



Excipient Compatibility as a Predictive Problem for Botanical Actives Across Chemical Stability, Interfacial Interactions, Processing Conditions, and Dosage-Form Performance

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ABSTRACT

Excipient compatibility is commonly treated as a screening property assigned to a drug–excipient pair, yet formulation failure usually emerges from a material system exposed to a particular environment and manufacturing history. This problem is amplified for botanical actives, whose solid state, intermolecular organization, carrier association, and chemical lability can change with formulation architecture. This original pharmaceutical-science framework reframes compatibility as a context-conditioned prediction problem spanning chemical degradation, moisture and oxygen exposure, microenvironmental pH, interfacial interactions, processing stress, and dosage-form performance. The analysis distinguishes intrinsic material attributes from state variables created by composition, storage, and processing; separates evidence of interaction from evidence of mechanism; and treats formulation performance as a downstream consequence rather than a surrogate definition of compatibility. A proposed predictive architecture integrates active identity and state, excipient grade and functionality, environmental exposure, process history, interface characteristics, analytical evidence, and endpoint-specific outcomes. Predictions are positioned as hypotheses for experimental prioritization rather than final compatibility verdicts, with orthogonal confirmation and model updating required before transfer across formulations. The framework is particularly cautious for complex botanical mixtures, where composition, batch variability, unidentified constituents, and co-solute effects may exceed available molecular representations. The approach therefore does not provide a universal compatibility score or validated decision threshold. Instead, it organizes how formulation-relevant context can be preserved so that compatibility failure can be forecast, interrogated, and revised more systematically before long-term stability and dosage-form performance are fully known.

Key Words: Botanical actives, Excipient compatibility, Formulation stability, Interfacial interactions, Pharmaceutical processing, Predictive pharmaceuticals

eIJPPR 2026; 16(4):10-19

HOW TO CITE THIS ARTICLE: Fedorova E, Volkov A, Morozova I, Kuznetsov D. Excipient Compatibility as a Predictive Problem for Botanical Actives Across Chemical Stability, Interfacial Interactions, Processing Conditions, and Dosage-Form Performance. Int J Pharm Phytopharmacol Res. 2026;16(4):10-19. <https://doi.org/10.51847/k5UWV2QnSY>

INTRODUCTION

Drug–excipient compatibility has traditionally been approached as a preformulation question: combine an active with a candidate excipient, apply stress, and classify

the pair as compatible or incompatible. That approach is useful operationally, but it compresses a conditional phenomenon into a material label. Recent machine-learning studies show that compatibility patterns can be predicted from curated drug–excipient data and then

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Received: 29 March 2026; **Revised:** 02 July 2026; **Accepted:** 08 July 2026

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challenged experimentally, supporting the premise that at least some failure risk is predictable before exhaustive testing [1, 2]. What such models learn, however, is defined by the historical labels, chemical representations, formulation domains, and validation conditions supplied to them. Predictability therefore does not imply that compatibility is an intrinsic, context-free property.

This article starts from a different premise: an excipient is part of the experimental environment experienced by the active ingredient. Excipients can influence stability through moisture handling, impurity burden, local acid–base conditions, molecular mobility, surface interactions, and other formulation-dependent mechanisms [3]. The relevant scientific object is therefore not only an active–excipient pair, but an active state exposed to a specified excipient state, composition, process history, storage environment, and dosage-form architecture. This distinction matters because the same nominal excipient may differ by grade, residual impurities, water content, particle characteristics, or processing response.

Computational formulation work further demonstrates that material composition and formulation structure can be represented as design variables rather than treated exclusively through sequential trial-and-error experiments [4]. The proposal developed here extends that logic specifically to compatibility. It does not assume one universal endpoint. Chemical degradation, solid-state transformation, process-induced change, adsorption or complexation, and loss of dosage-form performance should remain analytically distinguishable because each may require different features, experiments, and validation criteria. Compatibility is therefore framed as a conditional prediction about a formulation state and a defined failure mode, not as a permanent descriptor attached to either ingredient.

Why botanical actives complicate compatibility assessment

Botanical actives sharpen this problem because formulation can alter the state in which the nominal molecule actually exists. Curcumin–polyvinylpyrrolidone dispersions show that polymer characteristics affect amorphous-system behavior; resveratrol solid dispersions depend on freeze-drying conditions; and curcumin–hesperetin formulations demonstrate that added components can change the thermal process window of a polymeric system [5-7]. These studies do not establish a general law for botanical molecules, but together they show why molecular identity alone is an incomplete predictor of formulation behavior.

A second complication is that botanical actives are often developed with co-actives or carriers that create new intermolecular environments. Curcumin–piperine co-amorphous systems link intermolecular organization with stability and synchronized release behavior [8]. Resveratrol nanocrystal formulations incorporated into mesoporous material similarly demonstrate that carrier architecture can affect developability and downstream performance [9]. In neither case should improved release or pharmacokinetic behavior be mistaken for proof of chemical compatibility; performance is a consequence domain that must remain separate from the evidence used to infer interaction.

The construct used in this article therefore distinguishes the identity of the botanical active from its physical state, formulation partners, local environment, processing exposure, and measured endpoint. **Table 1** makes those distinctions explicit before later sections examine how they interact.

Table 1. Compatibility constructs that must remain separate when botanical actives are formulated

Construct	Working definition in this framework	Why separation matters
Active identity	Defined botanical molecule or characterized active fraction entering formulation	Identity does not specify solid state, local environment, or mixture context
Active state	Crystalline, amorphous, co-amorphous, confined, solvated, or otherwise formulation-dependent state	State can change reactivity, mobility, dissolution, and analytical response
Excipient state	Grade- and condition-dependent material presented to the active	Water, impurities, particle properties, and functionality can vary within a nominal excipient
Interaction evidence	Measured indication that components or states influence one another	An analytical change need not establish a chemical mechanism
Compatibility endpoint	Defined failure or acceptable-performance outcome being predicted	Chemical stability, physical stability, processability, and release are not interchangeable labels
Formulation context	Composition, ratios, architecture, processing history, and storage exposure	A pairwise observation may not transfer to the finished multicomponent dosage form

note. Definitions are proposed for this framework and are intended to preserve distinctions that are otherwise easily collapsed during compatibility screening.

The mature argument is summarized visually in **Figure 1**: compatibility is treated as an integrated, context-conditioned state in which chemical, interfacial,

processing, and performance domains remain distinct while feeding a common prediction-and-validation problem.

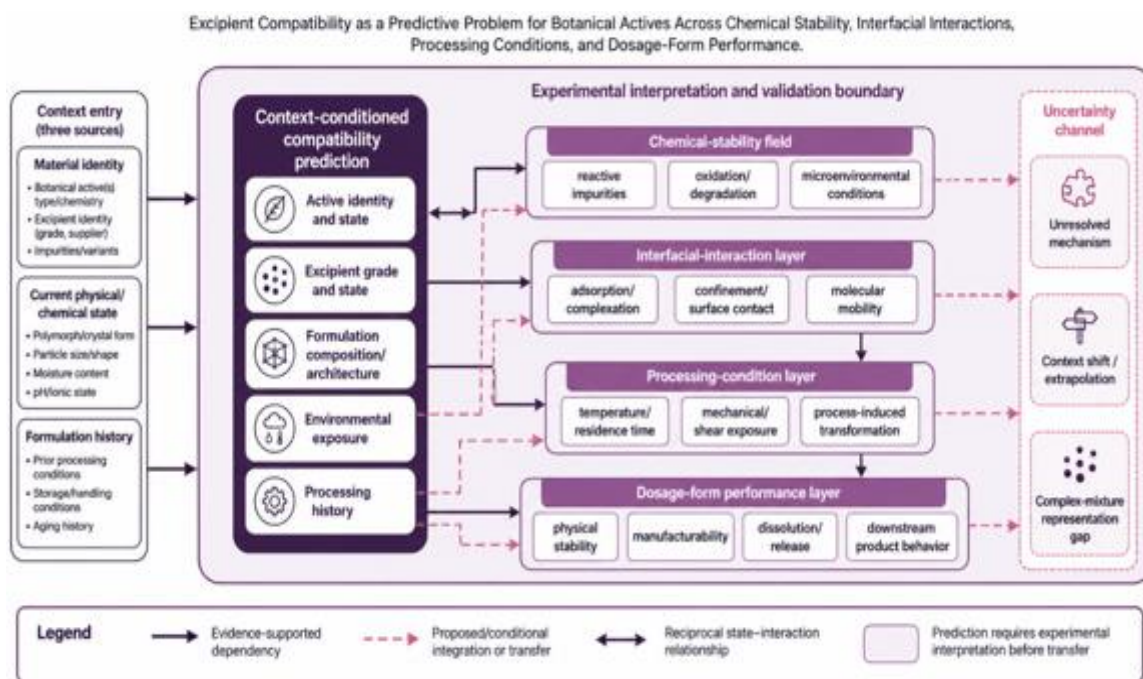


Figure 1. Context-conditioned architecture of excipient compatibility for botanical actives

Chemical degradation at drug–excipient interfaces

Chemical incompatibility is most informative when expressed as a plausible reaction pathway under specified conditions. Oxidative degradation provides a clear example: excipient-derived peroxides and related reactive impurities can contribute to drug oxidation, but their importance depends on active chemistry, oxygen availability, moisture, light exposure, and formulation state [10]. A screening result that identifies “incompatibility” without preserving those conditions loses information required for prediction and mitigation.

Material grade and processing can also interact. In hot-melt-extruded amorphous dispersions, copovidone properties and processing conditions have been associated with differences in impurity formation, release, and stability, showing that an excipient name alone may be too coarse a descriptor [11]. Excipient degradation products can themselves become formulation liabilities, as illustrated by impurity pathways documented for lipid-based excipients in liposomal products [12]. These examples differ in dosage form and chemistry, so the transferable conclusion is limited: excipient composition and transformation history can enter the degradation mechanism and should be represented when relevant.

Reaction-specific forecasting further supports a conditional view. Oxygen-dependent accelerated-stability modeling can parameterize degradation sensitivity to oxygen exposure [13], while a modified Arrhenius approach to solid-state nitrosation incorporated temperature, relative humidity, and excipient conditions into prediction of a defined reaction pathway [14]. These

models do not provide universal compatibility coefficients. Instead, they demonstrate the more modest but useful principle that formulation failure becomes more predictable when the model encodes mechanistically relevant exposures rather than relying on ingredient identity alone.

Moisture, oxygen, and microenvironmental pH

Moisture should not be represented as a single external relative-humidity value. Excipients differ in sorption, retention, redistribution, and moisture-scavenging behavior, thereby shaping the local water environment experienced by a drug [15]. The physical form of the formulation matters as well: lactose powders and tablets can show different moisture responses, demonstrating that material behavior measured before compaction need not map directly onto the finished dosage form [16]. Cross-scale work linking powder measurements to tablet stability reinforces this requirement. Moisture prediction improved when tablet structure and porosity were treated explicitly rather than assuming that powder sorption alone defined the product environment [17]. The proposed framework therefore treats environmental exposure and formulation-local state as separate features. One describes what the product encounters; the other describes what the formulation creates internally.

Microenvironmental pH adds another local variable. A quantitative method for formulation microenvironmental pH shows that local acid–base conditions can be measured rather than inferred only from bulk solution behavior [18]. Moisture may also arise from within a formulation: in-situ-

generated water has been shown to contribute to salt disproportionation [19]. Finally, relative-humidity cycling demonstrates that exposure history can matter, so identical terminal humidity values may not represent identical stability trajectories [20].

Together, these findings argue against static compatibility descriptors. Water activity, oxygen access, local pH, and exposure history can act as moderators of chemical or physical change. They should enter prediction only where supported by the active's chemistry and dosage-form mechanism; none should be treated as a universal causal driver.

Adsorption, complexation, and surface interactions

Interfacial interactions complicate compatibility because they can be stabilizing, destabilizing, or performance-enhancing depending on the system. Computationally supported ternary solid-dispersion design shows that formulation behavior can depend on the joint presence of drug, coformer, and polymer rather than on a single pairwise interaction [21]. This is important for botanical actives because carrier-rich formulations frequently place molecules in confined or highly interactive states.

At the molecular-modeling level, apparently reasonable compatibility surrogates also require validation. Molecular-dynamics work on drug–polymer amorphous dispersions has shown that solvation free-energy reasoning can become a trap when the selected metric does not correspond reliably to the formulation outcome of interest [22]. The lesson is methodological: a molecular descriptor is useful only if its physical interpretation and prediction target remain aligned.

Surface architecture adds a further layer. Mesoporous silica systems demonstrate that pore size can affect physical stability and oral performance, showing that the interface is not characterized solely by chemical composition [23]. For a direct botanical example, curcumin amorphous dispersions have been studied through molecular and interfacial interactions to explain differences in dissolution behavior [24]. Such observations justify representing surface contact, confinement, and intermolecular association as distinct compatibility features. They do not justify assuming that stronger interaction is always better, or that a spectroscopic sign of association proves a unique mechanism. The predictive problem is therefore relational: which interaction matters, under which physical state, and for which defined endpoint?

Thermal and mechanical processing as compatibility stressors

Manufacturing converts compatibility from a static mixture question into an exposure-history problem. In

twin-screw melt granulation, a material-sparing kinetic approach related gabapentin degradation to process-associated thermal exposure, demonstrating that degradation risk can be estimated within a defined manufacturing regime [25]. The transferable point is not the specific kinetic relation, but the need to encode temperature, residence history, and relevant material transitions whenever processing can alter chemical stability.

Real-time process analytics extend this idea. Selected-ion flow-tube mass spectrometry combined with multivariate analysis has been used during hot-melt extrusion to detect condition-dependent volatile signatures [26]. Such signals can support process-state monitoring, but they still require chemical interpretation; a volatile response is not automatically a degradation product. Prediction must therefore separate process sensing from mechanistic attribution.

Processing can also alter several outcome domains at once. Hot-melt extrusion of glibenclamide in different polymer matrices produced changes in physical and chemical state together with differences in dissolution behavior [27]. A formulation may therefore appear acceptable by one endpoint while failing another. For botanical actives, which may enter amorphous, co-amorphous, or carrier-confined states, thermal and mechanical processing should be treated as compatibility stressors only conditionally: they may induce degradation, enable beneficial state formation, modify interfacial organization, or do several of these simultaneously. The proposed framework consequently preserves process variables as independent context rather than burying them inside a final compatible/incompatible label.

From binary mixtures to multicomponent dosage forms

Binary compatibility mixtures are useful because they isolate a candidate interaction, but a finished dosage form redistributes water, changes contact geometry, introduces competing surfaces, and exposes materials to a shared process history. Functional excipients illustrate why this matters. Alginate ester materials have been developed specifically to scavenge moisture in directly compressible tablets, demonstrating that an excipient can actively reshape the stress environment rather than simply coexist with the drug [28]. In a botanical formulation, curcumin and piperine combined with polymer and phospholipid during hot-melt extrusion form a multicomponent system whose behavior cannot be reduced to a single drug–excipient pair [29].

The proposed distinction is therefore between pairwise compatibility evidence and formulation-state compatibility. The former asks whether a defined pair exhibits an interaction under a defined test. The latter asks

whether the assembled dosage form remains chemically, physically, and functionally acceptable under its process and storage trajectory. Binary evidence can inform the second question, but it cannot answer it alone.

Figure 2 shows how compatibility evidence changes in meaning as the formulation moves from isolated pair

testing toward multicomponent prediction, performance assessment, and experimental confirmation; the progression is conditional rather than automatically favorable.

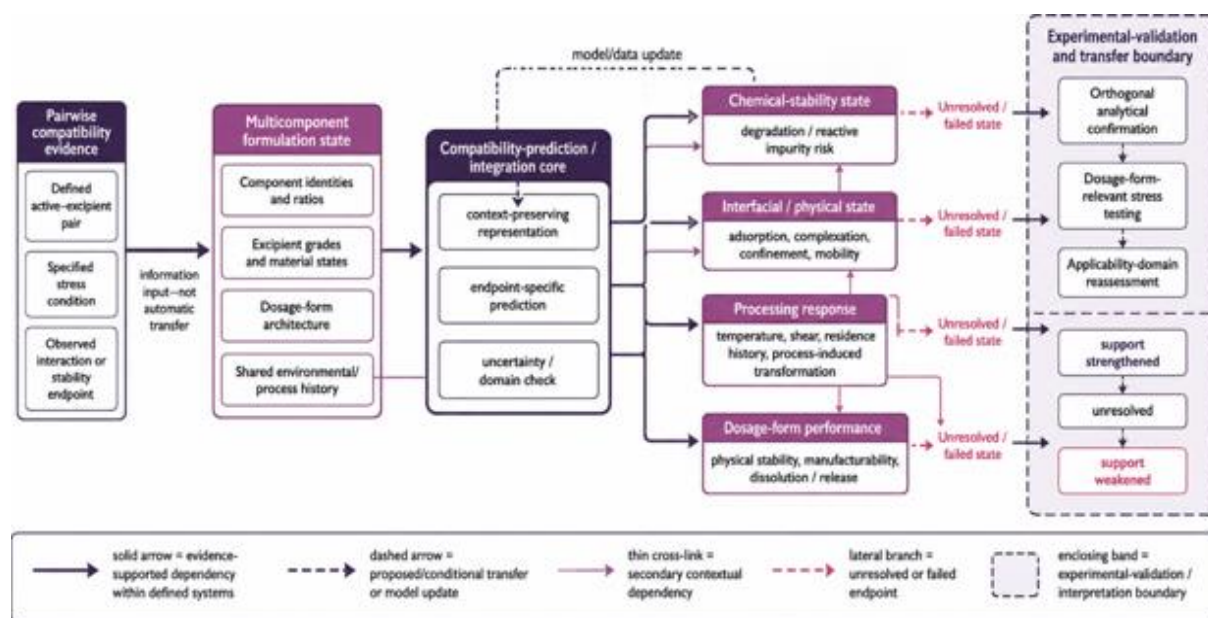


Figure 2. From pairwise evidence to context-preserving compatibility decisions

The distinctions exposed by that progression are summarized in Table 2.

Table 2. Distinguishing pairwise compatibility evidence from finished-formulation compatibility

Dimension	Pairwise evidence	Multicomponent formulation interpretation
Unit of analysis	Active plus one excipient	Active, all formulation components, ratios, and architecture
Environmental meaning	Imposed test condition	Local state created by storage, composition, and component interactions
Processing meaning	Often absent or simplified	Shared thermal, mechanical, and residence history
Interaction interpretation	Isolated signal or change	Competing, cooperative, or state-dependent interactions
Endpoint meaning	Defined compatibility observation	Multiple separable chemical, physical, process, and performance outcomes
Transfer implication	Evidence for one tested context	Requires confirmation before extrapolation to the assembled dosage form

note. The distinction is proposed as an analytical framework; it does not invalidate well-designed binary testing.

Building compatibility datasets that preserve formulation context

Prediction quality depends on what a compatibility record preserves. High-throughput microarray screening, machine-learning models of amorphous-dispersion stability, and tablet-property prediction show that experimentally grounded material and formulation descriptors can be linked to measured stability or product-property outcomes [30-32]. These studies address different tasks, so their labels should not be pooled as though

“compatibility,” physical stability, and tablet performance were equivalent endpoints.

For the present framework, a prediction-ready record should therefore preserve active identity and state, excipient identity and grade, component ratios, formulation architecture, relevant material attributes, processing conditions, environmental exposure, analytical modality, endpoint definition, and time of observation where available. This is a proposed representation rather than a validated minimum dataset standard. It is designed to prevent two formulations with identical ingredient

names but different states or histories from becoming indistinguishable training examples.

Automated formulation platforms add a further possibility: experiments can be generated iteratively and fed back into subsequent formulation decisions within a bounded design space [33]. Compatibility datasets could use the same logic, provided negative results, unresolved cases, context shifts, and analytical uncertainty are retained rather than discarded. A dataset becomes scientifically useful not simply by becoming larger, but by preserving the conditions under which its labels were produced.

A predictive excipient–active interaction framework

Existing computational formulation systems demonstrate that multiple formulation outcomes can be modeled within a common design environment rather than reduced to a single output [34]. Building on that precedent, this article proposes a context-conditioned excipient–active interaction framework with three analytical stages: representation, endpoint-specific prediction, and experimental adjudication.

Representation begins with the active and excipient as materials in states, not names alone. Active solid state, excipient grade, moisture condition, impurity burden, formulation ratios, interface architecture, process exposure, and storage environment are included only when relevant and measurable. Endpoint-specific prediction then estimates a defined risk such as chemical degradation, physical instability, process-induced transformation, or loss of dosage-form performance. The framework deliberately rejects a single undifferentiated compatibility score because different failure modes can coexist or diverge.

A compatibility prediction should consequently be indexed by four explicit coordinates: what material state was evaluated, what exposure generated the risk, what endpoint defines failure, and what formulation domain bounds interpretation. This indexing prevents a negative chemical-stability result from being reused automatically as evidence of acceptable processing or release, and it prevents a successful binary experiment from being converted into a formulation-wide label. Where evidence is sparse, the framework favors structured uncertainty over forced classification. A model may therefore return a ranked risk, an unresolved interaction, or an out-of-domain warning depending on what its training evidence can support. That asymmetry is deliberate: compatibility screening is most useful when it distinguishes missing evidence from reassuring evidence.

The third stage is interpretation. A computational signal is treated as a hypothesis about a formulation under stated conditions. Predictions may prioritize experiments, identify likely stress variables, or flag extrapolation

beyond represented chemical or formulation space, but they do not establish mechanism or final suitability. The framework also preserves interactions among domains: moisture can alter interfacial mobility; processing can change both chemical state and contact structure; and the resulting physical state can influence dissolution independently of chemical degradation. These cross-domain relations are therefore modeled as conditional dependencies rather than assumed causal chains.

Forecasting failure before long-term stability testing

The practical objective is not to replace long-term stability testing but to identify informative failures earlier. Oxygen-dependent accelerated modeling demonstrates that a chemically defined degradation pathway can be forecast when exposure terms are explicitly represented [13]. Reaction-specific temperature, humidity, and excipient effects can likewise be incorporated into a calibrated model [14]. Process degradation may also be estimated from manufacturing exposure within a defined regime [25]. Physical-stability models show separately that formulation descriptors can support earlier risk classification [31].

These precedents support a proposed tiered use of prediction. First, computational or accelerated evidence identifies a failure hypothesis. Second, short-duration or high-throughput experiments challenge that hypothesis under conditions relevant to the intended dosage form. Third, promising formulations progress to longer stability studies without treating early prediction as a substitute for them. High-throughput microarray approaches are especially useful at the prioritization stage because they can compare many drug–polymer conditions efficiently [30]. No universal cutoff is proposed: the required evidence depends on the failure mode, analytical uncertainty, and consequences of an incorrect prediction.

Linking compatibility predictions to dosage-form performance

Compatibility is valuable only if its endpoint remains connected to the intended product without being confused with product performance itself. Resveratrol solid dispersions demonstrate process-dependent solid-state outcomes [6]. Mesoporous resveratrol formulations show that carrier architecture can affect downstream performance [9]. Interfacial architecture can also change physical stability and oral performance in other drug systems [23]. Hot-melt extrusion provides a complementary warning because chemical and physical changes can occur alongside altered dissolution behavior [27].

The framework therefore treats chemical stability, physical state, manufacturability, dissolution or release, and downstream performance as related but separate outputs.

A formulation may be chemically stable yet physically unstable, analytically interactive yet functionally acceptable, or physically stabilized at the cost of release. Multicomponent botanical systems make these distinctions

particularly important because co-actives and carriers can modify both stabilization and release behavior [29].

Table 3 specifies how each predictive dimension should be interpreted without collapsing these outcomes.

Table 3. Framework dimensions linking compatibility prediction to dosage-form consequences

Predictive dimension	Primary question	Required context	Interpretation boundary
Chemical stability	Does a defined degradation pathway emerge?	Reactive environment, time, temperature, oxygen, moisture	Predicts chemical risk, not complete product suitability
Physical/interfacial state	Does formulation state remain acceptably organized?	Solid state, mobility, surfaces, confinement	Interaction evidence does not by itself prove mechanism
Processing response	Does manufacture alter state or chemistry?	Temperature, shear, residence history, process sequence	Process tolerance is formulation-specific
Dosage-form performance	Does the resulting product meet its functional endpoint?	Architecture, release conditions, physical attributes	Performance change is not synonymous with incompatibility
Transferability	Does the prediction apply outside the tested context?	Chemical space, excipient grades, process and storage domain	External validity requires new evidence

note. Dimensions are proposed for interpretation and may require different analytical and validation methods.

Experimental confirmation and model updating

Compatibility predictions become useful when they alter what is tested, not when they eliminate testing. Orthogonal analytical methods can reduce ambiguity because FTIR, Raman spectroscopy, and high-temperature X-ray diffraction interrogate different aspects of drug–excipient behavior [35]. Agreement across methods can strengthen an interpretation, whereas discordance may reveal a physical transition, measurement artifact, or alternative mechanism. No single spectral or thermal change should automatically be labeled a chemical reaction.

The proposed confirmation strategy therefore matches experiments to the predicted failure mode. Chemical-risk predictions require stability-indicating chemical analysis; solid-state predictions require appropriate structural or thermal characterization; interfacial hypotheses require methods capable of probing the relevant association; and process-risk predictions should preserve the manufacturing exposure being questioned. Negative and unresolved findings are retained as model information rather than treated as failed experiments.

Model updating should also distinguish correction from expansion. A prediction that fails within the represented domain may indicate model error, inadequate features, or label noise. A prediction made outside the represented domain is instead an extrapolation test. Iterative formulation platforms show how measured outcomes can be returned to a bounded decision system [33]. The proposed framework adopts that feedback logic while requiring uncertainty and domain membership to remain visible.

Boundaries for complex botanical mixtures

The strongest boundary is chemical representability. Machine learning can perform well for defined formulation

tasks such as chemical stability of hot-melt-extruded amorphous dispersions, but that performance is tied to the represented compounds, excipients, processes, descriptors, and labels [36]. It does not establish transfer to unrelated dosage forms or to chemically heterogeneous botanical mixtures.

A characterized single botanical molecule can often be represented using conventional molecular descriptors together with formulation context. An extract or enriched fraction may contain variable constituents, degradation products, minor components, and unknown co-solutes whose collective interactions are not captured by one molecular identity. Batch variation can also change the effective formulation without any change in the nominal product name. The framework should therefore permit an “insufficiently represented” outcome rather than force every botanical material into a numerical compatibility prediction.

These limits also constrain mechanistic interpretation. An observed change may arise from one constituent, several interacting constituents, the carrier system, processing, or a shift in physical state. Prospective external validation should therefore include unseen botanical chemistries, formulation-grade changes, process shifts, storage shifts, negative cases, and orthogonal measurements. Until such testing is performed, the framework is an organizing and hypothesis-generating structure rather than a validated general predictor.

Limitations

The framework is evidence-bounded in several ways. Much of the direct botanical formulation literature represented here concerns defined polyphenols rather than chemically heterogeneous extracts, and many predictive studies were developed for amorphous dispersions, tablets,

or other bounded formulation spaces. Their methods establish useful precedents but do not validate one transferable compatibility model across dosage forms. The selected evidence is also heterogeneous in endpoint definition: chemical degradation, physical stability, processability, interaction signals, dissolution, and product attributes are measured by different methods and at different time scales.

The proposed architecture does not specify an optimal molecular representation, learning algorithm, uncertainty metric, experimental threshold, or weighting among compatibility domains. It also does not resolve how batch-variable botanical mixtures should be encoded when important constituents are unknown. Some mechanistic dependencies represented conceptually may be correlated rather than causal in a particular formulation. Accordingly, the framework should be tested prospectively against explicit comparators and external formulation shifts before predictive performance, transferability, or decision utility is claimed.

Future evaluation should also distinguish calibration from discrimination, because a model that ranks formulations correctly may still assign poorly calibrated risks. Reproducibility across excipient lots and analytical laboratories would provide a separate test of robustness that internal resampling cannot supply.

CONCLUSION

Excipient compatibility is better framed as a conditional relationship among active state, excipient state, formulation architecture, environmental exposure, processing history, and a defined failure endpoint than as a permanent property of an ingredient pair. Botanical actives make this distinction especially important because solid-state organization, carrier interactions, co-active composition, and manufacturing conditions can change what the nominal active experiences.

The proposed framework preserves chemical degradation, interfacial behavior, processing response, and dosage-form performance as related but non-equivalent domains. It uses prediction to prioritize hypotheses and experiments, not to replace analytical confirmation or long-term stability assessment. Its practical value therefore depends on context-preserving datasets, endpoint-specific models, explicit applicability domains, orthogonal validation, and retention of uncertainty.

For well-defined botanical molecules, this approach offers a route toward more informative excipient screening. For complex botanical mixtures, representation may remain the limiting problem. Compatibility prediction should consequently remain capable of saying that available evidence is insufficient. A useful predictive system is not

one that always produces a verdict, but one that identifies what is being predicted, under which conditions, and what evidence is still required.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

- [1] Hang NT, Long NT, Duy ND, Chien NN, Phuong NV. Towards safer and efficient formulations: Machine learning approaches to predict drug-excipient compatibility. *Int J Pharm.* 2024;653:123884. doi:10.1016/j.ijpharm.2024.123884
- [2] Patel S, Patel M, Kulkarni M, Patel MS. DE-INTERACT: A machine-learning-based predictive tool for the drug-excipient interaction study during product development—validation through paracetamol and vanillin as a case study. *Int J Pharm.* 2023;637:122839. doi:10.1016/j.ijpharm.2023.122839
- [3] Veronica N, Heng PWS, Liew CV. Ensuring product stability—choosing the right excipients. *J Pharm Sci.* 2022;111(8):2158-71. doi:10.1016/j.xphs.2022.05.001
- [4] Hornick T, Mao C, Koynov A, Yawman P, Thool P, Salish K, et al. In silico formulation optimization and particle engineering of pharmaceutical products using a generative artificial intelligence structure synthesis method. *Nat Commun.* 2024;15(1):9622. doi:10.1038/s41467-024-54011-9
- [5] Samsoen S, Dudognon É, Le Fer G, Fournier D, Woisel P, Affouard F. Impact of the polymer dispersity on the properties of curcumin/polyvinylpyrrolidone amorphous solid dispersions. *Int J Pharm.* 2024;653:123895. doi:10.1016/j.ijpharm.2024.123895
- [6] Almeida H, Teixeira N, Sarmiento B, Vasconcelos TC. Freeze-drying cycle optimization of an amorphous solid dispersion of resveratrol. *Eur J Pharm Sci.* 2024;200:106855. doi:10.1016/j.ejps.2024.106855
- [7] Wdowiak K, Tajber L, Miklaszewski A, Cielecka-Piontek J. Sweeteners show a plasticizing effect on PVP K30—a solution for the hot-melt extrusion of fixed-dose amorphous curcumin-hesperetin solid dispersions. *Pharmaceutics.* 2024;16(5):659. doi:10.3390/pharmaceutics16050659

- [8] Han J, Yang Y, Hou Y, Tang M, Zhang Y, Zhu Y, et al. Insight into formation, synchronized release and stability of co-amorphous curcumin-piperine by integrating experimental-modeling techniques. *J Pharm Sci.* 2024;113(7):1874-84. doi:10.1016/j.xphs.2024.02.009
- [9] Ainurofiq A, Rahayu BG, Murtafda FA, Kuncahyo I, Windarsih A, Choiri S. QbD-based formulation development of resveratrol nanocrystal incorporated into soluble mesoporous material: Pharmacokinetic proof of concept study. *Int J Pharm.* 2024;661:124459. doi:10.1016/j.ijpharm.2024.124459
- [10] Gabrič A, Hodnik Ž, Pajk S. Oxidation of drugs during drug product development: Problems and solutions. *Pharmaceutics.* 2022;14(2):325. doi:10.3390/pharmaceutics14020325
- [11] Saraf I, Jakasanovski O, Stanić T, Kralj E, Petek B, Williams JD, et al. Investigation of the influence of copovidone properties and hot-melt extrusion process on level of impurities, in vitro release, and stability of an amorphous solid dispersion product. *Mol Pharm.* 2024;21(11):5703-15. doi:10.1021/acs.molpharmaceut.4c00707
- [12] Wang C, Gamage PL, Jiang W, Mudalige T. Excipient-related impurities in liposome drug products. *Int J Pharm.* 2024;657:124164. doi:10.1016/j.ijpharm.2024.124164
- [13] Waterman KC, Krisch MJ, McDonald TJ, Theriault R, Wood C, Bielak MD, et al. Oxygen-dependent accelerated stability modeling of drug products. *Mol Pharm.* 2025;22(7):3987-98. doi:10.1021/acs.molpharmaceut.5c00239
- [14] Takegawa Y, Sugimoto M, Uchiyama H, Kadota K, Tozuka Y. Construction of a modified Arrhenius equation for predicting drug nitrosation in solid dosage form. *Int J Pharm.* 2025;685:126212. doi:10.1016/j.ijpharm.2025.126212
- [15] Veronica N, Heng PWS, Liew CV. Understanding the roles of excipients in moisture management in solid dosage forms. *Mol Pharm.* 2024;21(5):2484-500. doi:10.1021/acs.molpharmaceut.4c00031
- [16] Shi C, Fang Y, Liu Z, Wang Y, Shen L, Zhao L. Effect of moisture sorption and lactose type on tablet quality: A hygroscopicity study between lactose powder and tablets. *Mol Pharm.* 2025;22(1):544-57. doi:10.1021/acs.molpharmaceut.4c01164
- [17] Ibrahim I, Mann J, Abbott A, Winge F, Davis A, Hens B, et al. Linking powder to tablet stability: Length- and time-scale prediction of moisture sorption. *Int J Pharm.* 2025;684:126154. doi:10.1016/j.ijpharm.2025.126154
- [18] Romero-Gonzalez M, Van Horn RD, Liu Y, Jonuzaj S, Hanson JC, Sperry DC, et al. Development of a quantitative method for formulation microenvironmental pH assessment. *Mol Pharm.* 2025;22(9):5493-503. doi:10.1021/acs.molpharmaceut.5c00514
- [19] Weldeab AO, McElderry JD, Lin Y. The effect of in-situ-generated moisture on disproportionation of pharmaceutical salt. *Mol Pharm.* 2023;20(1):561-71. doi:10.1021/acs.molpharmaceut.2c00765
- [20] Veronica N, Heng PWS, Liew CV. Relative humidity cycling: Implications on the stability of moisture-sensitive drugs in solid pharmaceutical products. *Mol Pharm.* 2023;20(2):1072-85. doi:10.1021/acs.molpharmaceut.2c00812
- [21] Niederquell A, Herzig S, Schönenberger M, Stoyanov E, Kuentz M. Computational support to explore ternary solid dispersions of challenging drugs using coformer and hydroxypropyl cellulose. *Mol Pharm.* 2024;21(11):5619-31. doi:10.1021/acs.molpharmaceut.4c00592
- [22] Higginbotham T, Meier K, Ramírez J, Garaizar A. Predicting drug-polymer compatibility in amorphous solid dispersions by MD simulation: On the trap of solvation free energies. *Mol Pharm.* 2025;22(2):760-70. doi:10.1021/acs.molpharmaceut.4c00810
- [23] Qi W, Chen J, Rui S, Li S, Ding Y, Feng S, et al. Variable pore size of mesoporous silica in improving physical stability and oral bioavailability of insoluble drugs. *Int J Pharm.* 2025;674:125394. doi:10.1016/j.ijpharm.2025.125394
- [24] Li J, Wang X, Li C, Fan N, Wang J, He Z, et al. Viewing molecular and interface interactions of curcumin amorphous solid dispersions for comprehending dissolution mechanisms. *Mol Pharm.* 2017;14(8):2781-92. doi:10.1021/acs.molpharmaceut.7b00319
- [25] Pradhan A, Yang F, Karan K, Durig T, Schwing Q, Haight B, et al. Material-sparing degradation-kinetics model for thermolabile drug stability assessment during twin-screw melt granulation—insights with gabapentin. *Int J Pharm.* 2025;674:125421. doi:10.1016/j.ijpharm.2025.125421
- [26] Smith AD, Bordos E, Devlin M, Hastie C, Perkins MJ, Langford VS, et al. Process optimization in pharmaceutical hot-melt extrusion: Real-time volatile detection via SIFT-MS combined with multivariate analysis. *Int J Pharm.* 2026;691:126623. doi:10.1016/j.ijpharm.2026.126623
- [27] Zupan N, Yous I, Danède F, Vérin J, Kouach M, Foulon C, et al. Impact of hot-melt extrusion on glibenclamide's physical and chemical states and dissolution behavior: Case studies with three polymer blend matrices. *Pharmaceutics.* 2024;16(8):1071. doi:10.3390/pharmaceutics16081071

- [28] Sanchez-Ballester NM, Trens P, Rossi JC, Soulairol I. Alginate ester: New moisture-scavenging excipients for direct compressible pharmaceutical tableting. *Carbohydr Polym.* 2022;297:120063. doi:10.1016/j.carbpol.2022.120063
- [29] Wdowiak K, Miklaszewski A, Cielecka-Piontek J. Amorphous polymer-phospholipid solid dispersions for the co-delivery of curcumin and piperine prepared via hot-melt extrusion. *Pharmaceutics.* 2024;16(8):999. doi:10.3390/pharmaceutics16080999
- [30] Ghazi NF, Burley JC, Dryden IL, Roberts CJ. High-throughput microarray approaches for predicting the stability of drug-polymer solid dispersions. *Mol Pharm.* 2025;22(1):343-62. doi:10.1021/acs.molpharmaceut.4c00955
- [31] Han R, Xiong H, Ye Z, Yang Y, Huang T, Jing Q, et al. Predicting physical stability of solid dispersions by machine learning techniques. *J Control Release.* 2019;311-312:16-25. doi:10.1016/j.jconrel.2019.08.030
- [32] Hamaguchi M, Adachi T, Arai N. Application of AI in tablet development: An integrated machine learning framework for pre-formulation property prediction. *Pharmaceutics.* 2026;18(4):452. doi:10.3390/pharmaceutics18040452
- [33] Abbas F, Salehian M, Hou P, Moores J, Goldie J, Tsioutsios A, et al. Accelerated drug development using a digital formulator and a self-driving tableting data factory. *Nat Commun.* 2026;17(1):4739. doi:10.1038/s41467-026-71204-6
- [34] Dong J, Gao H, Ouyang D. PharmSD: A novel AI-based computational platform for solid dispersion formulation design. *Int J Pharm.* 2021;604:120705. doi:10.1016/j.ijpharm.2021.120705
- [35] Rojek B, Gazda M, Plenis A. FTIR, Raman spectroscopy and HT-XRD in compatibility study between naproxen and excipients. *Spectrochim Acta A Mol Biomol Spectrosc.* 2023;302:123048. doi:10.1016/j.saa.2023.123048
- [36] Jiang J, Lu A, Ma X, Ouyang D, Williams RO III. The applications of machine learning to predict the forming of chemically stable amorphous solid dispersions prepared by hot-melt extrusion. *Int J Pharm X.* 2023;5:100164. doi:10.1016/j.ijpx.2023.100164