



Review Article

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Amorphous Solid Dispersions Across the Stability–Performance Trade Space

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ABSTRACT

Amorphous solid dispersions (ASDs) are commonly developed to increase the apparent solubility and dissolution of poorly water-soluble drugs, yet formulation success cannot be defined by amorphization or physical stability alone. Polymer selection, drug loading, molecular interactions, moisture exposure, hydrated-state phase behavior, precipitation, downstream dosage-form composition, and absorptive flux can alter stability and performance in different directions. This systematic review examines ASDs as formulations occupying a multidimensional stability–performance trade space. The aim is to distinguish evidence supporting physical stabilization, supersaturation generation, dissolution, absorption-relevant drug availability, and translational performance from assumptions that these outcomes necessarily improve together. Peer-reviewed literature published from 2017 through 2024 was systematically screened using predefined eligibility, evidence-extraction, and quality-appraisal criteria. Evidence was separated by analytical level, including molecular and polymer attributes, physical stability, hydrated-state phase behavior, dissolution and supersaturation, dosage-form effects, and biopharmaceutic translation. Selection arithmetic was maintained in the review ledger without substituting reference-list size for included-evidence counts. The literature demonstrates no universal correspondence between maximal ASD stability and maximal pharmaceutical performance. Polymer–drug interactions may suppress crystallization yet retard release, while in other systems persistent interactions stabilize supersaturation. Drug loading can produce abrupt transitions from congruent release toward phase-separated or drug-rich surface states. Moisture, process history, nanoscale heterogeneity, downstream tableting excipients, dissolution conditions, and absorption sinks further modify apparent performance. These findings support a state-dependent interpretation in which storage stability, hydration behavior, supersaturation, precipitation, and absorption-relevant drug availability are related but analytically non-equivalent endpoints. ASD development is more appropriately treated as selection within a conditional stability–performance trade space than as optimization of a single stability or dissolution metric. Formulation decisions require explicit separation of stored-state stability, hydrated-state transformations, release mechanisms, and downstream biopharmaceutic relevance.

Keywords: Amorphous solid dispersion, Physical stability, Drug–polymer interactions, Supersaturation, Dissolution, Biopharmaceutics

INTRODUCTION

Amorphous solid dispersions improve the thermodynamic activity of poorly soluble drugs by maintaining the active pharmaceutical ingredient in a high-energy noncrystalline state, but the same formulation variables that resist crystallization can also alter drug liberation after contact with aqueous media. In lumefantrine ASDs, polymer selection changed both crystallization resistance and dissolution, demonstrating that the most strongly stabilized dispersion was not automatically the most rapidly releasing formulation [1]. Controlled destabilization

studies likewise showed that increasing stability may become counterproductive when matrix properties impede release, establishing stability and dissolution as potentially competing rather than obligatorily aligned objectives [2]. The hydrated state further introduces supersaturation, liquid–liquid phase separation, precipitation, polymer partitioning, and colloidal drug-rich phases that cannot be inferred simply from the presence of an amorphous starting material [3].

Storage stability itself is conditional. Polymer identity and relative humidity alter long-term crystallization risk, showing that “stable” is meaningful only with respect to a defined formulation, temperature, moisture environment, and time horizon [4]. Nor can dissolution concentration be interpreted automatically as absorption-relevant drug availability. Experiments linking ASD dissolution, speciation, membrane transport, and preclinical absorption demonstrated that molecularly dissolved drug, colloidal or drug-rich species, and precipitated material can contribute differently to mass transport [5].

Drug loading provides another source of nonlinearity. A range of compositions can support congruent release of drug and polymer, whereas increased loading may move a formulation into a qualitatively different release regime rather than producing a gradual decrement in performance [6]. Phase homogeneity can also alter the relation between dissolution and systemic exposure: in a felodipine/PVPVA system, inhomogeneity reduced preclinical bioavailability despite dissolution behavior that could not be interpreted through concentration ranking alone [7]. More recently, absorption-coupled dissolution experiments showed that removing permeable drug from the medium can alter supersaturation, precipitation, and formulation ranking compared with conventional nonabsorptive testing [8].

The inferential problem is therefore broader than asking whether an ASD remains amorphous or dissolves rapidly. The relevant question is whether a particular composition occupies an acceptable region in which storage stability, chemical integrity, hydrated-state release, supersaturation persistence, dosage-form behavior, and absorption-relevant availability remain compatible under the intended product and physiological conditions. This review consequently treats the stability–performance trade space as a proposed organizing construct rather than an established universal model. Evidence derived at molecular, formulation, dissolution, and preclinical levels is kept distinct, and disagreement among studies is interpreted through differences in polymer chemistry, drug physicochemistry, loading, water exposure, phase morphology, assay conditions, and translational level.

MATERIALS AND METHODS

The review was structured according to PRISMA 2020 reporting principles for identification, screening, eligibility, and inclusion [9]. Searches covered literature published from 2017 through 2024 and were constructed around amorphous solid dispersions combined with terms addressing polymer–drug interaction, physical and chemical stability, crystallization, moisture, phase separation, drug loading, dissolution, supersaturation, precipitation, bioavailability, absorption, and biorelevant testing.

Evidence was classified before synthesis according to its principal analytical level. Primary experimental studies were separated from computational studies, methodological investigations, translational studies, and contextual reviews. This prevented evidence derived from molecular interaction measurements, bulk solid-state characterization, dissolution testing, permeability models, or in vivo exposure from being treated as interchangeable.

Protocol and eligibility criteria

Eligible primary evidence required an ASD-specific formulation or drug-product context and information directly relevant to at least one prespecified domain: polymer or drug attributes, physical or chemical stability, hydrated-state transformation, supersaturation or dissolution, precipitation, dosage-form performance, or biopharmaceutical translation. Publications were restricted to the defined 2017–2024 period and peer-reviewed journal literature.

Studies were retained only when the ASD-specific result could be separated from broader amorphous-formulation observations. Methodological and review articles were used when they established assay interpretation, evidence boundaries, or review context; they were not assumed to represent primary formulation evidence simply because they addressed ASDs. Computational compatibility or stability studies were similarly distinguished from experimentally validated performance evidence.

Search strategy and study selection

The source strategy comprised PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, and supplementary backward or forward citation identification. Search logic combined the phrases “amorphous solid

dispersion” or “amorphous solid dispersions” with terms covering stability, crystallization, phase separation, dissolution, supersaturation, precipitation, bioavailability, absorption, drug loading, polymer properties, drug–polymer interactions, and biorelevant dissolution.

Source-specific retrieval, deduplication, title/abstract screening, report retrieval, full-text assessment, exclusion reasons, and final inclusion were reconciled in the selection ledger. The reference list was treated separately from the number of eligible evidence units so that methodological or contextual citations did not alter the systematic-review inclusion arithmetic.

Data extraction and quality appraisal

Extraction was designed around the transition from the stored dispersion to the hydrated and potentially absorbing system. For each study, the extracted variables included drug and polymer identity, drug loading, manufacturing or processing context, physical-state evidence, molecular or microstructural characterization, storage condition, dissolution environment, phase or precipitation behavior, comparator, analytical method, and the level at which a performance inference was made.

Quality appraisal was mechanism-sensitive rather than score-based. A claim of physical stability required evidence appropriate to crystallinity, phase separation, or molecular heterogeneity rather than reliance on a single bulk descriptor. Dissolution evidence was appraised according to sink state, medium, pH trajectory, polymer release, phase behavior, precipitation, and whether the method was intended for quality control or biopharmaceutical interpretation. Translational claims were additionally bounded by species, absorption model, permeability assumptions, and availability of in vivo comparison.

The central extraction distinction was between observation and inference. A decline in dissolved concentration, for example, could arise from surface crystallization, phase separation, matrix-controlled drug retention, precipitation after supersaturation, or changes in absorption-driven depletion. Conversely, persistence of apparent supersaturation could reflect molecularly dissolved drug or drug-rich colloidal species with different implications for membrane transport. The resulting appraisal therefore asked not only what was measured, but which competing mechanism remained compatible with the measurement.

These distinctions are compressed in **Table 1** because a linear description cannot show simultaneously how phase state, temporal behavior, competing explanations, and the test needed to discriminate them constrain interpretation.

Table 1. Mechanism-discrimination matrix for interpreting stability and performance observations in amorphous solid dispersions

Manuscript-derived case	Observable drug phase or availability	Characteristic time dependence	Inference that cannot be made from the observation alone	Discriminating evidence required	Consequence for the stability–performance assessment
Stored ASD remains X-ray amorphous while molecular mixing changes	Bulk amorphous signal with possible submicrometre heterogeneity	Develops during processing or storage	Bulk amorphousness does not establish molecular homogeneity	Spatial or molecular-resolution characterization combined with stability follow-up	Physical-state confidence remains conditional on heterogeneity and storage history
Moisture exposure produces demixing before detectable crystallization	Amorphous but compositionally heterogeneous drug-rich and polymer-rich regions	Emerges with water uptake and storage time	Absence of crystals does not establish structural stability	Moisture-controlled microstructure analysis and subsequent crystallization/release testing	Phase separation becomes a distinct failure mode
Hydrated matrix releases polymer and drug at different rates	Dissolved drug plus drug retained in or enriched at the dissolving surface	Evolves during wetting and matrix erosion	Reduced release cannot be assigned automatically to low intrinsic drug solubility	Drug/polymer release measurements with surface or phase-state characterization	Stabilization may become a kinetic release constraint
Supersaturation generates drug-	Molecular drug coexists with colloidal or	Often transient and	Apparent concentration does not equal	Speciation or particle characterization alongside dissolution	Performance interpretation must separate

rich dispersed species	liquid drug-rich phase	composition dependent	molecularly available drug		concentration from drug phase
Supersaturation collapses during the dissolution experiment	Dissolved drug decreases as precipitated or crystallized material appears	Induction-time dependent	Concentration decline does not identify the precipitation pathway or its origin	Time-resolved solid/solution analysis under defined hydrodynamics and medium	Precipitation resistance becomes part of performance, not merely initial release
Absorption or permeation removes soluble drug while dissolution continues	Continuously depleted absorbable fraction with dynamic replenishment	Coupled to dissolution and membrane flux	A nonabsorptive dissolution profile need not preserve in vivo rank order	Absorption-coupled or dissolution-permeation experiment qualified for the product	Biopharmaceutic relevance depends on flux as well as supersaturation

Because evidence entered the synthesis only after source resolution, deduplication, eligibility assessment, and mechanism-sensitive appraisal, the review flow is best read together with the analytical gates applied to the included evidence.

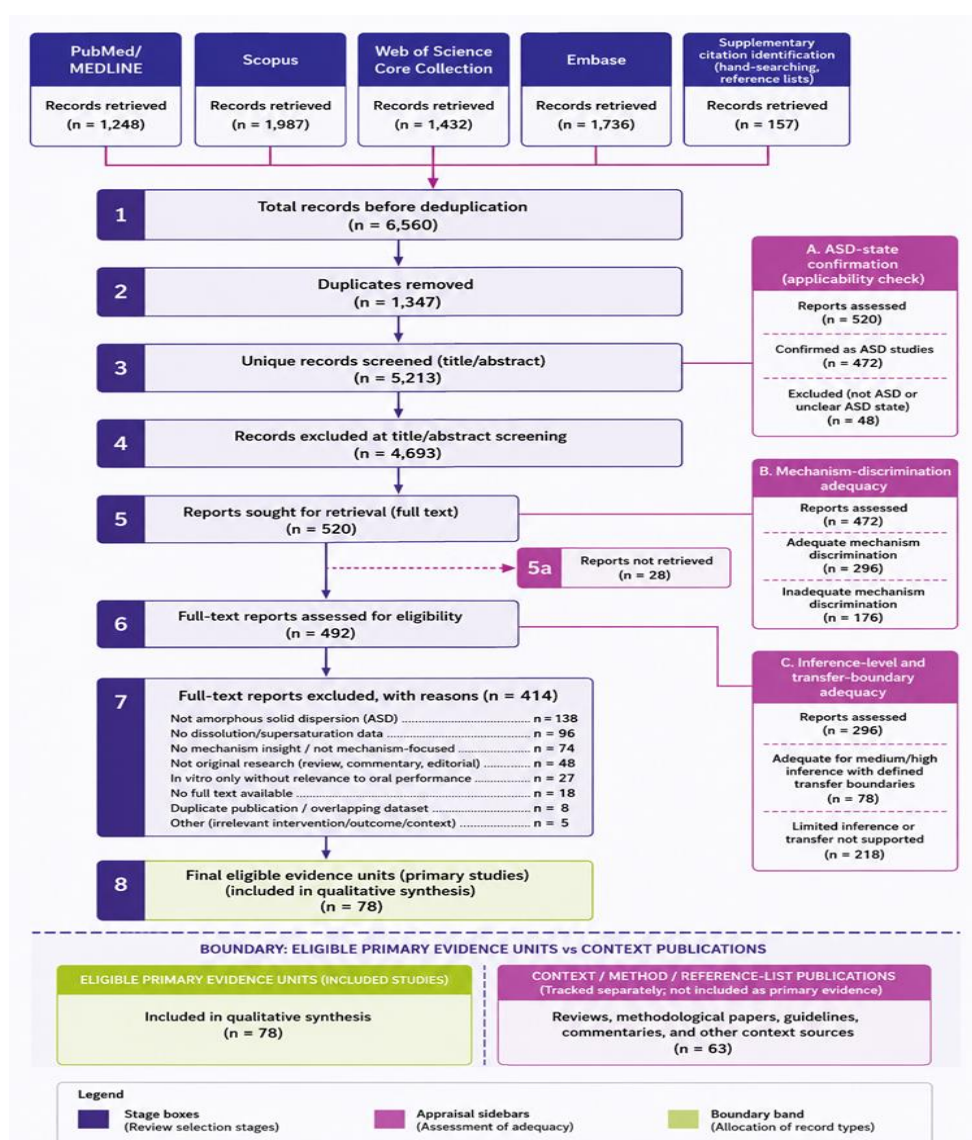


Figure 1. Source Resolution and Mechanistic Appraisal Gates Governing Entry of ASD Evidence into the Stability-Performance Synthesis

RESULTS AND DISCUSSION

The eligible evidence occupied several analytical layers rather than a single homogeneous study class. Experimental formulation studies examined molecular interactions, crystallization resistance, drug loading, moisture, phase separation, release, supersaturation, and downstream dosage-form behavior. Other publications evaluated modeling approaches, analytical discrimination, biorelevant dissolution, absorption-coupled testing, or product-specific translational performance. The synthesis therefore emphasizes mechanistic convergence and disagreement rather than treating unlike outcomes as directly commensurable.

Across these layers, three distinctions repeatedly governed interpretation. First, a formulation can be physically stable during storage yet release drug inefficiently after hydration. Second, the hydrated phase can reorganize into surface-enriched, phase-separated, colloidal, or crystalline states that were absent in the stored material. Third, dissolution concentration is not automatically equivalent to the fraction of drug available for absorptive transport. These distinctions structure the following results.

Polymer and drug attributes

Polymer selection changes more than glass-transition temperature. Comparative work showed that polymer functionality and drug–polymer miscibility can alter crystallization inhibition in ways not captured by a simple Tg-centered explanation [10]. Polymer hydrophobicity can likewise influence both solid-state stability and maintenance of supersaturated solution, although the direction observed in one drug–polymer system should not be converted into a universal hydrophobicity rule [11].

Analytical resolution also matters. Solid-state nuclear magnetic resonance can identify molecular mixing and specific drug–polymer associations that bulk measurements may obscure [12]. Such evidence establishes interaction or proximity, however, not that the interaction necessarily improves release or absorption. Physical and chemical stability must likewise remain distinct: in carbamazepine ASDs, polymer-related effects on crystallization resistance and chemical degradation did not collapse into one common stability outcome [13].

The trade space is therefore not inevitably restrictive. Electrospinning of flubendazole with a compatible polymer produced a high-loading ASD that remained amorphous while improving dissolution, demonstrating that polymer–process selection can shift the feasible formulation region rather than merely choose between two losses [14]. Polymer chemistry may similarly be designed around hydrated-state performance. Modified poly(vinylpyridine) excipients supported rapid posaconazole release together with sustained supersaturation in the studied formulations [15].

The opposite pattern is also mechanistically credible. With HPMCAS-based ASDs, strong hydrated drug–polymer association could restrict drug release despite physicochemical conditions otherwise favorable for dissolution [16]. Thus “strong interaction” is not intrinsically a favorable formulation descriptor; its meaning depends on where the interaction operates and whether it stabilizes the amorphous solid, retains drug within the hydrated matrix, or stabilizes drug after release.

Computational compatibility methods provide an upstream filter rather than proof of product performance. COSMO-SAC-based predictions can prioritize drug–polymer combinations and identify phase-separation tendencies within their validation domain, but equilibrium compatibility does not by itself resolve crystallization kinetics, processing history, hydrated-state transformation, dissolution, or exposure [17].

The failure modes produced by these attributes are easier to compare by beginning with the misleading inference rather than with polymer classes. **Table 2** therefore organizes attribute evidence around the diagnostic error it can create.

Table 2. Attribute-Driven Failure Modes That Can Misclassify an ASD’s Position in the Stability–Performance Trade Space

Misleading formulation pattern	Polymer/drug comparison anchor	Biorelevant or hydrated-state readout needed	Release or availability consequence	Plausible failure mechanism	Corrective article-level test
High Tg interpreted as sufficient evidence of stability	Polymer functionality, miscibility and interaction environment	Storage behavior under relevant humidity and temperature	May remain stable or fail despite similar bulk Tg	Mobility is only one contributor to nucleation, mixing and phase behavior	Verify molecular compatibility and time-dependent crystallization rather than ranking by Tg alone

Polymer hydrophobicity treated as a universal optimization axis	Drug hydrophobicity relative to polymer aqueous affinity	Supersaturation maintenance and polymer behavior after hydration	Can favor solution stabilization in one system yet impede hydration or release in another	Competing drug affinity, water uptake and polymer partitioning effects	Test both solid-state and aqueous-state consequences for the actual API–polymer pair
Strong drug–polymer interaction assumed automatically beneficial	Interaction strength and persistence before and after hydration	Drug liberation from hydrated matrix plus supersaturation persistence	May suppress crystallization, retard release, or do both under different conditions	Interaction location changes from stored matrix to aqueous environment	Distinguish dry-state stabilization from hydrated-state drug availability
“Stable ASD” defined only through crystallization resistance	API chemical liability and polymer microenvironment	Chemical assay during stability study	Physical stability may coexist with chemical degradation	Polymer microenvironment alters reaction pathway independently of crystallization	Track physical and chemical stability as separate failure states
High drug loading presumed inherently incompatible with acceptable performance	Drug loading combined with polymer/process compatibility	Release congruence and phase behavior across loading	High loading may succeed or may cross a nonlinear release boundary	Process-dependent mixing and composition-dependent hydrated morphology	Establish formulation-specific loading boundary rather than a universal cutoff
Good dry-state compatibility treated as evidence of efficient release	Polymer aqueous compatibility and ionization environment	Polymer/drug release, supersaturation and phase speciation	Strong matrix association may become a release bottleneck	Persistent complexation or slow polymer hydration	Re-characterize interaction in the hydrated state
Computational compatibility treated as final formulation selection	Model-predicted drug–polymer compatibility	Empirical stability and dissolution under intended conditions	Predicted miscibility need not establish kinetic or biopharmaceutical performance	Model omits kinetics, process history or hydrated-state transformations	Use computation for prioritization followed by experimental confirmation

Physical stability

Physical stability is not adequately represented by the presence or absence of detectable crystals. Water can induce phase separation in spray-dried ASDs, creating drug-rich and polymer-rich domains before or independently of obvious crystallization [18]. Such microstructural changes matter because the route from a homogeneous glass to a phase-separated glass may subsequently alter both crystallization probability and hydrated-state release.

Analytical scale further modifies what “homogeneous” means. Spin-diffusion NMR demonstrated that pharmaceutical dispersions classified as amorphous by bulk methods can contain process-dependent heterogeneity below 100 nm [19]. The observation does not establish that nanoscale heterogeneity will necessarily impair a product; rather, it identifies a hidden structural variable whose relevance requires correlation with storage or release outcomes.

Crystallization is also kinetic. Time–temperature–transformation analysis showed that drug–polymer interactions can shift crystallization times and thermal stability windows [20]. Long-duration studies coupling water sorption with crystallization further demonstrated that API, polymer, drug loading, temperature, and humidity jointly determine observed stability [21]. Modeling of those coupled processes can support long-term stability estimation when calibrated within an appropriate formulation domain, but it does not eliminate the need for external validation outside that domain [22].

The final drug product adds another layer. Diluent choice during tableting can alter compaction behavior, dissolution, and recrystallization tendency, meaning that a robust ASD intermediate is not guaranteed to preserve the same stability–performance balance after conversion into a tablet [23]. Additional polymers, surfactants, and other ternary excipients can likewise modify stability and release in different directions, with effects dependent on the API, primary polymer, additive, processing history, and dissolution environment [24].

Physical stability should therefore be treated as a set of failure modes—crystallization, phase separation, chemical deterioration, nanoscale heterogeneity of uncertain consequence, and dosage-form-induced change—rather than a single binary property. Their practical importance depends on whether they alter the subsequent hydrated state and the drug fraction that becomes available for release.

Supersaturation and dissolution performance

Hydration is the point at which a formulation optimized for storage encounters a new thermodynamic and kinetic environment. Drug–polymer hydrogen bonding, surface crystallization, and the wet-state mobility of the matrix can govern whether drug and polymer release congruently or whether drug becomes retained or enriched at the dissolving surface [25]. Consequently, a stabilizing dry-state interaction cannot be assigned a fixed direction of effect once water enters the system.

Strong interactions are not uniformly release-limiting. In ketoconazole ASDs, persistent ionic drug–polymer interactions increased resistance to crystallization and supported sustained supersaturation [26]. The contrast with release-restricting systems indicates that interaction strength alone is an incomplete descriptor. What matters is whether the interaction prevents liberation from the matrix, stabilizes drug after liberation, or changes during pH-dependent hydration.

Drug physicochemistry further changes the pathway. Comparative ASD experiments showed that polymer identity, drug properties, and loading influence release behavior and the formation of drug-rich nanodroplets [27]. Water-resistant drug–polymer association can persist within such nanospecies, as demonstrated in felodipine dispersions [28]. These species contribute to measured apparent concentration but should not automatically be equated with molecularly dissolved drug or with a proven increase in absorptive flux.

Drug loading can also produce an abrupt mechanistic boundary. Experimental work on the limit of congruency showed that increasing drug fraction can shift the dissolving surface toward drug enrichment and reduce synchronized drug/polymer release [29]. Related studies demonstrated that water-induced phase separation and domain morphology can reorganize the hydrated matrix and control release [30]. Thus a formulation may remain an acceptable amorphous solid during storage yet cross into an unfavorable hydrated-state morphology during dissolution.

The assay itself determines which transition becomes visible. Dissolution testing can be sensitive to crystalline material only when drug properties, drug-product composition, crystalline fraction, medium, and sink conditions create sufficient discrimination [31]. A dissolution method optimized to detect crystallinity therefore answers a different question from one intended to approximate gastrointestinal behavior.

Biorelevant testing introduces its own boundary conditions. The need for sequential gastric-to-intestinal or pH-shift testing depends on ionization, precipitation propensity, and formulation behavior rather than being a universal requirement for ASDs [32]. Method development should consequently specify whether the intended inference concerns equilibrium solubility, initial release, maintenance of supersaturation, precipitation, product discrimination, or likely gastrointestinal behavior [33].

Ternary drug–polymer–water phase diagrams provide a useful mechanistic representation of these hydrated transitions. Within studied systems, they can rationalize why composition changes produce abrupt shifts in release and why a limit of congruent release emerges, although the predicted boundary remains sensitive to kinetic effects and validation domain [34]. Taken together, composition-dependent congruency loss, hydrated morphology, and ternary phase behavior support a formulation-specific release-transition interpretation rather than a universal drug-loading threshold [29, 30, 34].

Table 3 converts these findings into a design-space constraint map. Its purpose is not to rank formulations, but to show how the same nominal objective—high supersaturation—can represent different pharmaceutical states and require different confirmatory measurements.

Table 3. Design-Space Constraints Linking Supersaturation Generation to Absorption-Relevant Drug States in ASDs

Governing formulation or test condition	Hydration or transformation event	Drug phase or availability that may result	Time-dependent performance readout	Coupled constraint that limits interpretation	Unresolved stability–performance question
Low-to-moderate drug loading with coordinated polymer hydration	Congruent matrix dissolution	Predominantly released drug with polymer remaining available to inhibit precipitation	Rapid rise followed by maintained supersaturation where precipitation is delayed	Result depends on polymer aqueous behavior and drug-specific crystallization tendency	Does the same composition remain physically stable over the intended shelf-life conditions?
Loading approaches a formulation-specific congruency boundary	Surface drug enrichment or asymmetric drug/polymer release	Drug retained in surface-rich domains despite amorphous starting state	Release plateaus or declines relative to lower loading	Dry-state amorphousness does not predict wet-surface composition	Has increased loading crossed a hydrated-state release boundary before it compromises storage stability?
Strong drug–polymer association persists after hydration	Matrix retention or solution-phase complexation	Either poorly liberated drug or interaction-stabilized dissolved/supersaturated drug	Direction depends on interaction location and aqueous persistence	“Interaction strength” cannot distinguish release restriction from precipitation inhibition	Which hydrated-state interaction function dominates for the actual API, polymer and pH?
Water induces liquid–liquid or nanoscale phase separation	Drug-rich droplets or nanospecies appear	Molecularly dissolved drug coexists with drug-rich dispersed phase	Apparent concentration may remain high despite changing speciation	Total measured drug does not specify the fraction immediately available for membrane transport	Does colloidal drug contribute to useful replenishment or mainly inflate dissolution concentration?
Supersaturation exceeds precipitation resistance	Nucleation, crystal growth or other solid precipitation	Molecularly available drug decreases as precipitated fraction increases	Peak concentration followed by concentration loss after an induction period	Precipitation kinetics depend on medium, polymer, hydrodynamics and seed state	Is precipitation sufficiently delayed relative to gastrointestinal transit and absorption?
Gastric-to-intestinal transition changes ionization and solubility	pH-shift supersaturation and possible precipitation	Transiently elevated free drug followed by system-dependent phase transformation	Strong dependence on timing of pH change and polymer response	One-stage testing may miss relevant precipitation; two-stage testing may be unnecessary for other APIs	Which physiological transition must the method reproduce to answer the intended product question?
Absorptive removal operates during dissolution	Permeable drug is continuously depleted from the medium	Absorbable fraction is replenished from matrix, colloids, or supersaturated solution	Concentration and precipitation behavior differ from nonabsorptive systems	Formulation ranking can depend on imposed permeability/flux conditions	Does adding an absorption sink resolve a real translational uncertainty for this product?

The section’s central mechanistic problem is therefore best represented as a time-resolved state field rather than as a single dissolution curve. **Figure 2** separates the stored ASD, hydrated matrix, supersaturated solution, drug-rich phases, precipitation, and absorption-relevant drug pool while preserving the conditional boundaries between them.

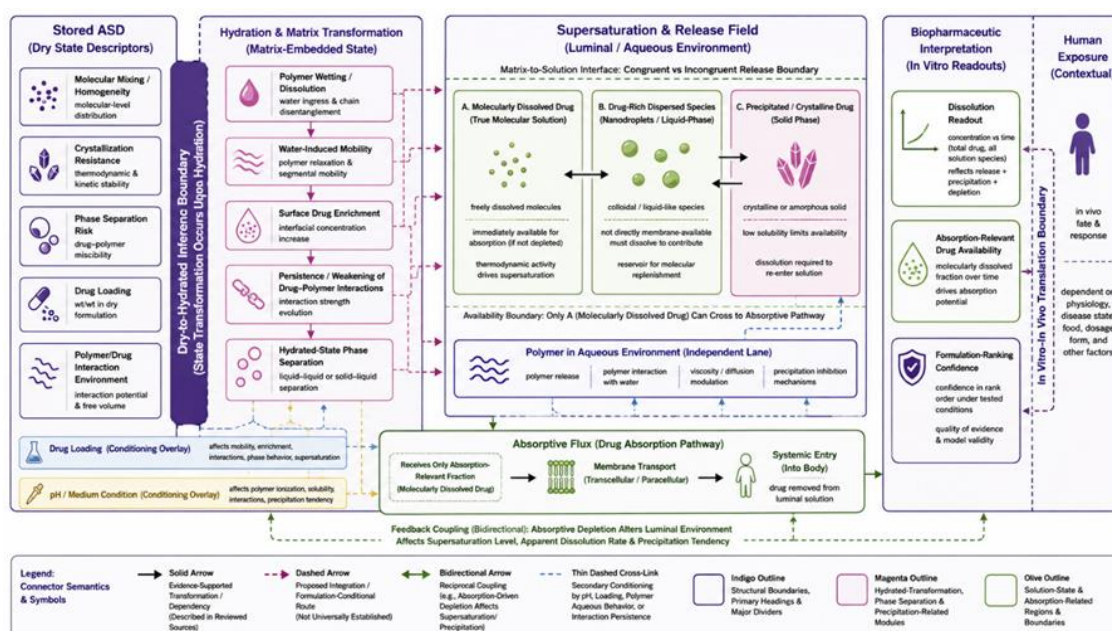


Figure 2. Hydration-Triggered State Transitions That Decouple ASD Dissolution Readouts from Absorption-Relevant Drug Availability

In vivo and biopharmaceutical performance

Evidence linking ASD dissolution behavior to systemic exposure is substantially thinner than evidence describing solid-state or dissolution mechanisms. This distinction matters because improvements in amorphization, apparent concentration, or supersaturation do not establish improved exposure without an absorption-relevant bridge.

A formulation developed for GDC-0334 illustrates how ASD selection can address a product-specific problem rather than merely maximize dissolution. The dispersion was developed to mitigate mechanical instability associated with the crystalline form while improving biopharmaceutical performance for early clinical development [35]. The result supports ASD use as an integrated drug-product strategy, but it does not establish that the same formulation logic generalizes across drugs, dose levels, or gastrointestinal conditions.

Translation can also be limited by material attributes that are poorly represented in conventional dissolution. A biorelevant dissolution–permeation method developed for an ASD containing a challenging drug impurity demonstrated that dissolution and permeation can be coupled to interrogate formulation behavior more meaningfully than concentration alone [36]. Such systems are valuable because they introduce an absorption sink and distinguish released drug from drug capable of contributing to downstream membrane transport.

Taken with absorption-coupled dissolution evidence [8], these findings indicate that translational confidence should increase only when the test reproduces the specific physiological process responsible for uncertainty. A permeability component is not automatically necessary for every ASD, just as a two-stage pH transition is not universally necessary. Its value depends on whether absorptive removal, precipitation, speciation, or gastrointestinal transition is likely to change formulation ranking.

The evidence therefore supports a hierarchy of claims. Solid-state stability establishes resistance to a defined physical transformation. Dissolution demonstrates release under a defined test environment. Supersaturation describes a transient solution-state condition. Permeation or absorptive-flux models address transport-relevant availability. In vivo studies provide a higher translational level but remain specific to formulation, dose, species or population, and study conditions. None of these levels should be substituted automatically for another.

Stability–performance trade-off patterns

Across the reviewed evidence, the central pattern is not a universal inverse relationship between stability and performance. Instead, the literature supports several conditional configurations within the trade space.

One configuration is **stability with release restriction**. Strong matrix stabilization, reduced polymer hydration, persistent drug–polymer association, or surface drug enrichment may suppress crystallization yet delay liberation after hydration. Direct stability–dissolution comparisons and polymer-dependent stability studies collectively support this possibility [1, 2, 13].

A second configuration is stability with preserved performance, in which sufficient miscibility or intermolecular stabilization is obtained without crossing into matrix-controlled release failure. High drug loading is therefore not intrinsically unacceptable, provided that process, polymer, and API attributes preserve both storage integrity and favorable hydrated-state behavior [14].

A third configuration is rapid release with insufficient persistence. A formulation may generate a high initial concentration but permit rapid nucleation, precipitation, or phase conversion, producing a short-lived supersaturated state. Initial dissolution rate and maintenance of supersaturation should therefore be treated as distinct performance dimensions.

A fourth configuration is apparently strong dissolution with ambiguous absorptive relevance. Drug-rich droplets, colloidal species, or other nonmolecular drug populations may contribute to measured concentration while differing in immediate membrane availability [5]. Their pharmaceutical value may nevertheless be indirect if they replenish molecularly dissolved drug as absorption proceeds; that contribution requires system-specific demonstration rather than assumption.

The interaction evidence further shows why no single molecular descriptor can resolve these states. Drug–polymer association may inhibit release in one hydrated system while suppressing crystallization after release in another [16, 25, 26]. Interaction strength must therefore be interpreted jointly with interaction location, persistence after hydration, polymer ionization, drug loading, and the timescale of release and precipitation.

These patterns lead to a proposed decision-state interpretation of the trade space. It is not a validated predictive algorithm. Rather, it specifies when the available evidence is sufficient for progression and when a formulation should be reassessed because stability and performance observations remain mechanistically unresolved.

The decision states are summarized in **Table 4** because the critical distinction is not which formulation characteristic is “good” or “bad,” but what can defensibly be concluded at each stage of evidence.

Table 4. Decision States for Progressing or Reassessing an ASD Across the Stability–Performance Trade Space

Decision state	Dosage-form or formulation state	Physiological or test context	Information currently sufficient	Unresolved uncertainty	Permissible action and reassessment trigger
Stable but release mechanism unresolved	Stored amorphous intermediate or dosage form	Accelerated or long-term storage followed by aqueous exposure	Crystallization resistance is established under specified conditions	Whether stabilization restricts hydration or drug liberation	Continue mechanistic dissolution testing; reassess if drug/polymer release becomes incongruent
High loading remains structurally acceptable	Homogeneous or apparently homogeneous ASD	Storage plus initial dissolution characterization	Loading has not produced detectable solid-state failure	Whether hydration crosses a composition-dependent release boundary	Progress only with loading-dependent release and phase-state testing
Strong supersaturation with uncertain drug phase	Hydrated ASD producing high apparent concentration	Biorelevant dissolution medium	Supersaturation generation is demonstrated	Molecularly dissolved fraction versus drug-rich dispersed species	Add speciation or phase-sensitive analysis before making absorption claims
Supersaturation decays through precipitation	Hydrated formulation after concentration peak	Defined pH, medium and hydrodynamics	Precipitation-sensitive performance failure is demonstrated	Whether precipitation occurs early enough to limit absorption	Modify polymer, loading or release environment; reassess against physiologically relevant timing
Dissolution rank changes when	ASD under dissolution–	Simulated intestinal	Absorptive depletion	Whether the imposed	Give greater weight to absorption-coupled

absorption is introduced	permeation or absorptive-flux conditions	absorption environment	materially affects system behavior	permeability model reflects the target drug and dose	testing while retaining in vivo validation boundary
Storage and hydrated performance are jointly acceptable	Final dosage form with qualified stability and dissolution evidence	Intended product conditions and relevant gastrointestinal transitions	No dominant failure mode is detected within the tested domain	External transfer to dose, population and clinical exposure	Progress development while defining conditions that would trigger re-evaluation

The reviewed evidence changes the interpretation of ASD optimization in two ways. First, physical stability is only one state in a sequence that continues through water uptake, matrix reorganization, release, supersaturation, precipitation, and absorption. Second, the optimal formulation at one state may not be optimal at the next.

This explains apparently contradictory polymer findings without requiring a universal ranking of excipients. A polymer can improve storage stability by reducing molecular mobility or altering drug–polymer interactions, yet its hydrated matrix may release drug slowly. Conversely, a polymer supporting rapid release can generate a less persistent supersaturated state. The decisive variable is therefore not polymer identity alone but the interaction between API physicochemistry, polymer properties, drug loading, process history, moisture, dosage-form composition, and physiological environment.

The evidence also argues against using maximal amorphous stability as a surrogate development endpoint. Water-induced phase separation and nanoscale heterogeneity demonstrate that formulations may undergo structurally important changes without immediately becoming crystalline [18, 19]. Long-term water-sorption studies further show that humidity and time can change crystallization risk substantially [21]. Stability assessments should consequently define both the failure mode and the exposure condition against which stability is claimed.

Dissolution requires equally careful qualification. Congruent release, surface drug enrichment, nanodroplet formation, precipitation, and phase separation represent different mechanisms even when conventional concentration profiles appear superficially similar. The formulation-specific release transitions described by loading-dependent and ternary phase analyses are particularly important because they suggest that small compositional changes can produce qualitatively different hydrated states rather than smooth changes in performance.

For translation, the principal unresolved issue is how much each measured drug population contributes to absorption. Conventional dissolution remains indispensable for formulation development and product discrimination, but absorption-coupled methods can be more informative where membrane flux materially changes precipitation or formulation ranking [8]. Such methods should complement rather than automatically replace simpler tests.

Formulation decision framework

The synthesis supports a proposed formulation decision framework organized around sequential evidence gates. The first gate is stored-state integrity. The formulation must demonstrate appropriate resistance to crystallization, phase separation, and chemical deterioration under conditions relevant to manufacture and shelf life.

The second gate is hydration compatibility. Drug loading, polymer hydration, and molecular interactions should be examined for evidence of surface enrichment, matrix retention, or water-induced phase separation. Passing the first gate does not imply passing the second.

The third gate is solution-state performance. Dissolution should establish not only peak concentration but the mechanism and persistence of supersaturation, including precipitation and relevant drug-rich phases.

The fourth gate is biopharmaceutic relevance. Absorption-sensitive testing is warranted when permeation, pH transition, precipitation, or drug speciation is expected to alter formulation interpretation.

The final selection objective is therefore not the formulation with the greatest value for any individual metric. It is the formulation for which no dominant failure mechanism emerges across the states most relevant to the intended product. This framework remains a proposed synthesis; prospective testing across chemically diverse APIs would be required before it could be used predictively.

Limitations

The evidence base is heterogeneous in API chemistry, polymer type, manufacturing method, drug loading, storage conditions, dissolution media, hydrodynamics, analytical resolution, and biopharmaceutical models. Direct quantitative comparison across studies is therefore inappropriate.

Much of the mechanistic literature relies on model compounds and in vitro systems. Evidence concerning human exposure is comparatively limited, and preclinical or absorption-simulator findings cannot establish clinical equivalence or superiority. Drug-rich particles and nanodroplets remain especially difficult to interpret because their contribution to absorption may depend on dissolution, redissolution, membrane transport, and gastrointestinal residence time.

Analytical sensitivity also creates an evidence boundary. Failure to detect crystallinity or phase separation does not prove their absence below the method's detection scale. Conversely, detecting nanoscale heterogeneity does not establish pharmaceutical failure without a demonstrated connection to stability or performance.

Future validation should therefore test whether the proposed decision states reproduce formulation ranking across multiple APIs, polymer chemistries, loading levels, storage histories, physiologically relevant media, and absorption conditions. Particular priority should be given to studies linking dry-state structure, hydrated-state speciation, precipitation kinetics, absorptive flux, and in vivo exposure within the same formulation series.

CONCLUSION

Amorphous solid dispersions are best understood as dynamic drug–polymer systems whose pharmaceutical behavior changes between storage, hydration, supersaturation, precipitation, and absorption. Maximizing resistance to crystallization does not necessarily maximize release, while maximizing early dissolution does not guarantee persistence of supersaturation or absorption-relevant availability.

The central formulation problem is therefore conditional rather than scalar. Drug physicochemistry, polymer properties, loading, molecular interactions, moisture, dosage-form composition, gastrointestinal conditions, and absorptive removal jointly determine where a formulation resides within the stability–performance trade space. A defensible development strategy separates these states, identifies the dominant failure mechanism at each transition, and advances formulations only when performance remains acceptable across the product-relevant sequence of conditions.

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