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PREDICTING EXCIPIENT COMPATIBILITY USING THERMAL DEGRADATION, HYGROSCOPICITY, AND FORCED-DEGRADATION DATA

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ABSTRACT

Excipient selection is a critical but laborious step in pharmaceutical preformulation because incompatibilities can derail development even when the active pharmaceutical ingredient appears chemically stable alone. Thermal analysis, hygroscopicity, and forced-degradation data contain predictive signals that are often generated during routine screening but are rarely unified in a quantitative decision model. Current compatibility screening is commonly treated as a manual, binary-decision process. This approach does not fully leverage historical information across drug–excipient pairs, which can lead to repeated experiments, delayed formulation choices, and overlooked incompatibility risks. The objective of this manuscript is to describe a conceptual machine learning model that predicts the compatibility of a drug–excipient binary mixture. The model would use descriptors derived from differential scanning calorimetry, thermogravimetric analysis, moisture sorption, and forced-degradation profiles. A gradient-boosted classification model would be developed using curated compatibility outcomes and engineered descriptors from thermal degradation, hygroscopicity, and stress-testing data. Input features would include glass-transition changes, melting-point shifts, enthalpy changes, temperature-dependent mass loss, moisture uptake indices, and forced-degradation readouts. Conceptually, the model would provide a compatibility probability together with interpretable feature attributions. Such output could help scientists rule out high-risk combinations earlier and reserve experimental compatibility studies for borderline or strategically important cases. A predictive compatibility tool of this type would accelerate early formulation development, reduce material waste, and embed data-driven decision-making into preformulation science. Its practical value would depend on careful curation, conservative interpretation, and continued expert oversight.

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Introduction

Excipient compatibility is central to formulation robustness because a chemically acceptable active pharmaceutical ingredient can become unstable when placed in intimate contact with a reactive excipient. Predictive compatibility systems have therefore been proposed to support earlier selection decisions, including expert-system and machine-learning approaches designed to anticipate drug–excipient risks before extensive laboratory screening [1]. Late recognition of an incompatibility may force reformulation, additional stability work, and renewed analytical method development, especially when degradation pathways are accelerated by moisture or reactive impurities [2]. A predictive model for compatibility would therefore address a practical bottleneck in preformulation rather than merely adding another computational layer.

Current practice often begins with binary-mixture screening, where differential scanning calorimetry and thermogravimetric analysis are used to detect peak shifts, new events, melting-endotherm changes, or abnormal weight-loss behavior. Thermal compatibility investigations have shown that DSC and TGA can reveal potential interactions, but their interpretation can depend strongly on analyst judgment and experimental context [3]. Forced-degradation follow-up then provides a more direct view of chemical instability, yet this staged workflow still tends to convert complex curves and chromatographic responses into a simple compatible-or-incompatible decision [4]. A systematic model would allow those intermediate signals to be retained as quantitative predictors instead of being discarded after manual review.

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Preformulation laboratories increasingly accumulate thermal scans, moisture-sorption profiles, material-property descriptors, and stress-testing outcomes that are structured enough to support supervised learning. Machine-learning work in oral solid dosage development has already shown that excipient and material libraries can be used to connect formulation inputs with product-relevant behavior [5]. Broader reviews of machine learning in solid oral dosage development also indicate that small, heterogeneous pharmaceutical datasets can support useful predictive tools when feature engineering and validation are aligned with formulation science [6]. These observations suggest that compatibility screening is well suited to a model that learns from historical binary-mixture evidence rather than treating each new pair as an isolated experiment.

The thesis of this manuscript is that a machine learning model could integrate thermal analysis, moisture uptake, and forced-degradation fingerprints to predict the compatibility of new drug–excipient pairs. Recent compatibility-focused systems such as PharmDE and DE-INTERACT illustrate the feasibility of computational decision support for drug–excipient interaction assessment [7, 8]. However, a model that explicitly combines DSC-derived transitions, TGA-derived degradation descriptors, hygroscopicity indices, and forced-degradation labels would provide a more unified preformulation framework [9]. Such a tool should be positioned as a conservative decision-support system that guides excipient selection while preserving the role of expert scientific review.

Background

Drug-Excipient Compatibility in Preformulation

Drug–excipient incompatibility can arise through chemical reactions, physical phase changes, or coupled mechanisms that alter the local microenvironment of the solid mixture. Reactive impurities in excipients, including reducing species or oxidants, may initiate degradation even when the nominal excipient is regarded as pharmaceutically acceptable [10]. Moisture, acidity, alkalinity, and functional groups can further modulate hydrolysis, Maillard-type reactions, salt formation, and polymorphic instability [2]. A predictive model should therefore encode both material identity and mechanistic risk factors rather than relying only on excipient category labels.

Thermal Analysis as a Compatibility Screening Tool

Thermal analysis remains a common compatibility screen because DSC can detect melting-point shifts, disappearance of endotherms, new exothermic events, and changes in glass-transition behavior, while TGA can identify abnormal mass loss or altered degradation onset. Combined DSC and TGA workflows have been used to assess drug–excipient compatibility, demonstrating that thermal endpoints can provide evidence of possible interaction but may not always distinguish chemical degradation from physical mixing effects [3]. Chemometric interpretation of FTIR and thermogravimetric data has also been proposed to strengthen compatibility assessment when individual thermal events are ambiguous [11]. For model development, these limitations are useful because they motivate feature extraction from entire thermal fingerprints rather than reliance on a single visual cue.

Role of Hygroscopicity and Moisture

Hygroscopicity is a key modifier of solid-state compatibility because absorbed water can plasticize amorphous regions, increase molecular mobility, dissolve reactive impurities, and create microenvironments that accelerate degradation. Recent work on excipient moisture management emphasizes that excipients differ not only in total water uptake but also in how they retain, release, and redistribute water within solid dosage systems [9]. Particle-level investigations of excipient stability under different storage conditions further show that moisture content and swelling behavior can change substantially with environmental exposure [12]. A compatibility model should therefore include dynamic vapor sorption descriptors and humidity-dependent features rather than treating water as a binary stress condition.

Forced-Degradation Studies

Forced-degradation studies provide the most direct training endpoint for a compatibility model because they expose binary mixtures to stress conditions and measure whether new impurities or increased degradation emerge. Vial-in-vial compatibility designs have been proposed as benchmark approaches for studying drug–excipient interactions under controlled stress while reducing confounding from direct sample handling [4]. Preformulation studies of individual drugs such as gestrinone and levonorgestrel also illustrate how thermal stability, kinetic degradation, and compatibility-oriented interpretation can be linked during early development [13, 14]. In a predictive workflow, forced-degradation outcomes would define the target label, while thermal and moisture features would act as earlier, less resource-intensive predictors. Regulatory and analytical stability frameworks further support the need to connect compatibility prediction with scientifically interpretable degradation evidence. ICH Q1A(R2) emphasizes that stability testing should define how drug substances and products behave under storage conditions, while ICH Q1B identifies photostability as an important component of stress evaluation when light-sensitive degradation is plausible [15, 16]. Forced-degradation design should therefore be treated not only as a label-generating step, but also as a mechanistic probe for hydrolysis, oxidation, thermal stress, photolysis, and excipient-mediated reactivity [17, 18]. This is important because degradation products and impurity profiles often require structured analytical interpretation before they can be translated into reliable compatibility labels [19, 20]. In addition, excipient safety and functionality depend on grade, contaminant profile, moisture behavior, and intended use context, meaning that model features should capture excipient-specific risk rather than relying only on broad excipient names [21, 22]. Stability guidance for generic products also reinforces

the practical need for consistent study design, packaging context, and documentation when compatibility evidence is used to support development decisions [23].

Machine Learning in Preformulation and Stability Science

Machine learning has increasingly been applied to pharmaceutical formulation, material-property prediction, and stability-related decision support. Compatibility-specific models have been reported for drug–excipient evaluation and interaction prediction, showing that supervised learning can be adapted to preformulation questions [1, 8]. Stability modeling in packaging and solid oral dosage systems further indicates that predictive algorithms can incorporate environmental exposure, material properties, and degradation-relevant descriptors [24]. The remaining gap is a compatibility model that integrates all three major evidence streams—thermal behavior, hygroscopicity, and forced degradation—within a single interpretable prediction framework.

Model Development Overview

High-Level Prediction Pipeline

The proposed pipeline would begin by assembling drug properties, excipient properties, thermal descriptors, hygroscopicity descriptors, and forced-degradation summaries into a single feature vector for each binary mixture. A gradient-boosted classifier would then output a compatibility probability, while local explanation methods would identify which input features most strongly influenced a given prediction. Compatibility expert systems and machine-learning tools already demonstrate the value of structured input representations for drug–excipient decision support [7, 25]. The proposed model extends that idea by treating DSC, TGA, moisture uptake, and stress-testing data as complementary evidence rather than separate screening artifacts.

Figure 1 presents the proposed compatibility-prediction workflow linking binary drug–excipient evidence, engineered thermal and moisture descriptors, forced-degradation labels, calibrated machine-learning output, SHAP-based interpretation, and conservative preformulation decision support.

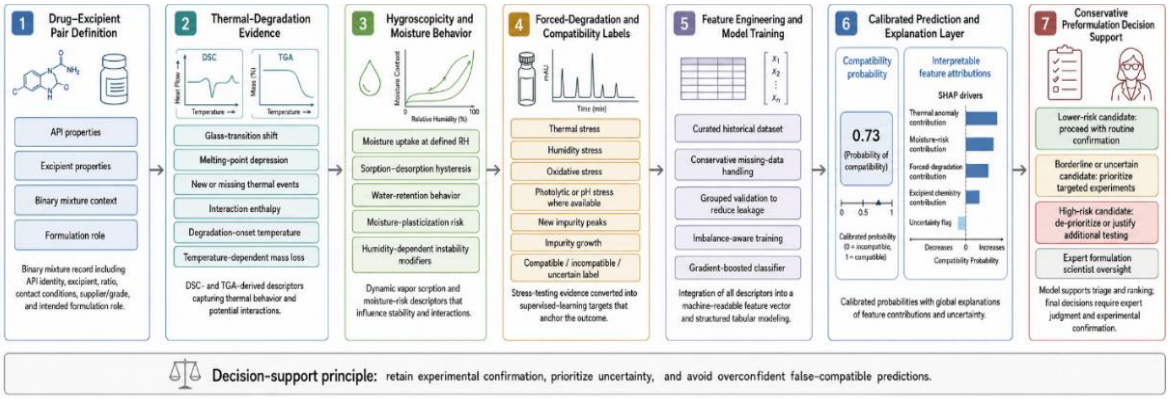

Figure 1. Predictive excipient-compatibility modeling workflow using thermal degradation, hygroscopicity, and forced-degradation data.

Core Input Features

Core thermal features would include glass-transition shifts, melting-point depression, interaction enthalpy, appearance or disappearance of thermal events, and TGA-derived mass-loss temperatures. Studies combining thermal analysis with chemometric interpretation show that these descriptors can capture subtle interaction patterns that may be missed in manual review [26, 27]. Hygroscopicity inputs would include moisture gain at defined relative-humidity conditions, sorption–desorption hysteresis, and water-activity-related descriptors, consistent with emerging moisture-stability modeling approaches [28]. Forced-degradation inputs would encode whether new chromatographic peaks, impurity growth, or stress-specific degradation signatures are observed, while avoiding any claim that a particular numerical outcome is expected.

Design Principles

The model should be interpretable, conservative, and suitable for small, imbalanced compatibility datasets. Recommendations for algorithmic drug product development emphasize that pharmaceutical machine-learning tools should be aligned with experimental design, domain constraints, and practical decision points [29]. Because false-compatible predictions may be more damaging than false alerts in early formulation, the classifier should be calibrated to favor cautious screening decisions. The system should also be updatable so that newly generated binary-mixture data can be incorporated without redesigning the entire workflow.

Data Sources and Feature Engineering

Curating a Binary-Mixture Compatibility Dataset

A binary-mixture compatibility dataset would be curated from peer-reviewed preformulation studies, internal archives, and standardized forced-degradation reports, with each record representing one drug–excipient pair under defined conditions. Thermal compatibility reports for drugs such as mirtazapine and minoxidil show how DSC, TGA, FTIR, and related methods can be combined to judge whether an excipient is likely to interact with an active ingredient [30, 31]. Expert labeling would translate forced-degradation and analytical evidence into compatible, incompatible, or uncertain categories using predefined scientific rules. Uncertain cases should be retained with caution because they can inform model calibration and identify regions where additional experimentation is warranted.

Extracting Thermal and Moisture Descriptors

Feature engineering would reduce each DSC curve into descriptors such as onset temperature, peak temperature, enthalpy, baseline shift, glass-transition change, and presence of new or missing events. Thermal and non-thermal compatibility studies demonstrate that combining multiple analytical descriptors can improve interpretation when a single signal is inconclusive [32]. DVS profiles would similarly be summarized through moisture uptake at selected humidity levels, sorption slope, hysteresis, and reversibility, reflecting the role of excipient water handling in solid dosage stability [9, 12]. These engineered descriptors would allow the model to learn from curve shape and moisture behavior without requiring direct comparison of raw instrument files across laboratories.

Table 1 organizes the proposed model's feature architecture by linking each descriptor class to its compatibility meaning, analytical source, model contribution, and interpretation risk.

Table 1. Feature Architecture for Predicting Drug–Excipient Compatibility from Thermal, Moisture, Chemical, and Forced-Degradation Evidence

Feature domain	Representative engineered variables	Scientific meaning for compatibility prediction	Main analytical source	Expected contribution to model reasoning	Key limitation or caution
Binary mixture context	API identity, excipient identity, mixture ratio, contact condition, intended formulation role, supplier or grade	Defines the actual compatibility question rather than treating the API or excipient in isolation	Preformulation records, formulation-development archives	Helps distinguish formulation-relevant incompatibility from generic material risk	Labels may vary if mixture ratios, grades, or preparation methods differ across studies
DSC transition behavior	Glass-transition shift, melting-point depression, peak broadening, new endotherm or exotherm, disappearance of API or excipient event	Captures possible physical interaction, eutectic behavior, phase transition, or early incompatibility signal	Differential scanning calorimetry	Provides sensitive early indicators that may precede visible degradation	Thermal anomalies may reflect physical mixing rather than chemical incompatibility
TGA degradation behavior	Degradation-onset temperature, staged mass loss, residual mass, abnormal weight-loss region, derivative thermogravimetric peak changes	Indicates altered thermal stability, moisture loss, volatilization, or degradation acceleration	Thermogravimetric analysis	Helps identify combinations with abnormal thermal-degradation patterns	Mass loss may be confounded by water, solvent, or excipient decomposition
Hygroscopicity and moisture response	Moisture uptake at selected RH levels, sorption slope, hysteresis, desorption reversibility, water-retention index	Represents the ability of water to plasticize solids, mobilize reactants, or enable hydrolysis and impurity-mediated degradation	Dynamic vapor sorption, moisture-content testing, water-activity assessment	Links compatibility risk to humidity-dependent behavior rather than treating moisture as a binary stress	Missing DVS data may reduce reliability for moisture-sensitive APIs or excipients
Excipient chemical risk	Reducing-sugar potential, peroxide risk, aldehyde or oxidative impurity risk, acidic or basic microenvironment, functional-group reactivity	Encodes known mechanistic routes for drug–excipient degradation	Excipient specifications, supplier data, literature, internal impurity profiles	Helps the model identify chemically plausible incompatibility mechanisms	Supplier-specific impurity profiles may not be consistently available
API physicochemical vulnerability	pKa, ionization state, hydrolysis liability, oxidation liability, amorphous tendency, polymorphic sensitivity, moisture sensitivity	Describes whether the API is intrinsically vulnerable under the conditions created by the excipient	API characterization, forced-degradation reports, solid-state studies	Supports interaction modeling between API vulnerability and excipient risk	Vulnerability descriptors may be incomplete for early-development compounds

Forced-degradation readouts	New chromatographic peaks, impurity growth, degradation-rate increase, stress-specific instability, compatible/incompatible/uncertain label	Provides the strongest evidence for supervised outcome labeling	Stress studies, vial-in-vial designs, chromatographic impurity profiling	Anchors the target label and prevents the model from relying only on indirect thermal or moisture signals	Stress conditions may not reflect real storage or formulation exposure
Preparation-sensitive descriptors	Particle size, surface area, morphology, milling history, blending intensity, binary-mixture contact mode	Captures physical contact and local microenvironment effects that influence degradation likelihood	Material characterization, SEM/image analysis, process records	Improves distinction between chemical incompatibility and preparation-driven artifact	Often absent from historical datasets and difficult to standardize

Engineering Drug- and Excipient-Specific Features

Drug- and excipient-specific descriptors would encode chemical and physical reactivity drivers such as pKa, ionization state, functional groups, reducing-sugar potential, peroxide risk, amorphous content, particle morphology, and moisture content. Reviews of reactive impurities in pharmaceutical excipients highlight the importance of excipient chemistry beyond compendial identity, especially when trace impurities can initiate degradation [10]. Image-based feature extraction from scanning electron microscopy has also shown that excipient particle morphology can be represented computationally for downstream formulation modeling [33]. Including these descriptors would help the compatibility model distinguish a chemically plausible incompatibility from a coincidental thermal or moisture signal.

Predictive Model Architecture

Choice of Classifier

A gradient-boosted tree classifier such as XGBoost would be a suitable conceptual architecture because it can handle nonlinear interactions, mixed feature types, missing values, and feature-importance analysis. Pharmaceutical formulation modeling has used neural networks, latent variable methods, and other machine-learning approaches, but tree-based models are particularly attractive when interpretability and tabular descriptors are central to the workflow [34, 35]. SHAP-based explanation methods are naturally aligned with tree models and can translate individual predictions into feature-level rationales [36]. The classifier would therefore be chosen not only for predictive flexibility but also for its ability to support transparent formulation decisions.

Input Vector Assembly and Pre-processing

Input vectors would combine continuous descriptors such as melting-point shift and moisture uptake with categorical descriptors such as excipient type, stress condition, and analytical method. Material-library modeling in pharmaceutical development illustrates how diverse material properties can be organized into machine-readable formats for predictive tasks [5]. Missing moisture or thermal descriptors would be imputed using conservative procedures, while categorical features would be encoded in a way that avoids introducing artificial ordinal relationships. Data splitting should keep related drug–excipient pairs grouped appropriately to reduce leakage and ensure that evaluation reflects prediction for genuinely new compatibility questions.

Output: Compatibility Probability

The model output would be a calibrated compatibility probability rather than an automatic formulation decision. Compatibility-focused prediction tools have already shown that computational outputs are most useful when they support expert assessment rather than replace it [1, 8]. A conservative decision threshold would be selected conceptually to reduce false-compatible predictions while allowing scientists to review borderline combinations. The accompanying explanation layer would show whether the probability was driven mainly by thermal anomalies, moisture sensitivity, forced-degradation evidence, or known chemical reactivity features.

Handling Small Datasets and Complex Degradation Signals

Strategies for Small-N Compatibility Studies

Compatibility datasets are often small because each binary-mixture experiment consumes material, analyst time, and stability-chamber capacity. The proposed model should therefore use grouped validation, conservative regularization, and domain-informed feature selection so that it learns reproducible compatibility patterns rather than laboratory-specific noise. Multivariate preformulation screening has been proposed as a bridge toward machine learning because it can extract structured signals from compatibility data even when sample availability is limited [37]. Small-data formulation modeling should also preserve uncertainty, so borderline predictions are flagged for experimental confirmation rather than converted into overconfident compatibility decisions [29]. **Table 2** summarizes practical modeling safeguards that can help small compatibility datasets support reproducible prediction without overstating model certainty.

Table 2. Small-N Modeling Safeguards for Excipient–API Compatibility Prediction

Small-N challenge	Modeling safeguard	Practical value for compatibility studies
Few binary-mixture experiments	Use grouped or leave-one-formulation-out validation	Reduces the risk that the model learns experiment-specific patterns instead of general compatibility behavior
High feature-to-sample ratio	Apply conservative regularization and domain-informed feature selection	Keeps the model focused on chemically meaningful predictors such as hygroscopicity, thermal shifts, degradation markers, and excipient class
Borderline compatibility signals	Report calibrated uncertainty or prediction confidence intervals	Helps identify API–excipient pairs that require confirmatory DSC, FTIR, HPLC, or stability testing
Laboratory-specific noise	Track batch, instrument, storage, and analyst-related metadata	Allows questionable predictions to be interpreted in relation to possible experimental variability
Risk of overconfident recommendations	Use "compatible," "incompatible," and "needs confirmation" decision categories	Prevents uncertain cases from being converted into definitive formulation decisions

Capturing Multi-Modal Degradation Pathways

A single drug–excipient pair may degrade through hydrolytic, oxidative, photolytic, or thermally accelerated pathways, and these mechanisms may not be equally visible in DSC, TGA, DVS, or chromatographic data. The model should therefore represent forced-degradation conditions as separate but related descriptors, allowing stress-specific incompatibility signals to contribute differently to the final probability. Predictive stability modeling in pharmaceutical packaging shows that environmental exposure and material context can jointly influence degradation risk, supporting the need for multi-condition inputs rather than a single stress label [24]. Dissolution and stability modeling work also illustrates how constrained machine-learning structures can encode pharmaceutical expectations while still learning complex relationships from experimental descriptors [38].

Transfer Learning Across Excipient Types

Transfer learning could help the model generalize from well-studied excipients, such as lactose, cellulose derivatives, starches, and common lubricants, toward less frequently studied or novel excipient chemistries. This approach would not imply that all excipients behave similarly, but it could allow the model to share latent information about moisture uptake, thermal transitions, and functional-group risk across related material classes. Material-library studies in tablet development show that shared representations of excipient and powder properties can support prediction across formulation contexts [5, 34]. Any transfer-learning component should remain conservative, especially when the target excipient has unusual reactive impurities or morphology that differs from the source materials [10, 33].

Model Interpretability and Formulation Guidance

SHAP-Driven Compatibility Drivers

SHAP explanations would allow the model to identify whether a predicted incompatibility is driven by high hygroscopicity, thermal-event shifts, abnormal mass loss, stress-induced impurity formation, or excipient-specific chemical risk. Tree-based explainability methods provide a practical route from local prediction to global understanding, making them suitable for formulation scientists who need mechanistic plausibility rather than opaque scores [36]. In this framework, a high-risk prediction might be interpreted as the combined effect of moisture uptake and melting-point depression rather than as a generic incompatibility label. Such explanations would help align model output with formulator intuition and guide follow-up experiments toward the most plausible degradation mechanism.

Figure 2 illustrates how SHAP-based compatibility drivers can translate a predicted API–excipient incompatibility score into mechanistic explanations and ranked excipient recommendations for formulation decision-making.

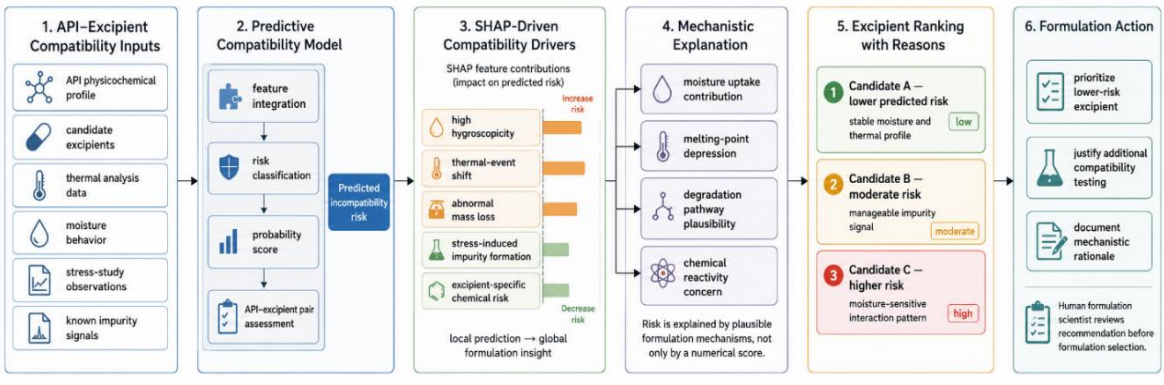

Figure 2. SHAP-Guided Excipient Compatibility Interpretation and Recommendation Workflow

From Prediction to Excipient Recommendation

The model could rank candidate excipients for a new active ingredient according to predicted compatibility risk while presenting the main reasons for each recommendation. Compatibility expert systems and machine-learning tools already indicate that computational approaches can assist excipient selection when the output is tied to interpretable formulation knowledge [1, 7]. A ranked recommendation list would be especially useful when several excipients are functionally acceptable but differ in moisture behavior, impurity risk, or thermal interaction signatures [16, 17]. Scientists could then prioritize lower-risk candidates while reserving higher-risk materials for cases where their functional performance justifies additional compatibility testing.

Integration into Preformulation Workflow

Screening Before Binary-Mixture Experiments

The model would be used before full binary-mixture screening to de-prioritize combinations that show a high predicted incompatibility risk based on available drug, excipient, thermal, and moisture descriptors. This use case is consistent with the broader direction of algorithmic drug product development, where predictive tools support experimental planning rather than replace laboratory evidence [29]. Compatibility studies using thermal and non-thermal techniques show that experimental screening remains essential, but a model could focus those experiments on the most uncertain or formulation-relevant combinations [30, 32]. The workflow should therefore treat predictions as a triage layer that reduces unnecessary testing while preserving confirmatory forced-degradation studies for important decisions.

Interactive Decision Support for Formulation Scientists

An interactive dashboard or spreadsheet implementation could allow formulation scientists to enter a drug's thermal profile, moisture behavior, and known chemical descriptors, then receive a ranked excipient shortlist with compatibility probabilities and explanations. Prior applications of artificial neural networks and machine learning in formulation development show that predictive tools are most useful when they are embedded in practical design workflows rather than kept as isolated research models [6, 35]. The interface should display uncertainty, missing-feature warnings, and mechanistic drivers so that users understand why a candidate is recommended or flagged. This would make the model a decision-support companion for preformulation teams rather than an automated substitute for scientific judgment.

Evaluation Strategy

Retrospective Classification Performance

Retrospective evaluation should assess whether the model can classify historical compatible and incompatible binary mixtures under group-wise hold-out conditions. Metrics such as sensitivity, specificity, receiver-operating-characteristic behavior, and precision–recall behavior could be considered, but they should be interpreted conceptually and without claiming performance results in the absence of a completed study. Compatibility prediction systems and preformulation multivariate analyses provide useful precedents for retrospective comparison against expert assessment or rule-based approaches [8, 37]. The key question is not whether the model achieves a stated numerical benchmark, but whether it can identify plausible incompatibility risk in a way that is reproducible and scientifically interpretable.

Table 3 defines the governance, evaluation, and decision-use controls required for a conservative compatibility-prediction model that supports formulation triage without replacing expert review or confirmatory testing.

Table 3. Model Governance, Evaluation, and Decision-Use Framework for Conservative Excipient-Compatibility Prediction

Decision-support layer	Core design question	Recommended implementation principle	Evaluation approach	Practical preformulation use	Risk-control requirement
Label governance	How should compatible, incompatible, and uncertain cases be defined?	Use predefined expert rules that combine forced-degradation evidence, impurity growth, thermal anomalies, and analytical confidence	Inter-rater agreement, label-audit review, adjudication of uncertain cases	Creates a scientifically defensible training endpoint	Avoid collapsing ambiguous cases into overconfident binary labels
Data-splitting strategy	Does the model generalize to new compatibility questions rather than memorize related pairs?	Use grouped splits by API, excipient family, or study source where appropriate	Group-wise hold-out validation and sensitivity analysis	Tests performance under realistic new-pair prediction conditions	Prevent leakage from similar drug–excipient records appearing in both train and test sets
Small-dataset handling	How can the model learn from limited historical compatibility evidence?	Use conservative feature selection, regularization, missingness indicators, and uncertainty flags	Compare performance across reduced-feature and full-feature models	Supports use in early formulation settings with incomplete records	Avoid high-dimensional feature expansion that exceeds dataset support

Imbalance management	How should rare but critical incompatibility cases be handled?	Favor sensitivity to incompatibility and calibrate thresholds to reduce false-compatible predictions	Precision–recall analysis, sensitivity/specificity trade-off review, false-compatible audit	Prioritizes patient-safety and development-risk avoidance	False-compatible predictions should receive stronger scrutiny than false alerts
Probability calibration	Is the compatibility probability meaningful for decision triage?	Calibrate outputs and define decision bands rather than using raw classifier scores	Calibration curves, reliability plots, threshold stability assessment	Enables low-risk, borderline, and high-risk triage categories	Do not interpret probability as automatic approval or rejection
SHAP explanation layer	Why did the model assign risk to a specific pair?	Report local drivers by evidence stream: thermal, moisture, forced degradation, chemical risk, and missing-data signals	Case-based explanation review by formulation scientists	Supports mechanistic interpretation and targeted follow-up experiments	Explanations should be checked for plausibility, not treated as proof of mechanism
Prospective demonstration	Does model-guided triage improve real formulation decisions?	Test predictions before full compatibility results are available	Compare predicted risk with later forced-degradation and impurity outcomes	Demonstrates whether the model helps prioritize experiments	Avoid claiming operational savings before prospective validation
Human oversight	Who makes the final compatibility decision?	Require expert formulation-scientist review for high-risk, borderline, novel, or chemically atypical cases	Documentation of overrides and post-decision outcomes	Keeps the tool as decision support rather than automated excipient selection	Maintain audit trails for model outputs, explanations, and expert decisions
Model updating	How should new compatibility evidence be incorporated?	Periodically retrain or recalibrate using newly adjudicated binary-mixture data	Temporal validation and drift monitoring	Allows continuous learning from routine preformulation work	New data should be quality-checked before inclusion
Implementation boundary	Where should the tool sit in the development workflow?	Use before full binary-mixture screening to rank candidates and identify uncertainty	Track experiments avoided, experiments reprioritized, and uncertain cases resolved	Reduces unnecessary testing while preserving confirmatory studies	The tool should not replace forced-degradation studies for important formulation decisions

Prospective Demonstration

A prospective demonstration would test whether the model can guide excipient selection for a new drug before full compatibility results are known. The predicted outcomes could then be compared with experimentally measured compatibility after forced degradation, using chromatographic impurity profiles and thermal or moisture follow-up as confirmatory evidence. Vial-in-vial compatibility approaches and preformulation degradation studies provide examples of experimental designs that could generate structured prospective labels for such a demonstration [4, 13, 14]. The prospective study should emphasize decision quality, uncertainty handling, and mechanistic explanation rather than unsupported claims of predictive performance.

Time and Resource Savings

Resource evaluation should estimate how many compatibility experiments could be avoided, deferred, or reprioritized if the model were used as an early screening filter. Pharmaceutical stability and formulation modeling studies show that predictive tools can help direct laboratory attention toward the most informative experiments when integrated into development workflows [23, 38]. In this setting, savings would be framed as a conceptual benefit arising from better triage, lower material consumption, and more focused forced-degradation testing. Any operational claims should be validated prospectively because savings depend on the diversity of the drug portfolio, the number of candidate excipients, and the organization's risk tolerance.

limitations

Limited Chemical Diversity in Current Datasets

The model may not generalize well to completely novel drug scaffolds, unusual excipient chemistries, or degradation mechanisms that are poorly represented in the training data. Compatibility labels derived from historical studies may also reflect differences in analytical method sensitivity, sample preparation, stress conditions, and expert interpretation. Reactive-impurity risks are especially difficult to capture unless excipient impurity profiles are available and standardized across suppliers. Predictions for chemically atypical systems should therefore be treated as hypotheses requiring expert review and confirmatory experimentation.

Impact of Particle Size and Mixture Preparation

The model assumes that sample preparation, milling, blending, and binary-mixture contact conditions are sufficiently standardized to make compatibility labels comparable. In practice, particle size, surface area, morphology, and mixing intensity can influence physical contact, moisture redistribution, and local reaction environments. These factors may be only partially captured by current excipient descriptors unless particle morphology and process-history features are added systematically. Future versions of the model should incorporate preparation-sensitive descriptors so that predicted incompatibility reflects both chemical risk and the physical circumstances under which the mixture is tested.

Conclusion

The proposed predictive model would estimate drug–excipient compatibility by integrating thermal degradation descriptors, hygroscopicity profiles, and forced-degradation evidence into a single preformulation decision framework. Rather than replacing experimental compatibility testing, it would help decide which binary mixtures deserve immediate testing, which appear lower risk, and which require additional mechanistic review.

A key strength of the approach is its integration of multiple preformulation data streams that are often interpreted separately. Thermal transitions, moisture uptake, material chemistry, and stress-induced degradation patterns would be combined into an interpretable compatibility probability, giving formulation scientists a more structured basis for early excipient selection.

Important challenges remain, including limited chemical diversity, inconsistent historical labels, missing moisture descriptors, and the need for prospective validation. Expert oversight would remain essential, particularly for atypical excipients, unusual drug scaffolds, supplier-specific impurity concerns, or cases where the model gives an uncertain prediction.

Collaborative preformulation databases would greatly improve the reliability of this type of model by expanding the diversity and consistency of available compatibility evidence. Pilot implementation in industrial formulation development groups would allow the model to be tested as a practical decision-support tool and refined through routine scientific use.

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