



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Co-Amorphous Systems For Poorly Water-Soluble Drugs: Molecular Interactions, Physical Stability And Formulation Design

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ARTICLE INFO

Published: 15 Oct. 2026

Keywords:

Co-amorphous systems;
Amorphous solid
dispersions; Physical
stability; Glass transition;
Poorly water-soluble drugs;
Solid-state characterization.

DOI:

10.5281/zenodo.23386276

ABSTRACT

Amorphous drugs dissolve faster and reach higher apparent solubility than their crystalline forms, but they are thermodynamically unstable and tend to recrystallize during storage or dissolution. Polymer-based amorphous solid dispersions are the established way of stabilizing them. Co-amorphous systems, in which a drug is combined with a low-molecular-weight co-former (another drug, an amino acid or another small molecule) to form a single homogeneous amorphous phase, have emerged as an alternative that may offer higher drug loading, specific molecular interactions and, in some cases, synchronized release of two drugs. This review examines co-amorphous systems from the standpoint of physical pharmaceutics. It summarizes the amorphous-state fundamentals that govern stability (glass transition, molecular mobility, miscibility and plasticization), the classes of co-formers and the principles used to select them, preparation and characterization methods, the evidence on physical stability and on dissolution and bioavailability, and a comparison with polymeric dispersions. Emerging data-driven approaches to predicting co-amorphous formation are also discussed. The evidence suggests that co-amorphization can improve stability and dissolution for suitable drug-co-former pairs, but that outcomes are strongly pair-specific, long-term stability data are limited, in vivo evidence is sparse, and regulatory expectations are not yet well defined. Priorities for future work are stated.

INTRODUCTION

A large proportion of drug candidates and many marketed drugs show poor aqueous solubility, which can limit dissolution and absorption, particularly for BCS class II compounds that have

low solubility but high permeability.¹ A range of strategies exists to address this problem, including particle-size reduction, salt formation, cyclodextrin complexation, lipid-based systems and solid dispersions.^{2,3}

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



Converting a crystalline drug to its amorphous form is among the most effective ways of raising its apparent solubility and dissolution rate, because the amorphous solid has higher free energy and lacks the lattice energy that must be overcome for a crystal to dissolve.⁴ The price of this advantage is physical instability: below a certain temperature the amorphous solid is a glass, but it is still a non-equilibrium state and may crystallize on storage, particularly in the presence of heat or moisture, or during dissolution, so that the solubility advantage is lost.⁴

The usual remedy is to disperse the drug in a polymer to form an amorphous solid dispersion (ASD), where the polymer raises the glass-transition temperature of the system, restricts molecular mobility and, in many cases, helps maintain supersaturation during dissolution.⁵ However, polymeric ASDs have recognized limitations, including limited drug loading before phase separation, sensitivity to moisture because many polymers are hygroscopic, and the effect of the polymer on the size of the final dosage form.⁵

Co-amorphous systems offer a different route. In a co-amorphous system, two or more low-molecular-weight components, typically a poorly soluble drug and a co-former, are mixed at the molecular level to form a single homogeneous amorphous phase.⁶ The co-former may be a second drug, in which case the system can also serve as a fixed-dose combination, an amino acid, or another small molecule such as an organic acid. Stabilization is believed to arise from specific interactions between the components, such as hydrogen bonding or ionic interaction (salt-like) between the components, and from the elevation of the glass-transition temperature relative to the neat amorphous drug.^{6,7} An early demonstration of this concept with a drug-drug pair involved amorphous naproxen-cimetidine mixtures

prepared by mechanical activation, which were reported to show enhanced dissolution rate and synchronized release of the two drugs.⁸

The field has grown rapidly since then, and several reviews now cover co-formability, molar ratio, preparation methods, physical stability, in vitro and in vivo performance and new formulation strategies.^{6,9-11} Despite this, the practical question for a formulator remains: for a given drug, when does a co-amorphous system offer a real advantage over a polymeric dispersion or a simpler approach, and how can its physical stability be judged and predicted?

This review addresses that question from the viewpoint of physical pharmaceuticals. It first summarizes the physical principles of the amorphous state that govern stability, then describes co-former classes and selection principles, preparation and characterization methods, the evidence on stability and performance, comparison with polymeric ASDs, emerging data-driven prediction and regulatory and quality considerations. Throughout, the emphasis is on distinguishing mechanisms that are well established from claims that rest on a small number of model systems.

2. LITERATURE SEARCH APPROACH

This is a narrative review and not a systematic review. Sources were identified through targeted searches of PubMed-indexed and publisher-hosted literature using combinations of the terms co-amorphous, coamorphous, amorphous solid dispersion, glass transition, physical stability, amino acid co-former, drug-drug co-amorphous, solubility, dissolution and machine learning. Foundational papers on the amorphous state and on co-amorphous systems were combined with recent reviews and studies. The reference set is selective and numerical results are quoted only



where they were reported by the original authors for their own data. Statements of general physical-pharmaceutical principle that are standard textbook knowledge are given without a specific citation.

3. PHYSICAL PHARMACEUTICS OF THE AMORPHOUS STATE

3.1 *Why amorphous solids dissolve faster, and why they do not stay amorphous*

A crystalline solid is a low-energy, long-range-ordered arrangement. An amorphous solid lacks long-range order, has higher enthalpy, entropy and free energy, and consequently higher apparent solubility and a faster dissolution rate than the crystal. These same properties make it a driving force for conversion back to the crystalline state.⁴ Whether conversion actually happens within a practical time depends on molecular mobility, that is, how freely molecules can rearrange to nucleate and grow crystals, and mobility is strongly temperature- and moisture-dependent.

3.2 *Glass transition and molecular mobility*

When a liquid is cooled fast enough to avoid crystallization it becomes a supercooled liquid and, at the glass-transition temperature (T_g), solidifies into a glass in which large-scale molecular motion is effectively frozen on the experimental time scale. The practical rule used in pharmaceutical development is that an amorphous system stored well below its T_g has low mobility and is more likely to remain stable, whereas storage near or above T_g allows rapid relaxation and crystallization. A commonly quoted rule of thumb is to keep storage temperature well below T_g , often by a margin of about 50 degrees, although the appropriate margin differs from compound to compound and the rule should not be applied rigidly.

T_g alone does not determine stability. Systems with the same T_g can differ in how rapidly mobility changes as temperature approaches T_g (the fragility of the glass), and local, secondary relaxations that persist below T_g can still allow nucleation. For this reason, direct measurement of relaxation behaviour and crystallization onset under realistic storage conditions is more informative than T_g alone.

3.3 *Miscibility, T_g of mixtures and interactions*

In a binary amorphous mixture, a single T_g between or above those of the components indicates that the components are mixed at the molecular level, whereas two separate T_g values indicate phase separation. The T_g of an ideal mixture can be estimated from the T_g values and mass fractions of the components with equations such as the Gordon-Taylor or Fox equations, and positive deviation of the measured T_g from the ideal value is commonly taken as evidence of favourable specific interactions between components, whereas negative deviation suggests weaker interaction or plasticization. These equations describe ideal mixing and their agreement with experiment should not be over-interpreted as proof of stability.

3.4 *Moisture and plasticization*

Water is a powerful plasticizer of amorphous pharmaceutical solids: absorbed water lowers T_g and increases mobility, and can also act as a medium for crystallization. Hygroscopicity of the components therefore directly affects storage stability, and a co-amorphous system that is stable in dry conditions may crystallize when exposed to humidity. Moisture uptake should be measured and stability studies should include humidity-controlled conditions relevant to the intended storage climate, which is particularly important for hot and humid regions such as many parts of India.



3.5 Crystallization from the amorphous state: nucleation and growth

Crystallization proceeds in two steps: nucleation, in which a stable crystalline embryo forms, and crystal growth, in which that nucleus enlarges by incorporating molecules from the surrounding amorphous matrix. The two steps have different temperature dependence. Nucleation is often most significant at temperatures not far above T_g , whereas growth rate tends to be highest at higher temperatures where mobility is greater, so the overall crystallization rate passes through a maximum between T_g and the melting point. For stability assessment this means that data collected at one elevated temperature cannot be assumed to represent behaviour at room temperature, because

the dominant step and the rate-controlling factor may change.

Crystallization also tends to begin at surfaces, where molecular mobility is higher than in the bulk, and at interfaces with moisture or with excipients. Particle size, surface area and surface composition of a co-amorphous powder can therefore influence the observed stability, and the same material may behave differently as a fine powder, a compact or a granule. A co-former can slow either nucleation or growth, or both, and distinguishing which step is affected is useful for rational design, although it requires more detailed kinetic studies than are reported in most formulation papers.

Table 1. KEY PHYSICAL-PHARMACEUTICAL CONCEPTS GOVERNING THE STABILITY OF AMORPHOUS SYSTEMS

Concept	What it describes	Implication for co-amorphous design
Glass transition (T_g) ⁴	Temperature below which large-scale molecular motion is frozen	A co-former that raises T_g of the mixture over the neat drug favours stability
Molecular mobility and relaxation	Rate of molecular rearrangement, including local motions below T_g	Stability depends on mobility at storage temperature, not T_g alone
Miscibility	Whether components form one homogeneous phase	A single T_g and absence of crystalline peaks support a true single-phase system
Specific interactions	Hydrogen bonding or ionic interaction between components	Strong drug-co-former interaction is thought to hinder drug-drug crystallization ^{6,7}
Plasticization by water	Lowering of T_g by absorbed moisture	Hygroscopic components can destabilize the system; humidity must be controlled
Nucleation and crystal growth	Two steps of crystallization from the amorphous state	Both must be considered; inhibition of growth alone may not prevent nucleation

Compiled by the author from standard physical pharmaceuticals and the cited references.

4. CO-AMORPHOUS DESIGN: CO-FORMER CLASSES AND SELECTION OF PRINCIPLES

4.1 Classes of co-formers

Three groups of co-formers have been most widely examined. In drug-drug systems, two active ingredients are co-amorphized, which can stabilize both and permit synchronized release; the naproxen-cimetidine mixture is an early example.⁸ The attraction for fixed-dose combinations is clear, but both drugs must be compatible in dose



ratio, and the molar ratio that gives a stable single phase may not match the therapeutic dose ratio. In drug-amino acid systems, an amino acid such as arginine or proline serves as the co-former; amino acids are attractive because they are small, generally regarded as safe in pharmaceutical use

and capable of both ionic and hydrogen-bonding interactions.^{12,13} A third group comprises other small molecules, such as carboxylic acids, sugars, urea and nicotinamide, which are discussed in the review literature.⁶

Table 2. CO-FORMER CLASSES, DESIGN LOGIC AND CAUTIONS

Co-former class	Rationale	Example systems reported	Cautions
Drug-drug	Stabilization of both components; fixed-dose combination; synchronized release	Naproxen-cimetidine ⁸	Dose ratio must suit therapy; interaction between actives must be assessed
Drug-amino acid	Ionic and hydrogen-bonding interactions; low toxicity concern; wide choice of side chains	Systematic screening of drug-amino acid pairs ¹² ; proline-containing systems ¹³	Results are strongly pair-specific; amino acid selection is non-trivial
Drug-small molecules (acids, others)	Salt-like interaction with acidic or basic drugs; additional functionality	Discussed in the review literature ⁶	Safety and regulatory status of the co-former need evaluation

Compiled by the author from the cited references.

4.2 Selection principles

No single rule predicts whether a pair will form a stable co-amorphous system, but several principles guide selection. First, complementary functional groups that can interact, for example an acidic drug with a basic amino acid, favour the formation of strong interactions, and the role of salt formation and of structural similarity between components has been examined for co-amorphous systems.⁷ Second, co-formers that give a mixture with higher T_g than the neat drug are preferred. Third, a systematic screening method has been described for combining drugs with amino acids, in which a series of amino acids is tested for their ability to form stable co-amorphous mixtures with a given drug, showing that a rational screening workflow is practical.¹² Fourth, the molar ratio matters: many studies use equimolar mixtures because strong interaction is expected at a 1:1 ratio, but the

optimum ratio may differ and the effect of ratio should be tested.¹⁰

One notable observation from the literature is that the addition of a highly water-soluble amino acid such as proline has been used to improve co-amorphous formulations, illustrating that ternary designs (drug plus two co-formers) are a way of tuning properties when binary systems fall short.¹³ In the author's assessment, outcomes appear to be strongly drug-specific and should not be extrapolated from one pair to another without testing.

4.3 Co-former dose burden and safety

A practical constraint that is easy to overlook is the mass of co-former that must be administered. Co-amorphous systems are commonly prepared at equimolar ratios, and because a co-former such as an amino acid has a much lower molecular weight than many modern drugs, the mass ratio is not the



same as the molar ratio. As a simple illustration, a 100 mg dose of a drug with a molecular weight of 400 corresponds to 0.25 mmol; an equimolar amount of arginine (molecular weight about 174) would then add about 44 mg of co-former, so the active-to-co-former mass ratio would be roughly 70:30. For high-dose drugs this may increase the total tablet or capsule size substantially, which is a recognized practical limit for any carrier-based amorphous approach and should be calculated early in design.

Safety and regulatory status of the co-former also matter. Amino acids and certain organic acids are naturally occurring or widely used in food and pharmaceutical products, which is an attraction, but the daily amount delivered by a high-dose product may be large compared with typical excipient use, and the pharmacology of the co-former at that amount should be considered. Where the co-former is a second drug, its own dose, safety and interaction profile become part of the assessment. These factors argue for choosing co-formers not only on the basis of physical stability but also on dose burden, safety and cost.

5. MOLECULAR INTERACTIONS AND STABILIZATION MECHANISMS

Three mechanisms are generally proposed to explain why co-amorphous systems resist crystallization. The first is the antiplasticization or Tg-raising effect when a co-former with a high Tg or strongly interacting character is mixed with the drug. The second is the formation of specific intermolecular interactions, such as hydrogen bonds between the drug and co-former, which can reduce the tendency of drug molecules to arrange into a crystal lattice. The third is the possibility of

proton transfer, leading to a salt-like amorphous form, in which ionic interaction between an acidic and a basic component gives more strongly bound structure.^{6,7}

Evidence for these interactions comes mainly from infrared and Raman spectroscopy (shifts in the vibrational bands of interacting groups), thermal analysis (a single, shifted Tg) and, in some cases, solid-state nuclear magnetic resonance and computational modelling. A caution is that spectral shifts show that interaction exists but not that it is sufficient to ensure stability; the strength of interaction, the molar ratio and the mobility of the system jointly determine whether the system remains amorphous.⁶

It is also helpful to distinguish co-amorphous systems from cocrystals and from simple physical mixtures of two amorphous solids. A cocrystal has a defined crystalline lattice with long-range order, whereas a co-amorphous system lacks it; a physical mixture of two separate amorphous phases would show two Tg values and offers no guarantee of mutual stabilization. Clear terminology is important both for scientific communication and for regulatory classification.

6. PREPARATION METHODS

Co-amorphous systems can be prepared by methods that either start from melt or from solution, or that use mechanical energy. Quench cooling of a melt, ball milling (including cryogenic milling), solvent evaporation, spray drying and freeze-drying have all been used at laboratory scale, and hot-melt extrusion and spray drying are generally regarded as the more readily scalable.⁶ Table 3 summarizes the main methods.

Table 3. PREPARATION METHODS FOR CO-AMORPHOUS SYSTEMS

Method	Principle	Advantages	Limitations
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Quench cooling	Melting the components followed by rapid cooling to a glass	Simple; no solvent; useful for screening	Requires thermal stability; small scale
Ball milling (including cryo-milling)	Mechanical energy converts crystals to a mixed amorphous phase	Solvent-free; suited to screening; works for thermolabile drugs	Heat and mechanical stress; scalability and batch variability
Solvent evaporation / spray drying	Dissolving components in a common solvent and rapidly removing it	Continuous and scalable (spray drying); good control of particle properties	Need common solvent; residual solvent; process optimization
Freeze-drying	Freezing a solution and sublimating the solvent	Gentle for sensitive compounds	Slow, energy-intensive; potential phase separation on freezing
Hot-melt extrusion	Melt mixing under shear in an extruder	Solvent-free and continuous; industrially established	Needs thermal stability; processing window

Compiled by the author from the cited reviews and general pharmaceutical technology.

The preparation method influences not only whether a system can be made but also its properties: different methods can give materials of different degree of mixing, residual crystallinity, particle properties and, consequently, different stability and dissolution. Reports of the same drug-co-former pair prepared by different methods should therefore not be compared without caution, and the method should be reported in sufficient detail for reproduction.

7. SOLID-STATE AND PERFORMANCE CHARACTERIZATION

Adequate characterization is essential to establish that a material is genuinely single-phase and

amorphous, and no single technique is sufficient. X-ray powder diffraction (XRPD) is the primary screen, with an amorphous halo and absence of Bragg peaks indicating the absence of long-range order within its detection limit, which is typically a few per cent of crystalline content. Differential scanning calorimetry (DSC), including modulated DSC, measures T_g and crystallization events. Fourier-transform infrared and Raman spectroscopy probe interactions. Dynamic vapour sorption measures moisture uptake, and polarized-light microscopy and scanning electron microscopy give complementary information on particle form.⁶ Table 4 summarizes what each technique answers.

Table 4. CHARACTERIZATION TECHNIQUES FOR CO-AMORPHOUS SYSTEMS

Technique	Question answered	Limitation
XRPD	Is the sample X-ray amorphous (halo, no Bragg peaks)?	Insensitive to low levels of crystallinity
DSC / modulated DSC	What are T_g , crystallization and melting events? Single or multiple T_g ?	Heating can induce crystallization; T_g can be weak or broad
FTIR / Raman	Do the components interact (band shifts)?	Shows interaction, not stability



Solid-state NMR	Are the components mixed on a molecular scale?	Specialized and costly
Dynamic vapour sorption	How hygroscopic is the system? How does it behave at different humidity?	Time-consuming
Dissolution and supersaturation testing	How fast and how far does the drug dissolve, and for how long?	Results depend on medium, volume and method
Stability studies	Does the system remain amorphous over time and conditions?	Accelerated conditions may not predict real-time behaviour

Compiled by the author from standard solid-state characterization practice and the cited reviews

Dissolution testing deserves a specific comment. Because co-amorphous systems may generate supersaturation, the usual practice of measuring concentration at a few time points may miss precipitation. Methods that follow concentration continuously, include non-sink conditions and record the solid form of any precipitate give a more reliable picture, and results should be reported for both components when two drugs are present, since synchronized release is one of the claimed advantages.⁸

7.1 Analytical pitfalls and interpretation of data

Several recurring pitfalls can lead to over-optimistic conclusions about amorphous character and stability. First, XRPD has a limited detection limit, so a sample that appears amorphous may still contain a small proportion of crystalline material that can act as seeds for later crystallization; for stability work, the absence of Bragg peaks should be interpreted as "amorphous within the detection limit" and complemented by a more sensitive method where possible. Second, in DSC the heating process itself can induce crystallization or relaxation, and a modest scan rate, repeated heating or modulated methods may be needed to separate events; a T_g that is hard to detect does not prove its absence. Third, the thermal and storage history of a sample affects its apparent T_g and its enthalpy relaxation, so samples should be treated in a consistent, documented way before analysis.⁶

Fourth, vibrational spectroscopy can show that an interaction exists but cannot, by itself, show that the interaction is the cause of stability; control experiments (neat amorphous drug, physical mixtures) are needed. Fifth, in humid storage the crystallizing species may be a hydrate or a salt rather than the original anhydrous drug, so the identity of any new crystalline phase should be established and not assumed. Finally, particle size and surface area affect both stability and dissolution, so comparisons between samples made by different methods should consider these differences before attributing results to composition alone.

8. PHYSICAL STABILITY: EVIDENCE AND PREDICTORS

Physical stability is the central issue for any amorphous formulation, and the review literature reports that co-amorphous systems can be more stable than the corresponding neat amorphous drugs, for suitable pairs.⁶ Stability is typically evaluated by storing samples under controlled temperature and humidity (often in dry conditions and at elevated temperature, and sometimes at elevated humidity) and monitoring for recrystallization by XRPD and DSC at intervals.

Several caveats apply. First, many reports use dry storage at one or two temperatures for a limited time, whereas products require stability for months to years under humid conditions; extrapolation

from short-term data to shelf life is uncertain. Second, stability depends strongly on the pair and ratio, and a system stable for one pair may fail for another with apparently similar chemistry. Third, stability upon storage differs from stability on dissolution, because a system that remains amorphous in the solid state may still convert (for example, to a hydrate or crystalline form) when it contacts aqueous medium. Fourth, mechanical stress, as in milling or compression during tableting, can destabilize some co-amorphous systems, which matters for downstream processing, although the behaviour of individual systems should be checked in the original reports.

Predictors of stability that have been proposed include the Tg of the mixture (and its distance from the storage temperature), the strength of drug-co-former interaction, the degree of structural similarity or complementarity between components, and the intrinsic crystallization tendency of the neat drug.^{6,7} None of these is individually reliable. Practically, a combination of thermal, spectroscopic and stability data, with a clear distinction between short-term and long-term evidence, is required before any claim of adequate stability is made.

Table 5. FACTORS AFFECTING THE PHYSICAL STABILITY OF CO-AMORPHOUS SYSTEMS

Factor	Effect on stability	Practical consequence
Tg of the mixture	Higher Tg relative to storage temperature reduces mobility	Measure Tg of the final composition, not only of components
Strength of drug-co-former interaction	Stronger interaction hinders drug crystallization	Confirm interaction spectroscopically; recognize it is not sufficient alone
Molar ratio	Optimum often near, but not necessarily at, 1:1	Test several ratios ¹⁰
Moisture / humidity	Plasticization lowers Tg; water supports crystallization	Include humid storage; choose protective packaging
Preparation method	Affects degree of mixing and residual crystallinity	Report method fully; confirm single phase
Processing stress (milling, compression)	May destabilize	Test the formulation through its intended processing

Compiled by the author from standard physical pharmaceuticals and the cited reviews.

9. DISSOLUTION, SUPERSATURATION AND BIOAVAILABILITY

The main reason for developing co-amorphous systems is to improve dissolution. Reports across the review literature describe enhanced dissolution rate and apparent solubility relative to crystalline and, in many cases, neat amorphous drug, and for drug-drug systems, synchronized release of the two components has been described.^{6,8} The magnitude of improvement varies widely with

drug, co-former and test conditions, and a general numerical expectation cannot be given.

Dissolution enhancement does not necessarily translate to better bioavailability. Absorption depends on the concentration profile in the gut, the persistence of supersaturation, precipitation kinetics, permeability and the effects of co-formers on intestinal transport or metabolism. The reviews note that in vivo data for co-amorphous systems are comparatively limited, and that the



number of studies that have measured pharmacokinetics is small relative to the number reporting only in vitro results.⁶ Co-amorphous systems also lack the polymeric precipitation inhibitors that sustain supersaturation in ASDs, so some systems may show rapid initial dissolution followed by precipitation, and a polymer may be added to prolong supersaturation, although the evidence for such ternary designs is still emerging.

The behaviour of a supersaturating system is often described by the "spring and parachute" concept. The spring is the rapid generation of supersaturation as the amorphous material dissolves faster than the crystalline form; the parachute is the maintenance of that supersaturated state for long enough for absorption, usually by inhibiting nucleation and growth of the crystalline phase in solution. An amorphous drug with a strong spring but no parachute may dissolve quickly and then precipitate before it can be absorbed. Co-amorphous systems provide the spring; whether the co-former also contributes a parachute depends on its effect on the solution-phase behaviour of the drug, and this is not generally known without measurement.

From the standpoint of evidence appraisal, the strongest claim a co-amorphous study can make is improved exposure in vivo with stable product quality; the next strongest is improved dissolution under physiologically relevant, non-sink conditions with documented stability; and the weakest is improved dissolution in a single, sink-condition test of a freshly prepared sample. Studies should be assessed accordingly.

9.1 Designing in vivo studies for co-amorphous formulations

Because in vivo evidence is limited, well-designed pharmacokinetic studies would be especially informative. A convincing study should include

appropriate comparators: the crystalline drug, the neat amorphous drug (if it can be kept amorphous long enough to be dosed) and, ideally, a polymeric dispersion of the same drug. The co-amorphous formulation should be characterized immediately before dosing to confirm that it is still amorphous and single-phase, since conversion in the dosing vehicle or during storage would confound the result. The dosing medium, fed or fasted state and species should be reported, and the possibility that the co-former itself influences absorption, transport or metabolism should be controlled for by including a co-former-alone or physical-mixture arm.⁶

Interpretation requires caution in animal-to-human translation. Differences in gastrointestinal volume, pH, transit time and bile secretion between species can change dissolution and precipitation behaviour, and rodent studies at high doses may exaggerate or hide supersaturation effects. Pharmacokinetic parameters such as the area under the curve and peak concentration should be reported with variability, and the number of animals should be sufficient to detect a meaningful difference. Finally, for drug-drug systems, the pharmacokinetics of both drugs should be reported, because the claim of synchronized release is meaningful only if it is verified in vivo and not just in vitro.⁸

10. CO-AMORPHOUS SYSTEMS VERSUS POLYMERIC AMORPHOUS SOLID DISPERSIONS

Polymeric ASDs and co-amorphous systems both stabilize the amorphous state, but through different means, and the choice between them depends on the drug and the product requirements. Polymers are large, high-T_g molecules that can substantially raise the T_g of the system and inhibit crystal growth, and they can also maintain supersaturation during dissolution.⁵ Low-molecular-weight co-



formers act by specific interactions and the Tg effect of a small molecule is often more modest, but they may allow higher drug loading in principle (although this has to be shown for each system) and, when the co-former is a drug, add therapeutic value.⁶ Table 6 compares the two approaches.

Table 6. COMPARISON OF POLYMERIC ASDS AND CO-AMORPHOUS SYSTEMS (AUTHOR'S SYNTHESIS)

Aspect	Polymeric ASD	Co-amorphous system
Stabilizing agent	High-molecular-weight polymer ⁵	Low-molecular-weight co-former (drug, amino acid, other) ⁶
Main stabilization mechanism	Higher Tg, reduced mobility, drug-polymer interaction	Specific interactions; Tg effect; possible salt-like interaction ⁷
Drug loading	Limited by miscibility with the polymer	Can be higher, since co-former is a small molecule
Supersaturation maintenance	Often good, using precipitation-inhibiting polymers	Can be limited; a polymer may be needed in ternary designs
Moisture sensitivity	Many polymers are hygroscopic	Depends on co-former; can also be hygroscopic
Added therapeutic value	Generally none	Possible when the co-former is a second drug ⁸
Maturity and regulatory familiarity	Established commercial products and guidance	Fewer products; regulatory expectations still developing ¹⁴
Predictability	More empirical rules established	Strongly pair-specific; prediction still immature ¹⁵

Compiled by the author from the cited references; the comparison is qualitative.

The most defensible conclusion from the literature is that co-amorphous systems are a complement to polymeric ASDs and not a replacement. They are most attractive when a drug has an interaction-capable functional group matching a safe co-former, when a fixed-dose combination of two poorly soluble drugs is desired, or when polymer-related limitations (drug loading, hygroscopicity, dosage-form size) are problematic. Head-to-head studies of the same drug formulated both ways under identical conditions are scarce and would be the most informative evidence.

10.1 Illustrative design decisions

Three short hypothetical scenarios illustrate how the principles above can guide decisions. They are constructed for teaching and do not describe real products or studies.

Scenario 1: an acidic, lipophilic BCS class II drug that crystallizes readily. A formulator screens a small panel of basic amino acids at more than one molar ratio, as in published screening approaches.¹² Promising mixtures are confirmed as single-phase (halo by XRPD, single Tg by DSC) and are then stored at dry and humid conditions. If the system remains amorphous under humid storage and gives sustained concentration in non-sink dissolution, development can proceed; if it crystallizes under humidity, the formulator should compare with a polymeric ASD before investing further effort.⁵

Scenario 2: a fixed-dose combination of two poorly soluble drugs. Co-amorphization may stabilize both and give synchronized release,⁸ but the molar ratio at which a stable single phase forms may differ from the therapeutic dose ratio. The



formulator must therefore test whether a stable composition can be reached at the required ratio, possibly by adding a third component, and must confirm that the interaction between the two actives does not compromise chemical stability or pharmacology.

Scenario 3: a drug with a low T_g and no functional group capable of strong interaction. The physical principles discussed in Sections 3 and 5 suggest that a co-amorphous system is unlikely to be stable, because there is neither a T_g-raising effect nor a specific interaction to hinder crystallization. In such a case, time is better spent on another strategy, such as a polymeric dispersion or a lipid-based formulation, than on extensive co-former screening.³

The common lesson is that early, inexpensive physical measurements (T_g, interaction spectra, humid-storage behaviour) should determine whether a co-amorphous route is pursued, and that the decision should be made against a clearly defined alternative.

11. DATA-DRIVEN PREDICTION OF CO-AMORPHOUS FORMATION

Because pair-specific behaviour makes experimental screening laborious, there is interest in predicting co-amorphous formation computationally. One study compiled a database of 244 systems from the literature and trained several ML models, including gradient boosting (XGBoost), random forest, support vector machine and k-nearest neighbour models, to predict whether a drug-co-former pair would form a co-amorphous system.¹⁵ The authors reported 79% accuracy on a small external test of 19 previously unseen systems (10 of 12 co-amorphous and 5 of 7 non-co-amorphous systems correctly identified).¹⁵

This work illustrates both the promise and the limits of the approach. A model that screens pairs before experimentation could save considerable effort. However, the external test set is very small, so the uncertainty around the 79% figure is wide, and literature-derived datasets are biased toward positive (successful) reports because failed attempts are less often published, so the model may over-predict formation. These are general weaknesses of ML in formulation science and are discussed in broader reviews of ML applied to drug formulation.^{16,17} A related line of work uses ML to predict amorphous solid dispersion formation from high-throughput screening data, which has the advantage that the training data are generated systematically, including negative results.¹⁸

Practical advice for researchers is to treat such models as tools to prioritize experiments, to examine whether the pairs of interest lie within the chemical space of the training data, to insist on external validation, and to avoid data leakage between training and test sets, a recognized source of over-optimistic performance in ML-based science.¹⁷ Progress will depend on larger, curated datasets that include failed co-amorphization attempts and report preparation method, ratio and stability conditions consistently.

12. SCALE-UP, QUALITY AND REGULATORY CONSIDERATIONS

Moving from laboratory screening to a manufacturable product raises several issues. Preparation methods must be scalable and reproducible, with control of critical process parameters that influence degree of mixing and residual crystallinity. Critical quality attributes include amorphous content, single-phase character (single T_g), moisture content, dissolution and physical stability, and the control strategy should include appropriate specifications and packaging



to protect against humidity. Downstream processing, such as granulation, compression and coating, can induce crystallization or phase separation, so the finished dosage form, not only the intermediate, must be tested for stability.

A Quality by Design view helps to organize these issues. Critical material attributes include the purity, particle properties and hygroscopicity of the drug and co-former and their molar ratio. Critical process parameters depend on the method:

for spray drying they include inlet and outlet temperature, feed concentration and solvent composition, and for hot-melt extrusion they include barrel temperature, screw speed and residence time. Critical quality attributes include amorphous content, single-phase character, residual solvent, moisture content, dissolution and physical stability. Table 7 shows how these elements can be linked, as a framework to be adapted for each product.

Table 7. ILLUSTRATIVE QBD FRAMEWORK FOR A CO-AMORPHOUS PRODUCT

Element	Examples	Link to quality
Critical material attributes	Drug and co-former purity, hygroscopicity, particle size, molar ratio	Determine miscibility, Tg and interaction strength
Critical process parameters (spray drying)	Inlet and outlet temperature, feed concentration, solvent composition, atomization	Influence degree of mixing, residual solvent and residual crystallinity
Critical process parameters (hot-melt extrusion)	Barrel temperature, screw speed, feed rate, residence time	Influence homogeneity and thermal degradation
Critical quality attributes	Amorphous content, single Tg, moisture, dissolution, stability, assay and impurities	Define product performance and shelf life
Control strategy	In-process monitoring, specifications, humidity-protective packaging, stability programme	Ensure consistent quality through shelf life

Prepared by the author as an illustration; it is not a validated framework.

Regulatory expectations for co-amorphous systems are not as established as for polymeric ASDs, and a recent review of prospective regulatory requirements suggests that well-optimized co-amorphous dispersions might be designated as co-processed active ingredients or premixes, which could streamline generic development.¹⁴ Points likely to be examined include the identity and safety of the co-former (especially where it is not an established excipient), justification of the molar ratio and demonstration of a single, stable amorphous phase. Where the co-former is a second active ingredient, the product would be considered in the context of

fixed-dose combinations, and both components would need to be characterized. Developers should consult the current guidance of the regulatory authority of their market, including Indian authorities, and seek early scientific advice for novel systems.

12.1 Downstream processing and packaging

A co-amorphous powder must usually be converted into a solid dosage form, and each downstream step introduces thermal, mechanical or moisture stress. Granulation, especially wet granulation, exposes the material to water and can trigger crystallization or hydrate formation, so dry

or non-aqueous routes are generally safer. Compression applies pressure and can generate local heating and shear; the compaction behaviour of amorphous powders differs from that of crystalline ones, and tablet hardness, disintegration and dissolution should be examined together with solid-state stability. Blending with excipients adds further components that may interact with the system, for example by absorbing or releasing moisture.

Packaging is part of the stability strategy. Because moisture is the principal threat to many amorphous systems, protective primary packaging with low moisture permeability and, where necessary, desiccants are important, and the stability programme should use the proposed pack. In hot and humid climates, accelerated and long-term studies at conditions relevant to the intended

markets are particularly important, and the label storage statement should reflect the data.

13. CHALLENGES AND RESEARCH GAPS

The main challenges and gaps identified in this review are summarized in Table 8. The most consequential are the shortage of long-term, humid-condition stability data, the scarcity of in vivo pharmacokinetic studies, the pair-specific nature of results that hinders generalization, and the lack of head-to-head comparisons with polymeric ASDs. Standardized reporting would greatly improve comparability: studies should state preparation methods and scale, molar ratio, residual crystallinity, T_g, storage conditions and duration, humidity, dissolution conditions and the solid form of any precipitate.

Table 8. RESEARCH GAPS AND SUGGESTED PRIORITIES

Gap	Why it matters	Suggested priority
Limited long-term and humid-condition stability data (author's appraisal)	Product shelf life requires months to years under realistic climate	Studies at ICH-relevant conditions with time points to at least the standard period
Few in vivo studies ⁶	Dissolution gains may not translate into exposure	Pharmacokinetic studies with stable, well-characterized formulations
Pair-specific outcomes	Prevents rational prediction and generalization	Systematic screening and curated datasets ^{12,15}
Few head-to-head comparisons with polymeric ASDs	Needed to judge when co-amorphous is truly advantageous	Same drug, same conditions, both approaches
Dissolution under non-sink and physiologically relevant conditions	Supersaturation and precipitation are missed in simple tests	Continuous monitoring and solid-form analysis of precipitate
Immature prediction tools ¹⁵	Small, biased datasets and small external test sets	Include negative results; external validation; avoid leakage ¹⁷
Regulatory clarity ¹⁴	Uncertainty slows translation	Early regulatory dialogue; co-former safety documentation

14. FUTURE PERSPECTIVES



Several directions appear promising. Combination of co-amorphous design with polymers in ternary systems may unite the interaction-based stabilization of co-formers with the supersaturation-maintaining ability of polymers. Systematic data generation by high-throughput screening, together with ML models trained on both positive and negative outcomes, may allow rational pre-selection of co-formers.^{15,18} Continuous manufacturing by hot-melt extrusion or spray drying may help produce co-amorphous materials reproducibly at scale. Process analytical technology could monitor amorphous content and mixing in real time. Finally, applications beyond

oral delivery, such as inhalation and other routes, are being explored in the literature.¹⁴

For students and early-career researchers in pharmaceuticals, co-amorphous systems offer a tractable experimental project. A small number of well-characterized drug-co-former pairs can be prepared by simple methods (for example solvent evaporation or ball milling), characterized by XRPD, DSC and FTIR, and stored under controlled conditions. Table 9 outlines a practical sequence for such a study. It is the author's suggestion and should be adapted to the facilities available and approved by the supervising faculty.

Table 9. SUGGESTED OUTLINE OF A SMALL EXPERIMENTAL STUDY ON A CO-AMORPHOUS SYSTEM (AUTHOR'S SYNTHESIS)

Step	Activity	Notes
1	Select a poorly soluble model drug and 2 to 3 co-formers with complementary functional groups	Use literature on similar pairs ^{7,12}
2	Prepare physical mixtures and co-amorphous materials at more than one molar ratio	Solvent evaporation or ball milling; record conditions exactly
3	Confirm amorphous, single-phase character	XRPD (halo), DSC (single T _g), compare with Gordon-Taylor estimate
4	Probe interactions	FTIR or Raman band shifts
5	Measure dissolution under non-sink conditions with continuous or frequent sampling	Report concentration-time profile and solid form of any precipitate
6	Run stability storage at dry and humid conditions with defined time points	Re-test by XRPD and DSC; measure moisture uptake
7	Compare with neat amorphous and crystalline drug (and a polymeric dispersion if feasible)	Controls are essential to attribute any benefit to co-amorphization
8	Report fully, including negative results	Follow the reporting items listed in the research-gaps section

Even a small, carefully reported study that includes the humid-storage and non-sink dissolution data that the literature lacks would add genuine value.

14.1 A reporting checklist for co-amorphous studies



Because comparability between studies is currently limited, a minimum reporting set would improve the usefulness of future papers. Table 10 lists items that authors, reviewers and readers can use.

Table 10. SUGGESTED MINIMUM REPORTING ITEMS FOR CO-AMORPHOUS STUDIES

Item	What to report
Materials	Drug and co-former identity, purity, supplier, solid form of the starting material
Composition	Molar and mass ratio; calculated co-former dose per unit dose
Preparation	Method, scale, equipment and critical parameters (temperature, time, solvent, milling conditions)
Amorphous and single-phase evidence	XRPD pattern, Tg value(s) with method and heating rate, estimated detection limit
Interaction evidence	Spectral shifts with controls (neat components, physical mixture)
Stability design	Temperature, relative humidity, packaging, time points, analytical methods; both dry and humid conditions
Dissolution design	Medium, volume, sink or non-sink, sampling frequency, solid form of any precipitate; results for both components if two drugs are present
In vivo design (if done)	Species, dose, comparators including co-former-alone arm, pre-dose characterization, variability
Negative and failed results	Compositions that did not form or did not remain amorphous

15. CONCLUSION

Co-amorphous systems are a physically sound and actively developing approach to stabilizing amorphous drugs and improving the dissolution of poorly water-soluble compounds. Their advantages are the potential for higher drug loading, specific stabilizing interactions and, with drug-drug pairs, combined delivery and synchronized release. Their stability and performance, however, are strongly pair-specific, and the literature contains limited long-term, humid-condition and in vivo evidence. Polymeric ASDs remain the more established option, and the two approaches should be regarded as complementary. Reliable progress will require standardized reporting, longer and more realistic stability studies, pharmacokinetic confirmation, head-to-head comparison with polymeric dispersions, curated data including negative results

for predictive modelling, and early engagement with regulatory expectations.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the Department of Pharmacy, Vikas Group of Institutions, Nunna, Vijayawada, for providing the academic environment and resources that supported the preparation of this review article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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HOW TO CITE: Dr. K. Narendra Kumar Reddy, K. Ravi *, Baiyanaboyina Veeranjanyulu, Cheeli Lavanya, Co-Amorphous Systems for Poorly Water-Soluble Drugs: Molecular Interactions, Physical Stability and Formulation Design, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 10, 2286-2303. <https://doi.org/10.5281/zenodo.23386276>

