



Choosing Co-Crystal Partners for Plant-Derived Drug Candidates Using Molecular Complementarity, Solid-State Interactions, Solubility Gain, and Developability Constraints

George Wilson^{1*}, Chloe Bennett², Ethan Wright¹, Jack Turner³

¹Department of Co-Crystal Partner Selection, Faculty of Pharmacy, University of Dundee, Dundee, United Kingdom.

²Department of Molecular Complementarity and Solid-State Interactions, Faculty of Pharmacy, Newcastle University, Newcastle, United Kingdom.

³Department of Solubility Gain and Developability, Faculty of Pharmacy, University of Aberdeen, Aberdeen, United Kingdom.

ABSTRACT

Co-crystallization has emerged as a promising strategy to enhance the physicochemical properties of plant-derived drug candidates, which often suffer from poor aqueous solubility and limited oral bioavailability. The selection of an appropriate co-crystal partner is a critical step that directly influences the success of co-crystal formation and the developability of the final solid form. This study proposes a systematic framework for choosing co-crystal partners for plant-derived drug candidates by integrating molecular complementarity, solid-state interactions, solubility gain, and developability constraints. Molecular complementarity was assessed through hydrogen-bonding capability, functional group matching, and molecular shape compatibility between the drug and potential co-formers. Solid-state interactions were evaluated using crystal packing analysis, interaction energy calculations, and thermal and spectroscopic characterization. Solubility gain was predicted and experimentally verified through equilibrium solubility studies, while developability constraints including stability, toxicity, regulatory status, and manufacturing feasibility were considered to ensure practical applicability. The proposed approach was applied to several plant-derived drug candidates, and the results demonstrated that a balanced combination of complementarity and solid-state interaction criteria leads to more reliable co-crystal partner selection. The framework provides a rational and efficient tool for screening co-formers, reducing trial-and-error experiments, and accelerating the development of co-crystalline formulations with improved solubility and developability for plant-derived drugs.

Key Words: Co-crystal, Plant-derived drug, Molecular complementarity, Solid-state interaction, Solubility gain, Developability

eIJPPR 2026; 16(4):80-88

HOW TO CITE THIS ARTICLE: Wilson G, Bennett C, Wright E, Turner J. Choosing Co-Crystal Partners for Plant-Derived Drug Candidates Using Molecular Complementarity, Solid-State Interactions, Solubility Gain, and Developability Constraints. Int J Pharm Phytopharmacol Res. 2026;16(4):80-8. <https://doi.org/10.51847/2LNGVPRnF9>

INTRODUCTION

Pharmaceutical co-crystal discovery is often operationalized as a search for a molecular partner that can satisfy an exposed hydrogen-bond donor or acceptor on the active pharmaceutical ingredient. That starting point is chemically useful, but it does not define the whole selection problem. Experimental, knowledge-based, and

computational screening methods make different assumptions about what constitutes a plausible pair and provide non-equivalent evidence about success [1]. A product-oriented search must therefore ask not only whether two molecules can associate, but which evidence is being used to infer that association, under which conditions, and what additional evidence would be

Corresponding author: George Wilson

Address: Department of Co-Crystal Partner Selection, Faculty of Pharmacy, University of Dundee, Dundee, United Kingdom.

E-mail: ✉ g.wilson@dundee.ac.uk

Received: 19 April 2026; **Revised:** 23 July 2026; **Accepted:** 30 July 2026

This is an **open access** journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.



required before the pair becomes pharmaceutically interesting.

Crystal engineering provides the necessary structural vocabulary but also shows why a single-interaction view is inadequate. Supramolecular synthons, intermolecular interaction networks, crystal packing, polymorphism, stoichiometry, and competition among possible solid forms can all influence the properties of a multicomponent crystal [2]. These considerations distinguish interaction plausibility from solid-form realization. A favorable donor–acceptor match can be frustrated by stronger self-association, alternative packing, another stoichiometry, or a different multicomponent state. Conversely, a co-crystal may form through an interaction network not captured by the screening feature initially used to prioritize it.

The computational problem is therefore hierarchical. Early screening should efficiently remove implausible partners, but later decisions should incorporate evidence that is closer to the intended product. Integrated quality-by-design workflows already show that computational prioritization can be coupled to low-material experimental verification rather than treated as a substitute for solid-form testing [3]. The framework proposed here extends that logic: structural complementarity generates a formation prior; prediction and experiment refine confidence in the solid form; measured or model-supported performance determines whether formation is useful; and developability constraints determine whether usefulness is actionable. These layers should remain analytically distinguishable even when combined in a final decision.

Why plant-derived candidates create difficult solid-state design problems

Plant-derived drug candidates make these distinctions especially consequential. Flavonoids and related natural-product scaffolds frequently motivate solid-form intervention because limited aqueous performance, complex hydrogen-bonding patterns, and multiple formulation options can restrict developability; co-crystal

and co-amorphous strategies have therefore been explored across this chemical class [4]. The published herbal-bioactive literature also shows substantial diversity in preparation methods, characterization strategies, and reported solubility outcomes [5]. That heterogeneity argues against assuming that “natural product” is itself a predictive formulation category.

The molecular architecture of many plant-derived candidates can further multiply plausible intermolecular arrangements. Polyhydroxy compounds may present several donors and acceptors while retaining substantial capacity for self-association. Direct comparison of quercetin, hesperidin, resveratrol, and curcumin systems shows that co-crystal formation can depend on competition between self- and heteromolecular interactions rather than on the existence of a single favorable contact [6]. For selection, this means that site count and nominal complementarity should not be interpreted independently of interaction competition and packing context.

Downstream examples illustrate both promise and the danger of overgeneralization. A Biochanin-A co-crystal formulation produced improved formulation and exposure-related outcomes in a specific preclinical setting [7]. A recent chrysin study likewise connected prediction, preparation, solid-state characterization, and biological performance within one candidate system [8]. These cases demonstrate that plant-derived co-crystals can progress beyond formation screening, but they do not establish a class-wide benefit or a universal choice of co-former. The proposed framework therefore treats plant origin as a source of chemically relevant design features and formulation challenges, not as evidence that co-crystallization will necessarily be the preferred intervention.

The distinctions established above are easier to use computationally when they are represented as non-equivalent constructs rather than compressed into a single early-stage score. **Table 1** organizes the resulting definitions and their immediate decision implications.

Table 1. Distinct early-stage constructs in product-oriented co-former selection for plant-derived candidates

Construct	Operational meaning	Plant-derived complication	Decision implication
Molecular complementarity	Plausibility of productive heteromolecular recognition	Multiple donor/acceptor sites and self-association create competing matches	Use as a formation prior, not an acceptance rule
Solid-form realizability	Ability of the pair to occupy a persistent multicomponent crystal state	Alternative packing, stoichiometry, polymorphism, or self-associated states may compete	Require direct solid-form evidence
Formation evidence	Support that the intended co-crystal forms under defined conditions	Outcome may depend on screening method and experimental route	Preserve method and uncertainty with the result
Pharmaceutical performance	Useful change in dissolution, supersaturation, stability, or related product behavior	Property gains are compound- and condition-dependent	Rank performance separately from formation

Developability	Compatibility with processing, acceptable partner space, and product constraints	Candidate chemistry may narrow practical formulation options	Apply constraints before advancing a high-scoring pair
----------------	--	--	--

Note: Proposed construct-definition synthesis. The constructs are intentionally non-equivalent and should not be collapsed into a single unqualified score.

Molecular complementarity at the co-crystal interface

Molecular complementarity is most useful when defined as a multidimensional compatibility hypothesis rather than a synonym for hydrogen-bond matching. Thermodynamic screening demonstrates that pair favorability can be interrogated through a distinct energetic framework, adding information that is not identical to geometric or synthon-based compatibility [9]. The practical implication is that complementary molecular surfaces, donor–acceptor patterns, and thermodynamic tendencies can all inform prioritization, but none independently establishes that the target co-crystal will nucleate, persist, or outperform competing forms.

Available screening studies reinforce this non-equivalence. No single complementarity criterion is sufficient across chemical space; combining thermodynamic or interaction-based heuristics with experimental validation provides more robust screening evidence [9–11]. The key point is not that every method should be used for every pair. Rather, each method should be treated as a measurement of a different component of the formation hypothesis. A molecular-complementarity score is strongest when its domain, representation, and failure modes are explicit.

For plant-derived candidates, this separation helps prevent a common computational shortcut: translating the number or apparent strength of heteromolecular contacts directly into a rank. A candidate rich in hydroxyl groups may appear highly compatible with many co-formers while simultaneously having strong self-association and numerous alternative packing solutions. The framework proposed here therefore represents complementarity as a vector of interpretable evidence—interaction opportunity, thermodynamic plausibility, structural fit, and competition risk—rather than as a single mechanistic truth. Experimental formation can then update that vector without retroactively proving that the original screening rationale was correct.

Hydrogen-bonding and competing interaction motifs

Hydrogen bonding remains central to pharmaceutical co-crystal design because it offers directional, chemically interpretable motifs, but its value lies in context rather than numerical abundance. Comparative screening based on hydrogen-bond propensity, molecular complementarity, and hydrogen-bond energy shows that these descriptors provide overlapping but non-identical predictive information within the tested space [11]. A co-former that ranks well by one criterion may not rank equivalently by

another because each compresses different assumptions about accessibility, geometry, competition, and solid-state realization.

Competition is especially important for polyfunctional plant-derived molecules. The natural-product systems examined across quercetin, hesperidin, resveratrol, and curcumin demonstrate that heteromolecular contacts must compete with pre-existing self-association and alternative intermolecular networks [6]. Thus, the relevant question is not merely “Can this pair hydrogen bond?” but “Is the proposed heteromolecular network competitive with the other states available to both components?”

The same logic cautions against treating aromatic or ionic interactions as secondary decorations around a dominant hydrogen-bond synthon. Crystal-engineering evidence indicates that multicomponent packing can be stabilized by interacting networks whose relative importance changes with molecular structure and crystal environment [2]. For computational selection, the implication is to preserve interaction classes separately long enough to detect conflicting signals. The framework does not assign universal weights to hydrogen-bonding, aromatic, ionic, or dispersion contributions. Instead, it proposes that their evidence be integrated conditionally, with uncertainty retained when multiple interaction motifs imply competing solid-state outcomes.

Predicting whether a co-crystal will form

Recent co-crystal-prediction work expands the available representation space well beyond hand-selected descriptors. Point-cloud molecular representations have been used to train machine-learning models for formation prediction, illustrating that the geometry and form of the molecular representation are themselves consequential modeling choices [12]. Hybrid strategies can also incorporate molecular thermodynamics into machine learning, providing a route for combining physical information with data-driven classification [13]. These approaches support formation ranking, but their reported performance remains conditional on dataset construction, chemical coverage, representation, and validation design. Other model families make different assumptions about how pair compatibility should be encoded. Deep supramolecular language processing treats molecular representations as learnable sequences for pair-level prediction [14]. Graph-neural-network approaches encode molecular connectivity and relational features for co-former discovery [15]. Earlier artificial-neural-network

work established that co-crystal formation can also be learned statistically from curated structural-database examples [16]. Collectively, these studies show that formation prediction is tractable as a data-driven task, while simultaneously making clear that “the model” is not a singular object: representation, training labels, split strategy, chemical-domain overlap, and the definition of a positive or negative pair all shape the inference.

For the proposed framework, model output is therefore a formation prior, not a pharmaceutical decision. A useful predictor should ideally report applicability and uncertainty alongside rank, preserve the distinction between what is learned from structural databases and what is verified experimentally, and avoid forcing chemically distant plant-derived candidates into confident classifications merely because a score can be produced. The computational objective at this stage is to allocate experimental attention more intelligently. Whether a correctly predicted co-crystal is worth developing is a separate question addressed by the subsequent performance and developability layers.

Formation probability is not the same as pharmaceutical value

A formation classifier answers a narrow question: whether an API-co-former pair resembles combinations that have produced a co-crystal under the evidence regime used to train or validate the model. Pharmaceutical selection asks a broader question: whether investing in that pair is justified after considering release behavior, solid-form persistence, processability, partner acceptability, and uncertainty. Property-driven active learning demonstrates that experimental selection can already be directed toward predicted properties and uncertainty rather than binary formation alone [17]. This distinction is central to the proposed framework because formation is treated as an intermediate state of evidence, not the optimization target. The practical difference becomes apparent when prediction is followed by direct characterization. Machine-learning-guided screening of imatinib co-formers coupled formation selection to physicochemical assessment, illustrating that successful prediction still requires product-relevant measurements [18]. Likewise, virtual-screening studies compare algorithms on formation labels, but a better formation benchmark does not by itself establish superior dissolution, stability, or manufacturability [19]. Confidence-aware models can improve the transparency of salt/cocrystal classification and ranking, yet model confidence remains a property of the prediction system rather than empirical pharmaceutical certainty [20]. A further limitation is the scarcity of reliable failed-pair labels; semi-supervised work explicitly addresses the fact that published cocrystal data contain many positives but

comparatively limited negative evidence [21]. The proposed selection logic therefore preserves formation probability, confidence, applicability domain, and downstream utility as separate fields.

Formation success is also conditional on the experiment used to observe it. A negative result under one solvent, stoichiometry, temperature, or preparation route is not automatically evidence that the molecular pair is intrinsically incapable of co-crystallization; equally, one positive preparation does not establish a robust manufacturing region. For computational use, the label should therefore remain attached to the experimental context that generated it. This preserves the difference between “not observed,” “observed under defined conditions,” and “reproducibly accessible,” which would otherwise be compressed into the same binary training target.

Solubility and dissolution gain

A co-crystal can be pharmaceutically attractive because it changes the free-energy landscape governing release, but “solubility gain” is too coarse to represent what happens during dissolution. ATR-FTIR spectroscopic imaging of a theophylline cocrystal demonstrates that dissolution can be spatially and temporally heterogeneous, revealing processes that a single endpoint concentration can obscure [22]. For selection, equilibrium solubility, dissolution rate, supersaturation generation, supersaturation persistence, and precipitation should therefore be treated as related but non-identical observables.

Cocrystal performance is governed jointly by solubility advantage, dose/solubility ratio and precipitation kinetics, so a high intrinsic solubility gain does not guarantee sustained supersaturation [23–25]. This makes the relevant objective closer to useful release under product-relevant conditions than to maximal thermodynamic solubility. The distinction also creates an explicit role for medium composition, pH, dose, additives, and the kinetics of nucleating a competing drug-rich phase.

Solution-mediated transformation further complicates ranking because an initially favorable cocrystal can generate supersaturation while simultaneously driving conversion at the solid–liquid interface; the transformation pathway can depend on the rate at which supersaturation is generated [26]. Predictive shortcuts must also respect their applicability domains. A recent rapid solubility method is explicitly scoped to neutral 1:1 cocrystals in aqueous media [27], whereas incongruently melting systems can exhibit phase-equilibrium behavior that makes simple stoichiometric expectations unreliable [28]. The proposed framework therefore carries both performance estimates and the conditions under which they are meaningful.

This conditional view matters for ranking because two co-formers can reverse order when the objective changes from equilibrium concentration to maintained supersaturation. The relevant comparison should therefore record the medium, pH, dose or loading, time horizon, and competing solid phase whenever those variables materially affect interpretation. Such metadata are not secondary annotations: they define the state under which the claimed

advantage exists. In a product-oriented model, missing condition information should lower interpretive confidence rather than be silently replaced by an assumed standard dissolution environment.

These distinctions are summarized in **Table 2** so that apparent “dissolution advantage” is not represented as a single interchangeable quantity.

Table 2. Distinguishing product-relevant meanings of apparent co-crystal dissolution advantage

Performance construct	What it represents	What can defeat the apparent gain	Selection meaning
Equilibrium solubility advantage	Thermodynamic concentration advantage under defined conditions	Different pH, stoichiometry, ionization, or phase equilibrium	Useful only within its stated domain
Dissolution-rate advantage	Faster transfer from solid to solution	Rapid depletion, surface conversion, or competing phase formation	Kinetic benefit; not persistence
Supersaturation generation	Transient concentration above drug equilibrium solubility	Insufficient duration or rapid nucleation	Requires time-resolved interpretation
Supersaturation persistence	Duration of elevated dissolved drug	Dose-dependent precipitation and medium effects	Closer to usable release performance
Solid-liquid transformation	Change of the dissolving solid to another phase	Loss of the intended co-crystal at the interface	Failure mode that must remain explicit

Note: Proposed conceptual distinction. These constructs should be measured or modeled separately before any product-level ranking is attempted.

Figure 1 integrates the manuscript’s mature argument: structural plausibility narrows the search, but partner ranking emerges only after formation, release, stability,

uncertainty, and developability are kept analytically distinct and repeatedly confronted with experiment.

84

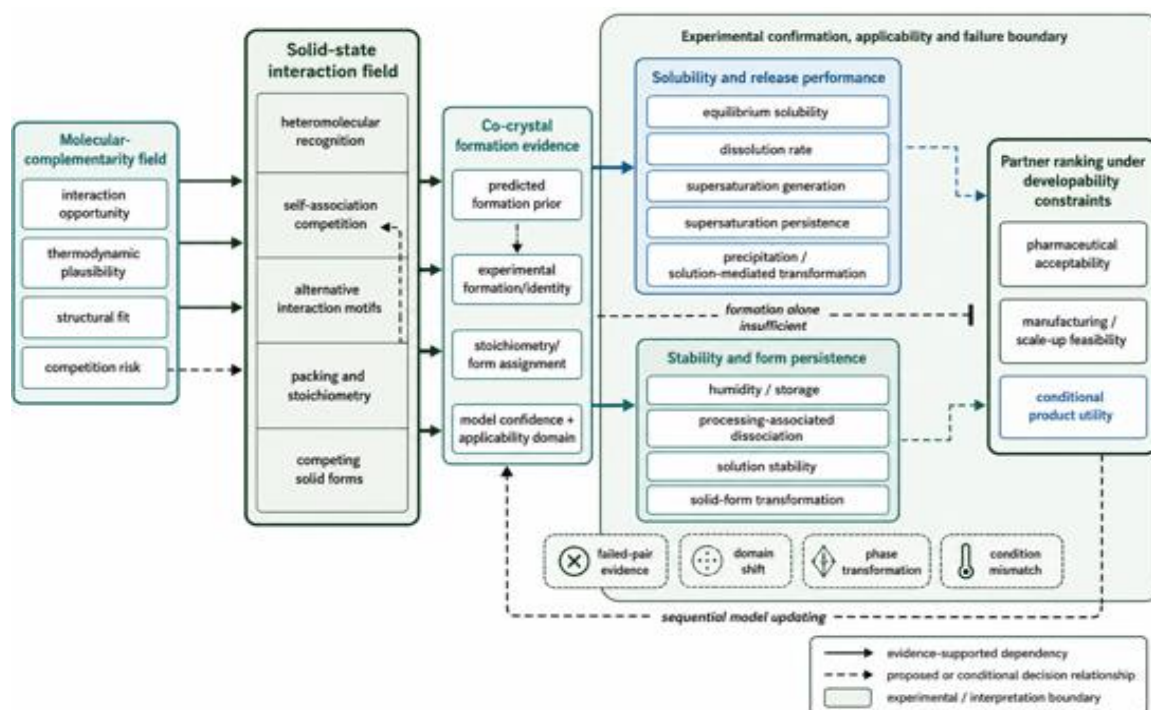


Figure 1. Product-oriented co-former selection as a constrained, uncertainty-updated solid-form decision system

Stability under humidity, temperature, and storage

Stability assessment must distinguish moisture sensitivity, processing-associated dissociation and solution-phase

stability because these failure modes arise in different contexts [29–31]. A pair that forms reproducibly under screening conditions can therefore remain unattractive if

the multicomponent phase is hygroscopically fragile, dissociates during manufacture, or transforms after contact with dissolution media. Treating all three behaviors as one “stability score” would conceal the conditions under which failure occurs.

Humidity is primarily a dry-state stress, and cocrystallization can modify moisture sensitivity without guaranteeing improvement for every system. Processing adds a different perturbation: spray-drying evidence shows that polymers and process conditions can influence whether a cocrystal is retained or dissociates. Solution stability is different again because concentrations, pH, cofomer activity, and competing phases change after wetting. In the proposed framework, these tests occupy separate fields and can veto or downgrade an otherwise attractive pair without changing the fact that the co-crystal formed successfully.

The same candidate may consequently occupy different positions in different stability subspaces. A co-crystal that is robust in a dry accelerated-storage study could still dissociate during wet granulation or transform after dissolution begins; the reverse pattern is also possible. This is why the proposed framework records the stress context alongside the outcome. Stability is used as a conditional constraint linked to environment and process history, not as a permanent molecular attribute inferred from the crystal structure alone.

A multi-criterion co-former selection framework

The central proposal is to treat co-former choice as a constrained, uncertainty-bearing decision rather than a single-score optimization problem. Formation evidence, release performance, stability, and developability answer different questions and should remain visible until the decision stage. This follows from the non-equivalence of screening evidence discussed earlier [1]. The framework therefore has two types of criteria: gates, which identify conditions that make a partner unacceptable or uninterpretable, and rankable objectives, which compare remaining candidates without implying universal weights. A practical implementation would begin with molecular and thermodynamic plausibility, then carry forward predicted formation probability together with model confidence and applicability information. Experimental formation, identity, stoichiometry, and form assignment update that prior. Candidates that survive enter performance assessment, where equilibrium solubility is interpreted alongside dissolution, supersaturation persistence, precipitation, transformation, and relevant conditions. Mechanistic dissolution evidence shows why these variables can trade against one another rather than move monotonically [23]. Stability and developability are then evaluated in parallel before conditional ranking.

No numerical weighting scheme is proposed because the literature does not establish a universal utility function across products. Instead, the framework proposes explicit abstention where evidence is insufficient, preservation of uncertainty where models extrapolate beyond their domains, and product-specific ranking among candidates that satisfy non-compensable constraints. The result is not a predicted “best co-former” in the abstract; it is a transparent account of why a particular partner deserves the next experiment for a defined product objective.

The decision architecture is therefore partially ordered rather than fully compensatory. Failure of identity confirmation, unacceptable partner status, or severe form instability should block advancement instead of being numerically cancelled by a favorable dissolution signal. By contrast, several surviving candidates may be compared on product-dependent objectives, such as stronger supersaturation persistence versus easier process control. This preserves traceability: a development team can see which criterion excluded a pair, which evidence merely lowered its rank, and where the ranking remains sensitive to missing information.

Filtering by safety and pharmaceutical acceptability

Molecular complementarity cannot compensate for an unacceptable co-former. Rational co-former-selection literature treats pharmaceutical acceptability as part of design rather than an afterthought [32]. This does not mean that food use, GRAS status, prior pharmaceutical use, or any other single designation automatically confers regulatory acceptability for a new drug product. Route, dose, exposure, jurisdiction, impurity profile, and product context remain relevant.

Manufacturing feasibility imposes a second practical filter. Development and scale-up evidence for solution cocrystallization shows that laboratory formability does not establish robust large-scale production [33]. Solvent choice, supersaturation control, nucleation, isolation, drying, and reproducible control of solid form can become decisive. The proposed framework therefore treats acceptability and manufacturability as constraints that cannot simply be offset by a high computational formation score. Candidates failing these gates should not remain highly ranked merely because their molecular complementarity is attractive.

This gate also prevents a common category error in computational screening: treating every molecule in a structural database or commercial co-former library as equally actionable. Chemical availability is not the same as pharmaceutical acceptability, and pharmaceutical acceptability is not the same as product-specific regulatory suitability. This distinction should remain visible

whenever candidate libraries are assembled computationally.

Balancing solid-state stability against release performance

A useful co-crystal must occupy an awkward middle ground: sufficiently stable to be manufactured, stored, and delivered as the intended form, yet capable of generating useful release when exposed to the relevant medium. High solubility advantage can increase the thermodynamic drive toward supersaturation and precipitation, making maximal intrinsic solubility an incomplete objective [23]. Rapid release may also accelerate solution-mediated transformation, so apparent early performance can coexist with loss of the original solid form [26].

The framework therefore interprets stability and release as a qualitative Pareto problem. A candidate need not maximize every property; it should avoid unacceptable failure while providing a product-relevant advantage over realistic alternatives. Solution-stability evidence reinforces that form persistence is condition-dependent rather than an intrinsic binary attribute [31]. No universal frontier or weighting is claimed. The proposed decision is conditional on product dose, medium, storage environment, process route, and the alternative solid forms available for the same API.

Accordingly, the framework favors dominated-solution removal over declaring one universally optimal balance. A pair clearly inferior in both persistence and release can be deprioritized, whereas trade-off cases should remain visible until the intended dosage form defines which compromise is acceptable.

Experimental screening as sequential model updating

Sequential experimentation is preferable to a one-shot computational ranking when measurements can materially alter the next decision. Property-driven active learning provides a formal precedent for selecting new cocrystal experiments using both predicted value and uncertainty [17]. In the proposed framework, early experiments should therefore be chosen not only to confirm the top-ranked pair but also to reduce uncertainty in regions where model predictions are influential but poorly supported.

Prediction–experiment disagreement is especially informative. Experimental validation studies demonstrate that *in silico* cocrystal predictions require direct checking [10]. A failed formation experiment should update beliefs about the pair, the local chemical neighborhood, and potentially the model representation rather than being discarded as an inconvenient negative. This is important because failed-pair information is already sparse in published datasets [21]. The proposed sequential loop consequently retains negative and ambiguous outcomes,

updates formation and performance evidence separately, and can redirect experimental effort when the original mechanistic rationale is weakened.

The most informative next experiment may therefore be a boundary case rather than the highest-ranked candidate. Testing a pair close to an applicability limit, or one for which structural and thermodynamic screens disagree, can reveal whether the current representation is missing a relevant feature. Sequential updating is thus proposed as both a discovery strategy and a model-diagnostics strategy.

Limits of current predictive evidence

The framework is constrained first by its evidence base. Published cocrystal datasets are enriched for successful outcomes, while failed or ambiguous pairs are less consistently available; this complicates calibration and the interpretation of unlabeled examples [21]. Representation-sensitive models can perform strongly on curated benchmarks, but such results do not establish external validity for chemically unusual plant-derived candidates [12]. Prospective testing across genuinely held-out natural-product scaffolds remains necessary.

Second, downstream property prediction has explicit applicability limits. A rapid solubility method developed for neutral 1:1 cocrystals should not be extrapolated without justification to ionizable systems, alternative stoichiometries, salts, or more complicated phase behavior [27]. Incongruently melting systems provide a direct reminder that phase equilibria can defeat simple ranking heuristics [28].

Third, translational evidence is uneven. The Biochanin-A example demonstrates that a plant-derived cocrystal can deliver downstream preclinical benefits in a defined formulation and experimental setting [7], but it does not establish class-wide therapeutic superiority or clinical effectiveness. The present framework consequently organizes decision evidence; it does not validate a universal algorithm, predict regulatory acceptance, or replace product-specific experimental development.

A further limitation is that the framework does not specify universal acquisition functions, acceptance thresholds, or endpoint weights. Those quantities would require prospective, product-specific calibration against formation and performance outcomes. Until such validation exists, the framework should be used to structure evidence and experiment choice rather than to generate an autonomous development decision.

CONCLUSION

Co-former selection for plant-derived drug candidates should be organized around the product question rather than the crystallographic event alone. Molecular

complementarity and supramolecular interactions remain essential because they define plausible heteromolecular states, but they are only the beginning of the decision. Formation evidence must remain distinct from useful dissolution, stability, process robustness, acceptability, and uncertainty.

The framework proposed here converts that distinction into a computational pharmaceuticals architecture in which structural plausibility generates hypotheses, experimental evidence updates them, performance and stability remain parallel decision dimensions, and developability constrains the final ranking. It deliberately avoids universal weights, deterministic thresholds, and claims that a predicted co-crystal is automatically a better drug product.

Its practical implication is a change in what is optimized. The preferred co-former is not necessarily the partner most likely to crystallize, nor the one producing the largest isolated solubility increase. It is the partner for which the combined, condition-specific evidence justifies the next development decision while important failure modes remain visible. Prospective validation is required before this framework can be treated as a predictive selection system.

Its value is therefore organizational and falsifiable: each stage exposes assumptions that can be challenged by the next measurement rather than hiding them inside one composite score.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

- [1] Parkes A, Ziaee A, O'Reilly E. Evaluating experimental, knowledge-based and computational cocrystal screening methods to advance drug-drug cocrystal fixed-dose combination development. *Eur J Pharm Sci.* 2024;203:106931. doi:10.1016/j.ejps.2024.106931
- [2] Bolla G, Sarma B, Nangia AK. Crystal engineering of pharmaceutical cocrystals in the discovery and development of improved drugs. *Chem Rev.* 2022;122(13):11514-603. doi:10.1021/acs.chemrev.1c00987
- [3] Ross SA, Ward A, Basford P, McAllister M, Douroumis D. A quality by design strategy for cocrystal design based on novel computational and experimental screening strategies: Part A. *Drug Deliv Transl Res.* 2025;15(7):2448-66. doi:10.1007/s13346-024-01743-2
- [4] Rode K, Maji I, Mahajan S, Singh PK. Unlocking the potential of flavonoid-based co-crystal and co-amorphous systems. *Drug Discov Today.* 2024;29(7):104050. doi:10.1016/j.drudis.2024.104050
- [5] Rathi R, Kaur S, Singh I. A review on co-crystals of herbal bioactives for solubility enhancement: Preparation methods and characterization techniques. *Cryst Growth Des.* 2022;22(3):2023-42. doi:10.1021/acs.cgd.1c01408
- [6] Li D, Chen W, Zhou L, Xu L, He F, Heng JYY, et al. Uncovering cocrystal formation and competition mechanism of polyhydroxy natural products: Cases of quercetin, hesperidin, resveratrol, and curcumin. *Cryst Growth Des.* 2024;24(11):4652-67. doi:10.1021/acs.cgd.4c00291
- [7] Sripadi HP, Kaur R, Koli SM, Sharma N, Vijaya Sarathi UVR, Nanubolu JB, et al. Biochanin-A cocrystal formulation improves bioavailability and ameliorates cerulein-induced pancreatitis by attenuating the inflammation. *Int J Pharm.* 2024;667(Pt A):124874. doi:10.1016/j.ijpharm.2024.124874
- [8] Zhang B, Xie Y, Ji W, Zhang L, Wang Q, Yang S, et al. Chrysin cocrystals: Prediction, preparation, characterization, and in vitro/in vivo evaluation. *Mol Pharm.* 2026;23(1):118-26. doi:10.1021/acs.molpharmaceut.5c00397
- [9] Veith H, Schleinitz M, Schauerte C, Sadowski G. Thermodynamic approach for co-crystal screening. *Cryst Growth Des.* 2019;19(6):3253-64. doi:10.1021/acs.cgd.9b00103
- [10] Sarjeant AA, Abourahma H, Thomas SR, Cook C, Yin Z. On the road to cocrystal prediction: A screening study for the validation of in silico methods. *Cryst Growth Des.* 2024;24(13):5486-93. doi:10.1021/acs.cgd.4c00220
- [11] Sarkar N, Gonnella NC, Krawiec M, Xin D, Aakeröy CB. Evaluating the predictive abilities of protocols based on hydrogen-bond propensity, molecular complementarity, and hydrogen-bond energy for cocrystal screening. *Cryst Growth Des.* 2020;20(11):7320-27. doi:10.1021/acs.cgd.0c00987
- [12] Ahmadi S, Ghanavati MA, Rohani S. Machine learning-guided prediction of cocrystals using point cloud-based molecular representation. *Chem Mater.* 2024;36(3):1153-61. doi:10.1021/acs.chemmater.3c01437
- [13] Song Y, Ding Y, Su J, Li J, Ji Y. Unlocking the potential of machine learning in co-crystal prediction by a novel approach integrating molecular



- thermodynamics. *Angew Chem Int Ed Engl.* 2025;64(21). doi:10.1002/anie.202502410
- [14] Birolo R, Özçelik R, Aramini A, Gobetto R, Chierotti MR, Grisoni F. Deep supramolecular language processing for co-crystal prediction. *Angew Chem Int Ed Engl.* 2025;64(29). doi:10.1002/anie.202507835
- [15] Jiang Y, Yang Z, Guo J, Li H, Liu Y, Guo Y, et al. Coupling complementary strategy to flexible graph neural network for quick discovery of coformer in diverse co-crystal materials. *Nat Commun.* 2021;12(1):5950. doi:10.1038/s41467-021-26226-7
- [16] Devogelaer JJ, Meekes H, Tinnemans P, Vlieg E, de Gelder R. Co-crystal prediction by artificial neural networks. *Angew Chem Int Ed Engl.* 2020;59(48):21711-8. doi:10.1002/anie.202009467
- [17] Appiah SA, McDonald MA. Property-driven cocrystal discovery via Gaussian processes and active learning. *Cryst Growth Des.* 2026;26(7):2688-702. doi:10.1021/acs.cgd.5c01417
- [18] Liang X, Liu S, Li Z, Deng Y, Jiang Y, Yang H. Efficient cocrystal coformer screening based on a machine learning strategy: A case study for the preparation of imatinib cocrystal with enhanced physicochemical properties. *Eur J Pharm Biopharm.* 2024;196:114201. doi:10.1016/j.ejpb.2024.114201
- [19] Jayachandiran R, Akkarapakam SJ, Thangavel K. Virtual screening of pharmaceutical cocrystals using machine learning algorithms. *Cryst Growth Des.* 2025;25(9):3100-9. doi:10.1021/acs.cgd.5c00149
- [20] Ghanavati MA, Khalili B, Alberico D, Rohani S. Machine learning-driven discovery of multicomponent pharmaceutical solid forms via DualNet: Confidence-aware prediction and ranking of salts and cocrystals. *Int J Pharm.* 2025;684:126117. doi:10.1016/j.ijpharm.2025.126117
- [21] Ghanavati MA, Moosavi SM, Rohani S. A multimodal semi-supervised learning framework for pharmaceutical cocrystals prediction. *J Chem Inf Model.* 2026;66(15):8942-55. doi:10.1021/acs.jcim.6c01386
- [22] Tatsumi Y, Shimoyama Y, Kazarian SG. Analysis of the dissolution behavior of theophylline and its cocrystal using ATR-FTIR spectroscopic imaging. *Mol Pharm.* 2024;21(7):3233-9. doi:10.1021/acs.molpharmaceut.4c00002
- [23] Cavanagh KL, Kuminek G, Rodríguez-Hornedo N. Cocrystal solubility advantage and dose/solubility ratio diagrams: A mechanistic approach to selecting additives and controlling dissolution-supersaturation-precipitation behavior. *Mol Pharm.* 2020;17(11):4286-301. doi:10.1021/acs.molpharmaceut.0c00713
- [24] Machado TC, Kuminek G, Cardoso SG, Rodríguez-Hornedo N. The role of pH and dose/solubility ratio on cocrystal dissolution, drug supersaturation and precipitation. *Eur J Pharm Sci.* 2020;152:105422. doi:10.1016/j.ejps.2020.105422
- [25] Newman LM, Kavanagh ON, Machado TC. DSPindex guides dose selection to extend drug supersaturation lifetime during cocrystal dissolution. *Int J Pharm.* 2025;671:125298. doi:10.1016/j.ijpharm.2025.125298
- [26] Fan R, Chen A, Yu Y, Cai T, Guo M. Solution-mediated phase transformation of cocrystals at the solid-liquid interface: Relationships between the supersaturation generation rate and transformation pathway. *Int J Pharm.* 2025;668:124969. doi:10.1016/j.ijpharm.2024.124969
- [27] Rasmussen AJ, Guidetti M, Hilfiker R, Bauer-Brandl A. A fast method to predict solubility of neutral cocrystals in aqueous media. *Eur J Pharm Sci.* 2026;221:107499. doi:10.1016/j.ejps.2026.107499
- [28] Nasrallah S, Gavali T, Yavuz I, Minceva M. Solubility of incongruently melting active pharmaceutical ingredient cocrystals: The hydrochlorothiazide-nicotinamide system. *Mol Pharm.* 2026;23(3):1770-84. doi:10.1021/acs.molpharmaceut.5c01520
- [29] Dhondale MR, Thakor P, Nambiar AG, Singh M, Agrawal AK, Shastri NR, et al. Co-crystallization approach to enhance the stability of moisture-sensitive drugs. *Pharmaceutics.* 2023;15(1):189. doi:10.3390/pharmaceutics15010189
- [30] Shao S, Stocker MW, Zarrella S, Korter TM, Singh A, Healy AM. In situ cocrystallization via spray drying with polymer as a strategy to prevent cocrystal dissociation. *Mol Pharm.* 2023;20(9):4770-85. doi:10.1021/acs.molpharmaceut.3c00564
- [31] Alvani A, Shayanfar A. Solution stability of pharmaceutical cocrystals. *Cryst Growth Des.* 2022;22(10):6323-37. doi:10.1021/acs.cgd.2c00787
- [32] Singh M, Barua H, Jyothi VGSS, Dhondale MR, Nambiar AG, Agrawal AK, et al. Cocrystals by design: A rational coformer selection approach for tackling the API problems. *Pharmaceutics.* 2023;15(4):1161. doi:10.3390/pharmaceutics15041161
- [33] Saha A, Ahangar AA, Dar AA, Thirunahari S, Parambil JV. Pharmaceutical cocrystals: A perspective on development and scale-up of solution cocrystallization. *Cryst Growth Des.* 2023;23(11):7558-81. doi:10.1021/acs.cgd.2c01553