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Designing within the Excipient–Process–Patient Triangle to Anticipate Formulation Failure before Clinical and Manufacturing Translation

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ABSTRACT

Pharmaceutical formulation failure is often investigated through separate assessments of composition, manufacturing process, stability, product performance, or patient use. This fragmented approach can overlook failures that arise only when an excipient attribute encounters a particular process exposure and the resulting dosage form is used under physiologically or behaviourally variable conditions. This article develops an original, non-empirical formulation-risk architecture organized around an Excipient–Process–Patient Triangle. The architecture distinguishes three interacting domains: excipient functionality, variability, compatibility, and impurity burden; process exposures capable of transforming material and product attributes; and patient physiology, behaviour, capability, and administration conditions. It proposes that formulation performance should be evaluated at the intersection of these domains rather than inferred from isolated compliance with material specifications, nominal process settings, or standard laboratory tests. Interaction-driven failure scenarios include latent incompatibility, process-activated instability, loss of release-controlling structures, physiology-revealed excipient effects, administration-induced performance shifts, and three-way translation mismatches. Early warning indicators are organized around unexplained material sensitivity, process-dependent state change, representative-use dependence, analytical discordance, and extrapolation beyond the evidence domain. Corresponding decision gates distinguish proceeding, conditional progression, targeted stress testing, reformulation or process redesign, evidence escalation, and suspension of translation. Validation would require controlled perturbation of excipient, process, and patient-relevant variables; orthogonal characterization; external-condition testing; manufacturing-scale evaluation; and representative-use studies. The proposed architecture is intended to structure risk recognition and evidence planning. It does not establish predictive accuracy, clinical superiority, regulatory acceptability, universal applicability, or readiness for routine deployment.

Key words: *Formulation, Pharmaceutical formulation, Dosage form, Excipient, Manufacturability, Stability*
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INTRODUCTION

Pharmaceutical formulation development requires decisions about material selection, dosage-form architecture, manufacturing route, stability strategy, performance testing, and progression into increasingly consequential stages of development. These decisions are commonly supported by staged experimental models, in-vivo or in-vitro assessments, and decision trees selected according to compound properties, formulation maturity, and the development question being addressed [1]. Such approaches are indispensable, but they can encourage a sequence in which material risk, process risk, and patient-facing performance are examined by different teams, at different times, and under different assumptions. A formulation may consequently appear acceptable within each local

assessment while retaining an unresolved interaction that becomes visible only during scale-up, storage, administration, or exposure to representative physiological conditions. The central problem is therefore not simply insufficient testing. It is the possibility that testing remains structurally separated from the interactions that generate failure.

Digital formulation design, machine learning, mechanistic simulation, and data-integrative development platforms have expanded the capacity to evaluate multidimensional formulation spaces. These approaches may support candidate prioritization, prediction of formulation attributes, optimization of process settings, and identification of patterns that would be difficult to recognize manually. Their usefulness, however, depends on the relevance, quality, and coverage of the data from which relationships are learned or parameterized, as well as on validation within the intended material, process, dosage-form, and performance domain [2]. A digital prediction may therefore strengthen formulation reasoning without establishing that a product will remain stable, manufacturable, bioavailable, or usable under conditions absent from the underlying evidence. The distinction between computational plausibility and pharmaceutical consequence is especially important when apparently accurate model outputs are used to compress experimental development or justify translation across formulation classes.

Patient-related variability creates an additional challenge because the conditions under which a dosage form performs are not fixed by its composition or manufacturing record. Gastrointestinal pH, fluid volume, motility, transit, bile composition, viscosity, food state, and other physiological variables can alter dissolution, release, absorption, and pharmacokinetic behavior [3]. Behavioural and administration factors may further determine whether the product is swallowed, prepared, dispersed, divided, injected, or otherwise used as intended. These influences are frequently assessed after substantial formulation and process commitments have already been made. Consequently, a product optimized under standard laboratory conditions may encounter a materially different performance environment during clinical translation, particularly in special populations or use contexts that depart from the assumptions embedded in early testing.

This article presents an Original Formulation-Risk Architecture Article rather than an empirical study, validation report, regulatory framework, or clinical guideline. Its objective is to develop the proposed Excipient–Process–Patient Triangle as an organizing architecture for anticipating interaction-driven formulation failure before manufacturing and clinical translation. The triangle integrates three evidence domains: excipient-related mechanisms and uncertainties, process-dependent transformations of material and product attributes, and patient physiology, behaviour, and administration conditions. It further proposes failure-pathway categories, early warning indicators, decision gates, and validation requirements. The architecture is intended to help determine when a locally acceptable result is insufficient because the relevant performance pathway crosses another domain. It remains a conceptual synthesis requiring product-specific operationalization and prospective evaluation.

Recurring sources of formulation failure

Formulation failures often reflect interactions among material properties, process exposure, and product history rather than a single ingredient or setting. Tablet capping, for example, may arise from powder behavior, stress transmission, elastic recovery, tooling, and compaction conditions [4]. A correction that removes the visible defect at one scale may therefore fail after changes in equipment, speed, environment, or raw materials.

Some failures remain latent. In amorphous solid dispersions, processing and storage conditions can alter phase stability, recrystallization, and supersaturation performance despite acceptable initial testing [5]. Likewise, the structure and release of long-acting poly(lactic-co-glycolic acid) formulations depend on polymer properties, drug distribution, particle formation, and manufacturing history [6]. Process-induced morphology, porosity, residual solvent, and encapsulation can influence release long after production.

Formulation failures may therefore be classified as visible, latent, delayed, use-dependent, or translation-emergent. These proposed categories may overlap and are intended to identify how failure develops rather than only when it becomes observable.

Excipient-related mechanisms and uncertainties

Compendial identity and purity do not fully describe excipient performance. Particle size, morphology, moisture, porosity, molecular characteristics, impurities, and lot history can affect flow, compaction, stability, disintegration, and dissolution [7]. Excipient suitability must therefore be demonstrated within the specific formulation.

Compatibility is also condition-dependent. Peroxides, trace metals, reactive species, microenvironmental pH, moisture, oxygen, packaging, and processing can contribute to drug degradation [8]. An excipient may be acceptable under one concentration or storage condition but unsuitable under another.

These uncertainties are particularly important when excipients form the functional structure of the product. In liposomes, component-derived impurities can affect degradation, membrane behavior, consistency, and analytical results [9]. Similar modality-specific risks occur in emulsions, suspensions, depots, biologics, and coated systems.

The proposed excipient assessment domain therefore includes identity, functional attributes, variability, compatibility, impurity burden, and material history. Their importance must be established for each formulation rather than inferred from nominal excipient designation alone.

Process-dependent changes in material and product attributes

Manufacturing can transform materials rather than merely combine them. In continuous wet granulation, variation in active-ingredient properties can alter processing behavior and downstream quality even when the formulation and nominal settings remain unchanged [10]. Compression may also induce polymorphic transformation through localized pressure and shear [11].

Equipment settings do not necessarily represent the exposure experienced by the material. Stress, temperature, deformation, residence time, geometry, and scale can differ between processes with similar nominal parameters and produce different material states.

In continuous manufacturing, disturbances may propagate through feeding, blending, granulation, compression, sensing, and control operations [12]. Monitoring is therefore useful only when measured signals reliably represent the transformations that determine product performance.

The proposed process framework follows an exposure–transformation–propagation–consequence sequence. Mechanical, thermal, chemical, and temporal exposure can produce structural or chemical transformations that propagate into changes in manufacturability, stability, dissolution, release, or dose delivery. This framework is a conceptual synthesis, and its pathways and limits require formulation-specific validation.

Patient physiology, behaviour, and administration conditions

The patient node recognizes that dosage-form performance occurs within a variable biological environment. Age, disease, surgical history, and other population factors may alter gastrointestinal pH, fluid availability, gastric emptying, transit, bile secretion, motility, and absorption [13]. These differences can affect disintegration, dissolution, drug release, supersaturation, and delivery to the intended absorptive region. Their relevance is formulation-specific: a physiological variation may be negligible for one product but critical for another with narrow dissolution, transit, or release requirements.

Patient-centric formulation also requires practical acceptability. Intended users may have limitations in swallowing, dexterity, cognition, vision, sensory tolerance, or ability to follow complex instructions. Acceptability therefore depends on attributes such as size, shape, texture, taste, dosing frequency, device operation, preparation burden, and caregiver support [14]. It should not be treated as equivalent to adherence or clinical benefit, but as one determinant of whether a product can be used as intended.

Disease-specific physiology may reveal formulation risks not captured by standard tests. In Parkinson's disease, altered gastric emptying, motility, secretion, and gastrointestinal function may change oral dosage-form behavior and justify patient-relevant in-vitro models [15]. This does not mean that every disease requires a unique test system; rather, targeted representative-use testing is warranted when the intended population differs materially from assumptions underlying standard media, transit times, administration procedures, or healthy-volunteer models.

The patient node therefore includes five dimensions: physiological state, behaviour, capability, administration context, and foreseeable use variation. These cover biological conditions, consistency and correctness of use, physical and cognitive ability, food and fluid intake, preparation and device handling, co-medication, caregiver support, and plausible deviations such as crushing, splitting, mixing, delayed dosing, or incomplete preparation. They identify factors that may influence use or performance but do not predict adherence, establish individualized treatment recommendations, or determine clinical superiority [13].

Proposed excipient–process–patient triangle

The proposed triangle is intended to integrate evidence that is frequently generated and interpreted in separate development domains. Model-informed drug development demonstrates the value of combining mechanistic,

experimental, and clinical information while maintaining a clear connection between model credibility and intended decision use [16]. The same principle motivates the present architecture: no single material test, process model, dissolution method, or patient-use assessment should be expected to establish translation readiness when the relevant failure pathway crosses multiple domains. The triangle therefore operates as a structured hypothesis-generating framework in which evidence is assembled around interactions rather than accumulated as independent confirmations. **Figure 1** presents the original conceptual synthesis for excipient–process–patient interaction triangle and failure pathways, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

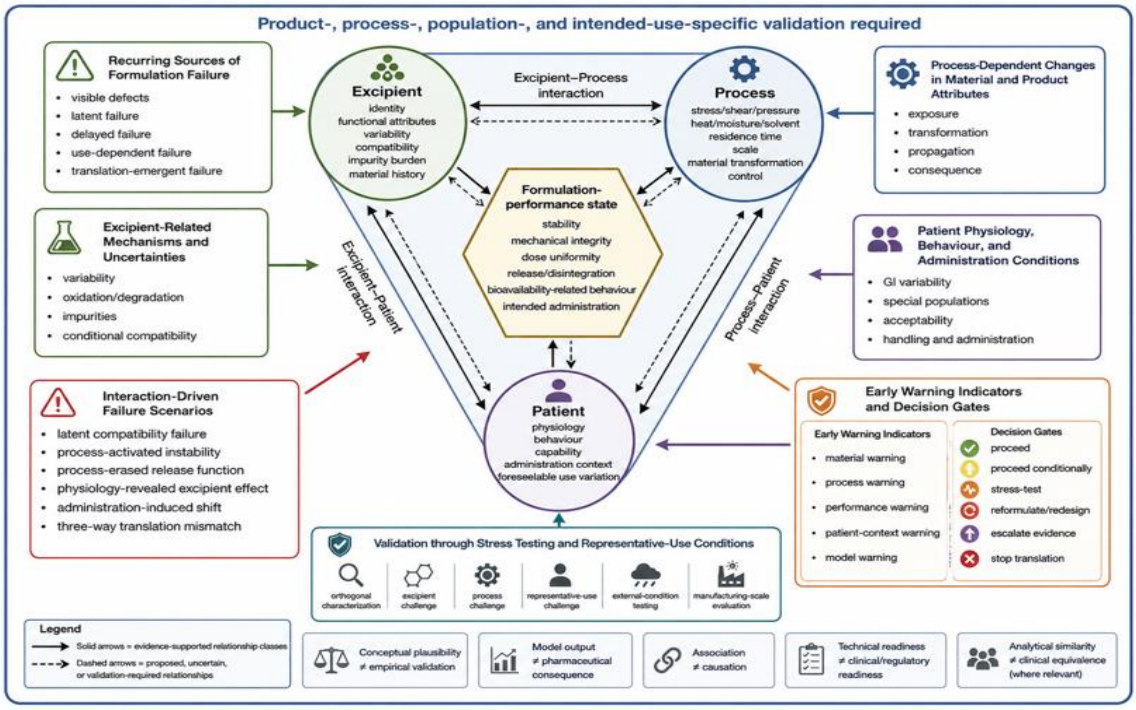

Figure 1. Excipient–Process–Patient Interaction Triangle and Failure Pathways.

The triangle contains three primary nodes and one central performance state. The excipient node represents identity, functional attributes, variability, compatibility, impurities, and material history. The process node represents operating conditions, equipment, scale, residence time, process exposure, material transformation, and control. The patient node represents physiology, behaviour, capability, administration context, and foreseeable use variation. At their intersection lies the formulation-performance state, defined as the condition of the dosage form with respect to stability, mechanical integrity, dose uniformity, release, bioavailability-related behavior, and ability to be administered as intended. A digital twin of continuous direct compression illustrates how raw-material and process inputs can be connected to predicted product attributes, but such a representation remains dependent on the process configuration, assumptions, and validation domain for which it was constructed [17].

The architecture distinguishes between node-level evidence and edge-level evidence. Node-level evidence describes a material, process, or patient condition in isolation. Edge-level evidence addresses an interaction: excipient–process, excipient–patient, or process–patient. Machine learning may help identify patterns within formulation-development data, but its performance remains conditional on how formulations, processes, endpoints, and experimental conditions are represented [18]. The triangle therefore does not treat a high-performing digital model as direct evidence of pharmaceutical consequence. Model outputs occupy an intermediate evidence layer and require mechanistic interpretation, experimental challenge, and confirmation under the conditions relevant to the intended decision.

The excipient–process edge concerns how a material responds to stress, temperature, moisture, solvent, shear, pressure, residence time, or scale. The excipient–patient edge concerns how composition influences disintegration, dissolution, release, stability, tolerability, or administration under route- and population-specific conditions. The process–patient edge concerns how manufacturing-created attributes alter use or performance in the patient environment. These pairwise edges may be sufficient to explain some failures, but other failures require the central three-way convergence. A filler may behave differently after a particular compression history and then

encounter a physiologically viscous medium; a coating may survive a nominal compaction test yet fail after storage and patient manipulation; or an impurity pathway may become consequential only after process exposure and prolonged in-vivo release.

A final layer distinguishes risk recognition from decision readiness. The triangle may organize plausible pathways, but a plausible pathway is not automatically causal, clinically important, or sufficiently controlled. The architecture therefore places evidence gates between identification of an interaction, demonstration of a material transformation, observation of a product consequence, and use of that evidence in manufacturing or clinical translation. These gates are original proposed constructs. They require product-specific definitions, test methods, uncertainty analysis, and prospective evaluation. The triangle is not a universal algorithm, risk score, or regulatory standard, and it does not predict the probability of formulation failure without operationalization in a defined dosage form and development context.

Interaction-driven failure scenarios

The first proposed scenario is physiology-revealed excipient failure, in which an excipient that performs acceptably under standard conditions contributes to altered product behavior under a representative physiological environment. Soluble fillers can influence tablet disintegration and dissolution differently in viscous simulated fed-state media, demonstrating that excipient function may depend on the patient-related condition under which it is evaluated [19]. The relevant failure is not necessarily intrinsic poor performance by the filler. It is a mismatch between the condition used to characterize the formulation and the environment in which the dosage form must function. This scenario supports targeted testing where food state, viscosity, fluid availability, transit, or disease-related physiology plausibly changes formulation behavior.

A second scenario is process-erased functional structure, in which manufacturing damages the feature responsible for the intended dosage-form performance. In multi-unit pellet systems, cushioning materials can reduce damage to coated pellets during tableting by modifying stress transmission and deformation behavior [20]. The example demonstrates an excipient–process relationship: the excipient does not merely facilitate compression but may protect a functional coating from mechanical failure. A formulation that appears compositionally correct can therefore lose its release-controlling architecture during manufacturing, particularly when pellet strength, cushioning capacity, compaction pressure, tablet geometry, and elastic recovery are not evaluated together.

A related scenario is interaction-driven release failure. Controlled-release multiparticulate tablets require simultaneous preservation of pellet coatings, adequate tablet strength, acceptable disintegration, uniform distribution, and manufacturability. Compression may damage coatings or alter pellet structure, while formulation changes intended to improve mechanical protection may affect tablet behavior or release [21]. The failure pathway therefore crosses formulation composition, unit-operation exposure, structural integrity, and patient-facing drug release. It cannot be resolved by confirming only assay, average tablet hardness, or nominal coating thickness. Evidence must show that the functional structure survives the process and performs under relevant use conditions.

Six proposed interaction-driven failure classes follow from these examples: latent compatibility failure, process-activated instability, process-erased release function, physiology-revealed excipient effect, administration-induced performance shift, and three-way translation mismatch. Latent compatibility failure involves an interaction not revealed by routine initial testing. Process-activated instability occurs when manufacturing initiates or accelerates a physical or chemical change. Process-erased release function occurs when the structure controlling release is damaged or transformed. Physiology-revealed effects emerge only under representative biological conditions. Administration-induced shifts follow preparation, handling, or use variation. Three-way translation mismatch occurs when composition, process history, and patient conditions jointly produce an outcome not predicted by isolated assessments. These categories are proposed pathway hypotheses rather than validated causal classes.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for integrated construct, components, evidence requirements, failure modes, and decision boundaries for designing within the excipient–process–patient triangle to anticipate formulation.

Table 1. Integrated construct, components, evidence requirements, failure modes, and decision boundaries for Designing within the Excipient–Process–Patient Triangle to Anticipate Formulation.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement

Excipient node	Nominal identity may not represent functional behavior	Grade, supplier, lot, particle properties, moisture, impurities, concentration, storage history	**Proposed:** excipient attributes influence manufacturability, stability, release, and administration conditionally rather than intrinsically	Earlier identification of material sensitivities	Functional characterization, lot challenge, compatibility testing, impurity assessment, formulation-specific performance tests; excipient variability may alter dissolution [7]	False assurance from compendial conformity; unrecognized reactive impurities; unsupported transfer across formulations	No excipient is universally compatible or functionally equivalent across products
Process node	Set points may not represent the exposure experienced by the material	Shear, stress, pressure, heat, moisture, solvent, oxygen, residence time, equipment, scale	**Proposed:** exposure produces transformation, which propagates into product attributes and performance	Mechanistic linkage between process design and failure pathways	Process perturbation, in-process sensing, orthogonal solid-state and structural analysis; process-induced transformation has been demonstrated during compression [11]	Unmeasured transformations; scale-dependent exposure; sensor variables weakly linked to consequence	Nominally similar processes cannot be assumed to create equivalent material histories
Patient node	Standard tests may omit relevant physiological and use conditions	Population, disease state, food, fluid, motility, capability, preparation, administration behavior	**Proposed:** patient and use conditions reveal or modify formulation behavior	More representative evaluation of dosage-form performance	Population-relevant physiology, acceptability assessment, use-condition testing; special-population physiology may alter absorption [13]	Overgeneralization from healthy or standard conditions; confusion of acceptability with adherence	Inclusion of patient variables does not establish clinical superiority or prescribe treatment
Excipient–process edge	Material functionality may change during manufacturing	Excipient mechanical properties, process stress, coating structure, moisture, temperature	**Proposed:** material attributes condition resistance or sensitivity to process exposure	Identification of protective or damaging formulation–process combinations	Factorial material–process testing and structural integrity assessment; cushioning pellets can protect coated units during tableting [20]	Apparent robustness restricted to one scale or formulation	A protective effect is product- and process-specific
Excipient–patient edge	An excipient effect may emerge only under representative physiological conditions	Disintegrant or filler properties, viscosity, food state, pH, fluid volume, transit	**Proposed:** physiological conditions modify the functional expression of an excipient	Detection of biopharmaceutical risk missed by standard media	Biorelevant testing with mechanistic interpretation; filler effects may change in viscous fed-state media [19]	In-vitro condition may not reproduce clinical consequence	Biorelevant behavior supports risk evaluation but does not alone establish in-vivo effect
Process–patient edge	Process-created attributes may alter administration or release	Coating integrity, tablet strength, particle size, depot morphology, device function	**Proposed:** process history modifies the way a dosage form responds during use	Connection of manufacturing decisions to patient-facing performance	Structural, release, administration, and representative-use testing; MUPS performance depends on preservation of functional pellets [21]	Release test may miss manipulation or physiological sensitivity	Product performance must be demonstrated under conditions relevant to intended use
Three-way convergence	Pairwise testing may overlook a failure that requires all	Excipient variability, process exposure, patient or	**Proposed:** a three-way interaction may amplify, reveal, or transform risk	Integrated formulation-risk reasoning	Deliberate perturbation across all three axes, orthogonal	Combinatorial complexity; false attribution; insufficiently	The triangle identifies hypotheses, not

	three domains	administration condition			measurement, causal analysis	representative conditions	probabilities of failure
Early-warning layer	Development may progress despite unexplained sensitivity	Model extrapolation, lot dependence, non-linear process response, analytical discordance	**Proposed:** warning indicators trigger evidence escalation before translation	Prioritization of unresolved interactions	Compatibility prediction with applicability limits [22]; structured raw-material variability assessment [23]	False-positive warnings or false reassurance from incomplete data	Warning indicators are not validated thresholds
Decision-gate layer	Evidence may be insufficient for the consequence of the next decision	Severity, reversibility, detectability, uncertainty, scale, population, evidence quality	**Proposed:** proceed, proceed conditionally, stress-test, redesign, escalate, or stop	Transparent and proportionate evidence decisions	Predefined evidence criteria and documented rationale	Subjective interpretation; inconsistent escalation	Gates are conceptual and do not replace product-specific control strategies
Validation and translation boundary	Retrospective plausibility may be mistaken for predictive readiness	External conditions, scale, representative use, independent data, negative cases	**Proposed:** decision use requires progressively stronger evidence as consequences increase	Separation of conceptual plausibility from deployment claims	Biorelevant dissolution and mechanistic modelling [24]; integrated dissolution/permeation and PBBM [25]	Overfitting, limited external validity, unmeasured clinical determinants	No model or test establishes universal clinical or regulatory acceptability

Early warning indicators and decision gates

An early warning indicator is defined here as an observation that increases the plausibility of an unresolved interaction without independently establishing failure. Compatibility prediction illustrates this distinction. Machine-learning methods may support prioritization of drug–excipient combinations for further investigation, but their predictions remain dependent on the training data, molecular representation, endpoint definition, and applicability domain [22]. A predicted incompatibility should therefore prompt targeted experimental assessment rather than immediate rejection, while a predicted compatibility should not replace stability studies, impurity analysis, or process-relevant challenge testing.

Raw-material variability provides a second basis for structured warning. A rational hierarchy can be used to determine when variability warrants routine characterization, deeper functional testing, process challenge, or lifecycle control [23]. Within the proposed architecture, escalation should be triggered when a material attribute changes without a well-supported link to product performance, when a process response becomes non-linear, when a previously stable relationship changes after scale-up, or when a model is applied beyond the combinations represented during development. The purpose is not to test every possible variable exhaustively. It is to recognize when the evidence no longer justifies treating a local result as representative.

The proposed early-warning layer contains five indicator classes. Material warnings include supplier, grade, lot, impurity, moisture, particle, or functional-property changes. Process warnings include unexplained sensitivity, drift, scale dependence, residence-time effects, or evidence of state transformation. Performance warnings include divergence among analytical methods, loss of discriminatory behavior, or instability under stress. Patient-context warnings include dependence on food, fluid, viscosity, motility, manipulation, capability, or disease-relevant conditions. Model warnings include extrapolation, poor uncertainty characterization, endpoint mismatch, or disagreement between prediction and mechanistic evidence. None of these indicators constitutes a validated threshold; each identifies a reason to examine the associated pathway.

Six decision gates are proposed. Proceed applies when relevant pathways have been challenged and uncertainty is proportionate to the intended decision. Proceed conditionally applies when a bounded uncertainty can be controlled through predefined monitoring or confirmatory work. Stress-test applies when nominal performance is acceptable but a plausible interaction remains unchallenged. Reformulate or redesign applies when the failure pathway is intrinsic to the selected composition, process, or dosage-form structure. Escalate evidence applies when laboratory or model evidence is insufficient for manufacturing or patient-facing translation. Stop translation

applies when a credible high-consequence pathway remains untested or uncontrolled. These gates are proposed aids to reasoning and documentation, not universal acceptance criteria or regulator-endorsed decisions.

Validation through stress testing and representative-use conditions

Validation of the proposed architecture would require more than retrospective classification of known failures. Biorelevant dissolution testing combined with physiologically based pharmacokinetic modelling can help evaluate whether observed in-vitro behavior is consistent with a plausible absorption mechanism, as demonstrated in formulation assessment of irbesartan [24]. Such approaches are valuable because they connect product behavior to physiological hypotheses rather than relying solely on compendial dissolution. They remain conditional on the credibility of the dissolution method, physiological assumptions, model structure, parameterization, and availability of suitable in-vivo evidence.

Integrated dissolution, permeability, and physiologically based biopharmaceutics modelling may provide a more discriminating assessment where dissolution alone does not capture the relevant absorption process. Their combined use in the evaluation of abiraterone acetate illustrates how formulation performance, permeability, physiology, and clinical relevance can be examined within one mechanistic chain [25]. The transferable lesson is methodological rather than numerical. Product-specific specifications, thresholds, or outcomes cannot be generalized to unrelated formulations. What can be generalized is the need to align the validation method with the mechanism through which a formulation difference could affect exposure.

A prospective evaluation of the triangle should employ controlled perturbation across the three axes. Excipient challenges could include representative lots, grades, impurity levels, moisture states, or functional-attribute ranges. Process challenges could include scale, equipment, residence time, stress, temperature, mixing, drying, compression, coating, or hold conditions. Patient-relevant challenges could include food state, fluid volume, viscosity, pH, transit, manipulation, administration technique, or population-specific physiology. The design need not evaluate every combination. It should select combinations based on a plausible pathway and test whether the integrated assessment identifies a risk that would be missed by node-level testing.

Validation should also distinguish several forms of credibility. Construct validity asks whether the triangle represents relevant formulation-risk domains. Mechanistic validity asks whether the proposed interaction can be linked to a measured transformation. Discriminative validity asks whether the approach distinguishes acceptable and unacceptable conditions. External-condition validity asks whether the relationship holds outside the conditions used to develop it. Manufacturing-scale validity asks whether the pathway remains informative after process transfer or scale-up. Representative-use validity asks whether the evidence reflects intended patient and administration conditions. Decision-usefulness validation asks whether use of the architecture improves the timing, transparency, or scientific quality of decisions. Retrospective explanation alone would support conceptual plausibility, not predictive readiness.

Limitations and translation priorities

The proposed architecture is limited by the heterogeneity of pharmaceutical products and by the uneven maturity of the evidence available for different nodes and interactions. Physiologically based models can support oral product development, but important challenges remain when local concentrations, food effects, disease states, complex absorption mechanisms, or adequate validation data are not represented [26]. Similar limitations apply to non-oral routes, where tissue physiology, administration technique, device performance, depot behavior, immune response, or local clearance may dominate. The triangle must therefore be operationalized differently for each route, modality, population, and intended use.

Digital prediction introduces an additional boundary. Machine-learning models may predict tablet release profiles within a represented formulation space, but their reported performance depends on the dataset, formulation descriptors, release conditions, kinetic definitions, and validation strategy [27]. A model trained on one set of excipients, manufacturing conditions, and test methods may fail after a change in grade, process, apparatus, or dosage-form architecture. The architecture should therefore require explicit declaration of model scope, uncertainty, and distribution shift. It should not treat a numerical prediction as evidence that the associated material transformation or patient consequence has been demonstrated.

CONCLUSION

The Excipient–Process–Patient Triangle is proposed as an original formulation-risk architecture for examining how material functionality and uncertainty, manufacturing exposure and transformation, and patient physiology and use conditions may converge to generate formulation failure. Its principal contribution is to shift attention from isolated compliance within separate development domains toward the pathways through which risk is amplified, revealed, or transformed across domains. The architecture organizes recurring failures, pairwise and three-way interactions, early warning indicators, decision gates, and staged validation requirements while preserving boundaries between conceptual plausibility, empirical validation, manufacturing readiness, and clinical translation. It does not establish predictive performance, universal risk categories, regulatory acceptance, or clinical recommendation. Its scientific value will depend on whether future product-specific studies can operationalize its constructs, test its proposed pathways prospectively, and demonstrate that interaction-focused evidence improves the recognition and management of formulation risk before consequential translation decisions are made.

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