre-ledger duplicate count not reconstructed
Evidence-fit assessment	52 assessed	Exact role in a scientific claim, mechanism, method, limitation, or validation question	Adjacent evidence retained only when analytically necessary
Scope/fit exclusions	15 excluded	9 peripheral/outside core predictive scope; 6 redundant or less claim-specific	No exclusion category inferred beyond screened rationales
Final inclusion	37 articles	Evidence suitable for at least one mapped development or validation domain	Inclusion does not imply equal methodological strength
Temporal profile	25 from 2024–2026; 12 from 2017–2023	Recent evidence prioritized without discarding necessary foundations	Publication year is not treated as evidence quality

Note: Counts describe the verified evidence-selection ledger. The table does not reconstruct unavailable upstream retrieval or duplicate-removal counts.

Protocol and reporting framework

The work was conducted as an evidence-mapping review rather than a systematic effectiveness review or meta-analysis. Its purpose was to characterize where predictive modeling has been applied within pharmaceutical nanocrystal development, how prediction tasks differ, and which validation boundaries constrain interpretation. Reporting was organized according to PRISMA-ScR-compatible principles for transparent identification, screening, eligibility, and inclusion [6].

Predictive modeling was operationalized broadly enough to capture direct machine learning together with semi-mechanistic, population-balance, molecular-simulation, empirical response-surface, Quality-by-Design, and biopharmaceutic modeling when defined inputs or mechanistic assumptions were used to anticipate a pharmaceutical endpoint. Pure formulation-performance studies were retained only when they established a mechanism, analytical limitation, validation condition, or transferability boundary required to interpret predictive evidence.

Because model types and endpoints were heterogeneous, pooled accuracy estimation was inappropriate. Particle-size prediction, milling kinetics, stabilizer ranking, physical stability, dissolution, flux, and oral exposure were treated as distinct predictive tasks rather than converted into a single comparative performance scale.

Eligibility criteria

Eligible records were peer-reviewed journal articles published from 2017 through 2026 with a verifiable DOI and Q1 status in a relevant subject category where quartile verification was available. Each article had to contribute directly to particle engineering, stabilizer behavior, process control, physical stability, dissolution or supersaturation,

solid-state behavior, oral performance, modeling methodology, validation, uncertainty, or transferability.

Conference papers, preprints, theses, patents, non-peer-reviewed material, duplicate versions, and records outside the publication window were excluded. Adjacent nanoparticle or suspension literature was retained only where its predictive construct directly addressed a prespecified nanocrystal-domain question.

Information sources and search strategy

Searches were completed in August 2026 using bibliographic-indexed records, publisher platforms, DOI and metadata services, targeted journal searches, and supplementary web-based discovery used to resolve titles, DOIs, publication details, and topical variants. Search concepts combined pharmaceutical nanocrystals and nanosuspensions with predictive modeling, machine learning, wet milling, precipitation, particle-size distribution, stabilizers, surface interactions, aggregation, physical stability, dissolution, supersaturation, permeation, solid-state transformation, oral absorption, bioavailability, in-silico modeling, validation, uncertainty, and transferability.

Boundary-oriented terms included model failure, external validation, media dependence, species effects, scale-up, redispersion, precipitation, and measurement interference. Source-specific raw retrieval counts were not retained in an auditable database-export format and were not retrospectively reconstructed.

Evidence selection

Records were consolidated at the DOI level and screened for publication eligibility and exact manuscript relevance. The formal evidence-fit inventory contained 52 unique Q1-eligible candidates. Each article was assessed for whether

it could support a specific scientific claim, methodological choice, uncertainty source, validation problem, or transferability boundary rather than merely mentioning pharmaceutical nanocrystals.

Fifteen candidates were excluded after evidence-fit assessment. Nine were outside the core predictive scope or too peripheral to the mapped questions, while six were redundant or less claim-specific than stronger eligible evidence. The final evidence map contained 37 included articles. No unavailable-full-text count was assigned because the verified ledger did not establish such a category.

Data charting and taxonomy development

For each included article, charting captured publication year, study design, pharmaceutical material or compound space, process or analytical context, data source, prediction task, model or analytical method, comparator where applicable, validation design, reported outcome, uncertainty source, stated limitation, and transferability boundary. Additional coding assigned the primary development domain: particle engineering, stabilization, process control, physical stability, dissolution or supersaturation, solid-state behavior, oral performance, or cross-cutting methodology.

Model family was coded independently from prediction target. Machine learning was not treated as a development stage, and mechanistic modeling was not assumed to confer stronger external prediction. Validation was similarly separated into internal evaluation, experimental agreement, cross-condition or cross-material transfer, biorelevant testing, and in-vivo correspondence where reported.

The resulting taxonomy is a proposed evidence-organization scheme. Missing fields remained not reported or not applicable rather than being inferred from related studies.

Mapping and synthesis approach

Synthesis proceeded along two intersecting dimensions. The first followed development from particle formation and size control through stabilization, process transformation, physical stability, dissolution and supersaturation, solid-state behavior, and oral performance. The second followed the epistemic structure of prediction: which inputs were represented, which endpoint was predicted, which model class connected them, and what validation established the permissible scope of interpretation.

This approach does not assume that nanocrystal development forms a fully linear predictive pipeline. A particle-size model can perform well within a milling domain without establishing storage stability; a stability

predictor can classify size drift without identifying its mechanism; and a dissolution model can describe concentration behavior without establishing oral exposure. Later observations can therefore reveal missing upstream state information.

Evidence density is interpreted descriptively. Greater representation around a task indicates greater concentration in the selected literature, not greater clinical importance or intrinsically stronger methodology.

Evidence-selection results

The final map contained 37 articles from the 52 DOI-level candidates entering evidence-fit assessment. Twenty-five included articles were published during 2024–2026, while earlier studies supplied foundational process concepts, analytical methods, direct early machine-learning evidence, Quality-by-Design reasoning, or translational comparisons not adequately replaced by newer work.

The major pattern was not a simple chronological replacement of empirical formulation by artificial intelligence. Predictive capability accumulated unevenly across development stages, with different modeling traditions forming around different pharmaceutical endpoints.

Predicting particle size and size distribution

Particle engineering was among the clearest predictive domains because milling provides controllable process inputs and directly measurable particle-size outputs. A semi-mechanistic wet-bead-milling framework demonstrated that temporal particle-size-distribution evolution could be represented rather than reduced to a terminal size measurement [7]. Population-balance modeling subsequently incorporated batch size, flow rate, and back-mixing, making hydrodynamic organization part of the predictive representation [8]. Mechanistic process modeling has also been connected to bounded manufacturing design-space and control-strategy development [9].

These approaches predict different aspects of size control. Population-level evolution, process trajectories, and manufacturing operating regions should therefore remain distinct evidence categories. Their shared limitation is transferability: adequate prediction within a particular mill, formulation, and operating range does not establish equivalent behavior for other equipment or material spaces.

Stabilizer selection and surface coverage

Stabilization introduces an interfacial level that particle-size models cannot resolve by themselves. Surface-bound stabilizer can be measured experimentally rather than inferred directly from bulk excipient concentration [10].

Surfactant–polymer competition at drug–nanocrystal interfaces can additionally affect crystallinity, linking stabilizer choice to material state [11].

Computational strategies increasingly move stabilizer selection upstream. Computer-aided molecular interaction and self-assembly analysis has been used to prioritize nanosuspension stabilizers before experimental testing [12]. Redispersion in biorelevant media nevertheless remains dependent on API, stabilizer, and medium [13]. Molecular-dynamics simulations provide molecular hypotheses for polymer–drug stabilization [14], whereas multi-criteria decision analysis coupled with solubility-parameter modeling has been experimentally evaluated for surfactant prioritization [15]. The literature therefore supports increasingly structured stabilizer selection without establishing a universal stabilizer recommender.

Process variables in milling and precipitation

Process prediction extends beyond nominal milling duration or energy input. Temperature-controlled laboratory milling demonstrates how process configuration itself can constrain variability during nanocrystal production [16]. High-throughput acoustic-resonance processing has linked nanosuspension preparation with scale-up and subsequent solidification in a defined formulation system [17], while milligram-scale media milling enables material-sparing development across several model drugs [18].

Process effects propagate beyond size. Milling conditions can alter morphology, thermal behavior, and dissolution together, meaning that a model restricted to final particle diameter can omit downstream material consequences [19]. Bottom-up nanocrystallization provides another predictive tradition in which Quality-by-Design and Design-of-Experiments approaches define bounded response relationships among formulation factors, process variables, and measured nanocrystal attributes [20]. These response surfaces remain conditional on the investigated design space.

Aggregation and physical stability

Physical stability is a distinct prediction problem because a successfully produced nanosuspension can change through aggregation, sedimentation, Ostwald ripening, redispersion failure, or solid-state alteration. Machine learning has been applied to structured pharmaceutical suspension datasets to connect formulation and process variables with particle characteristics and stability-related behavior [21]. More recent work has made size stability itself a quantified prediction target and evaluated machine-learning approaches against that operational endpoint [22]. These studies extend prediction downstream from production, but their formulation domains cannot

automatically be generalized to all oral nanocrystals. Aggregation, Ostwald ripening, sedimentation, and solid-state changes additionally arise through different physicochemical pathways [23]. The evidence map therefore avoids treating “stability” as one undifferentiated label when a study addresses a specific failure mode.

Dissolution and supersaturation prediction

Dissolution introduces measurement uncertainty in addition to formulation uncertainty. In-situ ultraviolet–visible analysis of nanosuspensions illustrates how particulate systems complicate optical concentration measurement and require methods able to discriminate relevant signal components [24]. Coupled dissolution/permeation approaches provide different information by separating suspended drug from molecularly available drug and examining transfer across a membrane system [25].

Evaluation conditions are themselves predictive boundaries. Dissolution media and sink conditions can change whether differences among nanocrystal systems remain experimentally discriminating [26]. Enhanced dissolution likewise does not imply identical supersaturation or permeation behavior across compounds; combined dissolution/permeation studies demonstrate compound-dependent trajectories [27].

Accordingly, dissolution rate, apparent concentration, molecularly dissolved drug, supersaturation, precipitation, and permeation are treated as related but non-interchangeable endpoints. Validation against one cannot automatically be transferred to another.

Solid-state transformation during processing and storage

The physical state entering a nanocrystal process cannot be assumed to remain unchanged throughout downstream handling. Wet-media milling followed by solidification of aprepitant nanocrystals demonstrated that production must be evaluated together with subsequent solid-state and redispersion behavior [28]. This aligns with earlier evidence that interfacial composition and milling conditions can influence crystallinity, morphology, and thermal characteristics.

Particle size is therefore an important state descriptor but not a complete material-state representation. Models intended to extend across manufacture and storage may need to represent crystal form, interfacial composition, drying history, and redispersion where these variables are decision-relevant. The available evidence does not establish that milling or solidification produces one universal transformation pathway.

Table 2 compares the study characteristics encountered from particle engineering through solid-state assessment

and emphasizes how validation boundaries change across development stages.

Table 2. Study characteristics defining predictive evidence from particle engineering to solid-state behavior

Development problem	Evidence design encountered	Principal endpoint	Main validation boundary
Size control	Semi-mechanistic and population-balance modeling	Particle-size distribution	Equipment and calibration domain
Stabilizer selection	Interface experiments, molecular simulation, predictive screening	Coverage or stabilizer performance	API–excipient chemical space
Milling	Controlled processing and mechanistic modeling	Size and process trajectory	Mill configuration and operating range
Precipitation	DoE/QbD response modeling	Bounded formulation/process response	Experimental factor space
Physical stability	Experimental datasets with ML	Size change or stability class	Formulation and storage domain
Dissolution	Spectroscopic and dissolution/permeation methods	Molecular availability and transfer	Medium and analytical conditions
Solid-state behavior	Milling/solidification characterization	Crystallinity, morphology, redispersion	Drug and downstream process

Note: Categories summarize characteristics of the included evidence and are not equivalent measures of predictive performance.

Oral exposure and bioavailability models

Late-stage prediction requires biological and physiological information not contained in particle size alone. In coated nintedanib nanocrystals, maintenance of supersaturation accompanied improved oral bioavailability in the studied formulation, supporting supersaturation as a formulation-specific translational variable rather than a universal surrogate [29]. An in vitro–in vivo investigation further showed that permeation-related measurements can relate to absorption behavior under defined compound and animal conditions [30].

Colloidal transport introduces another boundary. Particle-drifting behavior changes with dose and animal species, demonstrating that an apparently formulation-intrinsic phenomenon can depend on the in-vivo context [31]. Direct translational modeling has combined biorelevant flux measurements with mechanistic in-silico analysis to predict the in-vivo performance of piroxicam and apalutamide nanocrystals [32]. This supports the feasibility of downstream predictive integration while remaining limited by the compounds and validation settings examined.

Machine learning versus mechanistic nanocrystal models

Mechanistic and machine-learning approaches answer different questions. Particle-drifting analysis connects colloidal and drug properties to transport behavior through a mechanistic representation [33]. Quality-by-Design supplies another form of predictive reasoning by linking defined process variables and product attributes within bounded operating regions [34]. General pharmaceutical formulation machine learning instead learns associations from encoded development data and introduces specific

questions about dataset size, representation, interpretability, and validation [35]. Contemporary nanoparticulate drug-delivery literature extends these concerns to data quality and generalization across formulation systems [36].

No model family is therefore ranked intrinsically above another. Mechanistic transport modeling, general formulation-machine-learning frameworks, and contemporary nanoparticulate-machine-learning syntheses represent analytically distinct sources of predictive reasoning [33, 35, 36]. The relevant comparison is whether a model's structure, input data, validation strategy, and uncertainty characterization match its intended pharmaceutical decision.

Distribution of evidence across development stages, 2017–2026

The distribution of evidence was strongly stage-dependent. Representative predictive studies included direct machine-learning prediction of nanocrystal formulation outcomes, semi-mechanistic wet-milling prediction, and machine-learning analysis of pharmaceutical suspension formulation and stability [3, 7, 21]. Prediction has therefore entered several stages without becoming a continuous end-to-end development architecture.

Experimental scales were also heterogeneous. Some models were calibrated to particular milling equipment; others encoded molecular drug–stabilizer interactions; still later approaches incorporated biorelevant media, permeation or flux, animal observations, or mechanistic simulations. The evidence map therefore places validation proximity to the intended decision alongside model family. A sophisticated particle-size model remains an upstream

model if its target is particle engineering, whereas a simpler biopharmaceutic representation may operate closer to an oral-performance decision.

Where predictive models are concentrated

Within the included literature, prediction was concentrated where inputs and outputs are experimentally structured: milling variables, particle-size distributions, stabilizer choices, bounded process spaces, and physical size stability. Such tasks provide repeated measurement and comparatively direct encoding of formulation–response relationships.

Evidence becomes less continuous when outcomes depend simultaneously on formulation state and changing physiological conditions. Dissolution depends on medium and sink conditions; supersaturation can be lost through precipitation; permeation is compound dependent; and colloidal transport may vary with biological context. Late-stage prediction is therefore not simply a harder version of particle-size modeling. It requires richer state

representation and validation across additional experimental levels.

Where the evidence map remains empty

The clearest gap is continuity between stages. Few included studies connect particle engineering, storage stability, dissolution or flux, and oral performance within one prospectively tested predictive chain. Cross-API, cross-equipment, cross-laboratory, and cross-biological-context evaluation is also limited. Outcome definitions add another discontinuity: apparently similar “stability” or “dissolution” models may predict different physical quantities.

These observations identify sparse transitions within the selected evidence base rather than proving absence of relevant work outside the review boundaries. **Table 3** makes the principal discontinuities explicit without converting qualitative evidence density into fabricated bibliometric frequencies.

Table 3. Evidence-map concentration and unresolved transitions across nanocrystal development

Development region	Evidence-map pattern	Underrepresented transition	Principal validation deficit
Particle engineering	Comparatively concentrated	Size prediction → downstream material state	Cross-equipment transfer
Stabilization	Growing computational and experimental integration	Molecular ranking → durable formulation stability	External chemical-space validation
Physical stability	Emerging explicit predictive endpoints	Short-term size behavior → storage robustness	Cross-condition validation
Dissolution/supersaturation	Strong analytical grounding, heterogeneous endpoints	Concentration behavior → transferable drug	Harmonized endpoint validation
Oral performance	Sparse integrated prediction	In-vitro/flux behavior → organism-level exposure	Cross-compound and biological transfer
End-to-end development	Very sparse in mapped corpus	Engineering → stability → biopharmaceutics	Prospective multistage validation

Note: “Comparatively concentrated,” “growing,” “sparse,” and “very sparse” are qualitative evidence-map descriptors, not performance rankings or formal bibliometric frequencies.

Model validation and translation into formulation decisions

Biorelevant in-vitro experimentation has been combined with in-silico analysis to examine fasted and fed performance of a nanosized aprepitant formulation, demonstrating how formulation behavior can be interrogated under physiologically differentiated conditions [37]. Together, compound-specific studies indicate that biorelevant measurements coupled to in-vivo or in-silico absorption analysis can provide translational tests of nanocrystal performance [30, 32, 37].

This review therefore proposes a decision-matched validation principle. Internal predictive accuracy, cross-formulation transfer, mechanistic consistency, biorelevant agreement, and in-vivo correspondence answer different

validation questions and should not be treated as a mandatory universal ladder. A milling model intended for process control need not demonstrate organism-level correspondence, whereas a model used to infer oral performance requires evidence extending beyond particle-size accuracy.

The manuscript-wide synthesis is shown in **Figure 2**. The figure separates the pharmaceutical states being predicted, the model families used to represent them, and the validation boundaries that determine how far a prediction can reasonably be translated; dashed cross-stage connectors identify the proposed integration required for an end-to-end framework rather than relationships already validated throughout the development chain.

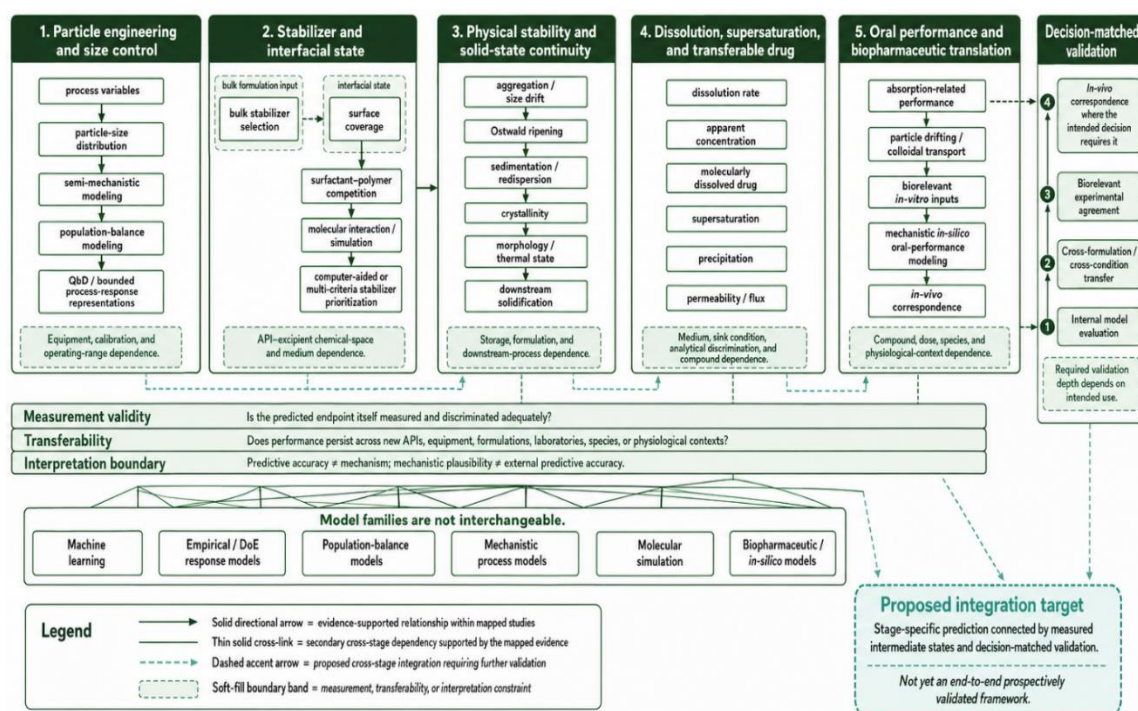


Figure 2. From stage-specific nanocrystal prediction to decision-matched validation across pharmaceutical development

RESULTS AND DISCUSSION

Across 2017–2026, pharmaceutical nanocrystal modeling evolved as a collection of stage-specific predictive practices rather than a unified computational discipline. The mapped evidence supports three central distinctions. First, the predicted pharmaceutical state matters: particle size, interfacial stabilization, physical stability, dissolution, supersaturation, molecularly available drug, and oral exposure cannot be substituted for one another. Second, model families encode different forms of prior information. Machine learning derives relationships from represented examples, whereas population-balance, mechanistic, molecular, QbD, and biopharmaceutic approaches introduce different structural assumptions. Third, validation must be interpreted relative to intended use.

The principal synthesis proposed here is therefore a stage-and-validation framework for nanocrystal prediction. It separates prediction-target fidelity from algorithmic sophistication and from translational proximity. This avoids two opposite errors: treating accurate empirical prediction as mechanistic proof and treating mechanistic plausibility as evidence of external predictive performance.

For formulation development, the implication is not that one modeling family should replace another. Models can instead be connected where intermediate pharmaceutical states are measured sufficiently well to justify a handoff

between stages. **Figure 2** makes this distinction explicit by treating multistage integration as a proposed target rather than an achieved capability. Prospective testing across chemical, process, analytical, and biological contexts remains necessary before an integrated architecture could be regarded as broadly transferable.

Review limitations

The evidence map was deliberately restricted by publication period, journal eligibility, DOI verification, and direct relevance to the defined pharmaceutical prediction domains. Potentially informative work outside those boundaries was therefore not used to fill sparse regions. Terminology also varied across nanocrystals, nanosuspensions, colloidal drug particles, and broader nanoparticulate formulation research, requiring bounded use of adjacent evidence.

Heterogeneity in endpoints, algorithms, experimental platforms, compounds, and validation designs prevented a meaningful pooled comparison of predictive accuracy. Raw source-specific retrieval and pre-ledger duplicate counts were not reconstructable from an auditable export and were not estimated. Several model classes were represented by system-specific demonstrations rather than extensive external validation.

Table 4 summarizes the thematic interpretation rules that follow from these limitations and from the cross-stage evidence synthesis.

Table 4. Proposed thematic categories for interpreting predictive nanocrystal evidence

Proposed theme	Interpretation	Required boundary
Target fidelity	Judge performance against the endpoint actually predicted	Do not substitute adjacent endpoints
Context specificity	Retain API, process, medium, and biological conditions	Do not assume unrestricted transfer
Measurement validity	Establish that the reference endpoint is adequately discriminating	Do not label measurement ambiguity as model failure
Mechanism–prediction separation	Distinguish explanatory structure from empirical accuracy	Neither establishes the other automatically
Decision proximity	Match validation depth to the intended formulation decision	Internal accuracy is not translational validation
Multistage integration	Connect stages through measured or justified intermediate states	Treat end-to-end capability as proposed until tested

Note: These categories are an original proposed synthesis of the mapped evidence and are not presented as a validated regulatory or implementation framework.

CONCLUSION

Predictive modeling of pharmaceutical nanocrystals now spans particle engineering, interfacial stabilization, process control, physical stability, dissolution, biopharmaceutics, and oral-performance questions, but these domains remain unevenly connected. The principal finding is therefore not the emergence of one dominant algorithm; it is the coexistence of different prediction targets, model logics, and validation depths across nanocrystal development.

A useful model should consequently be interpreted according to the pharmaceutical state it predicts and the decision for which it has been validated. The proposed stage-and-validation framework organizes these distinctions without implying universal transferability or end-to-end predictive readiness. Progress toward integrated prediction requires better-defined endpoints, cross-context validation, and experimentally justified connections between successive formulation states.

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