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Pharmaceutical Formulation as a Dynamic System Linking Molecular Stability, Process History, Manufacturability, and In-Use Performance throughout the Product Lifecycle

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ABSTRACT

Pharmaceutical formulations are commonly described through composition, manufacturing specifications, critical quality attributes, and stability endpoints. Although these descriptions are necessary, they may inadequately represent products whose molecular organization, physical state, processability, release behavior, and in-use performance depend on the sequence of conditions experienced throughout the product lifecycle. This Original Dynamic-Systems Theory Article proposes that a pharmaceutical formulation should be conceptualized as a path-dependent system in which current behavior emerges from the interaction of nominal composition, evolving state variables, manufacturing history, environmental exposure, administration conditions, and patient handling. The theory distinguishes formulation from dosage form, formulation stability from fixed shelf-life description, process design from isolated unit-operation settings, and manufacturability from endpoint conformity. It introduces a formulation-state vector, transition operators, process memory, observation variables, performance domains, validation gates, and lifecycle-update rules. Molecular interactions and physical-state evolution are connected conceptually with manufacturing transitions, storage and transport, product–container and product–device interfaces, administration, and real-world use. Patient handling is incorporated as a conditional performance domain without equating acceptability or usability with adherence, bioavailability, safety, or therapeutic effectiveness. Model validation requires comparison with simpler static representations, deliberately varied histories, orthogonal state measurements, challenge testing, uncertainty analysis, external evaluation, and monitoring after material, process, site, equipment, packaging, or use-context changes. The proposed theory is an original conceptual synthesis rather than an empirically validated prediction system. Its intended contribution is to organize testable explanations of when process history matters, how it may propagate, which states require observation, and where formulation-level inference must stop before manufacturing, clinical, regulatory, or implementation decisions are made.

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

Pharmaceutical formulation development is often organized around the selection of an active pharmaceutical ingredient, excipients, dosage-form architecture, manufacturing process, analytical specification, and stability strategy. This organization is indispensable, but it can encourage a representation in which the product is treated as a fixed composition moving through a sequence of separable operations. In practice, material properties, unit operations, process controls, and downstream quality attributes can be interconnected across the manufacturing

train. Continuous solid-dose manufacturing makes this interdependence particularly visible because material movement, processing conditions, and product quality must be understood as temporally connected rather than as isolated batch endpoints [1].

The dosage form itself is also not a passive container of composition. Performance can emerge through ordered transformations that occur after the product encounters its use environment. For an immediate-release tablet, for example, liquid penetration, wetting, swelling, deformation, rupture, erosion, and fragmentation may collectively determine disintegration behavior. These mechanisms demonstrate that a dosage form can move through multiple material states before its intended release-related function is expressed [2]. Similar temporal reasoning may apply, through different mechanisms, to amorphous dispersions, suspensions, biologics, implants, long-acting injectables, multiparticulate systems, and device-associated products.

The lifecycle also extends beyond molecular stability and factory release. A technically acceptable formulation may still be unsuitable for its intended use when its dimensions, route, preparation requirements, device interface, manipulation burden, or administration procedure conflict with patient capabilities and healthcare conditions. Patient-centric product design therefore treats the drug product as an interface between pharmaceutical attributes and the circumstances in which it will be handled and administered [3]. This perspective does not make patient preference equivalent to clinical effectiveness, but it establishes that real-world performance cannot always be inferred from composition, release testing, or manufacturing conformity alone.

This article develops an original, non-empirical dynamic-systems theory for linking molecular stability, physical-state evolution, process history, manufacturability, storage, administration, and patient-facing performance. The theory does not propose that all formulations are equally history-dependent or that every historical difference produces a meaningful downstream consequence. Instead, it provides a vocabulary and architecture for identifying candidate state variables, specifying transitions, representing retained process memory, tracing conditional propagation, defining observation requirements, and restricting decision use. Established mechanisms from formulation science and pharmaceutical manufacturing provide the evidentiary foundations, whereas the cross-lifecycle architecture, process-memory construct, validation gates, and decision rules are proposed conceptual synthesis requiring product-specific empirical evaluation.

Limitations of static formulation descriptions

Static descriptors are essential but may not reveal how a product reached its observed condition. Simplified models can inadequately represent drug–polymer miscibility [4]. Stability may depend on thermodynamic forces, kinetic barriers, mobility, moisture, temperature, and exposure history [5], while supersaturation, crystallization, precipitation, and phase redistribution create trajectories not predictable from composition alone [6]. Endpoint similarity therefore does not prove state equivalence, and every historical difference is not necessarily meaningful.

State variables, transitions, and process memory

The theory distinguishes inputs, states, transitions, observations, and outputs. Process memory is the retained influence of prior exposure on current state or later performance. Residence-time distributions capture delay, mixing, hold-up, and traceability [7], but not all physicochemical memory. Material and operating conditions can alter exposure duration [8], while process-train analysis supports temporal traceability [9].

Conceptually, $x(t + \Delta t) = T[x(t), u(t), m(t), b(t)]$. Variables should be retained only when mechanistically relevant, measurable, and linked to performance.

Proposed dynamic formulation-system theory

The formulation is treated as a path-dependent system spanning physical organization, manufacturing, release, storage, administration, and use. Process digital twins can represent selected evolving states, but do not establish a complete lifecycle model [10].

Proposed dynamic formulation-system theory

The proposed theory treats pharmaceutical formulation as a path-dependent system whose condition cannot always be reconstructed from nominal composition and endpoint specifications alone. Its first premise is that a formulation passes through linked domains: molecular and physical-state organization, manufacturing transformation, release-state definition, storage and transport, administration and in-use transformation, and patient-facing performance. Bounded digital-twin work in continuous powder blending demonstrates that residence-time models and data-driven methods can represent selected evolving process states, but such

implementations do not establish a complete lifecycle model [10]. The present contribution extends the underlying dynamic logic conceptually while preserving a clear distinction between process-specific evidence and the proposed cross-lifecycle architecture.

Figure 1 presents the original conceptual synthesis for dynamic pharmaceutical formulation system across the product lifecycle, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

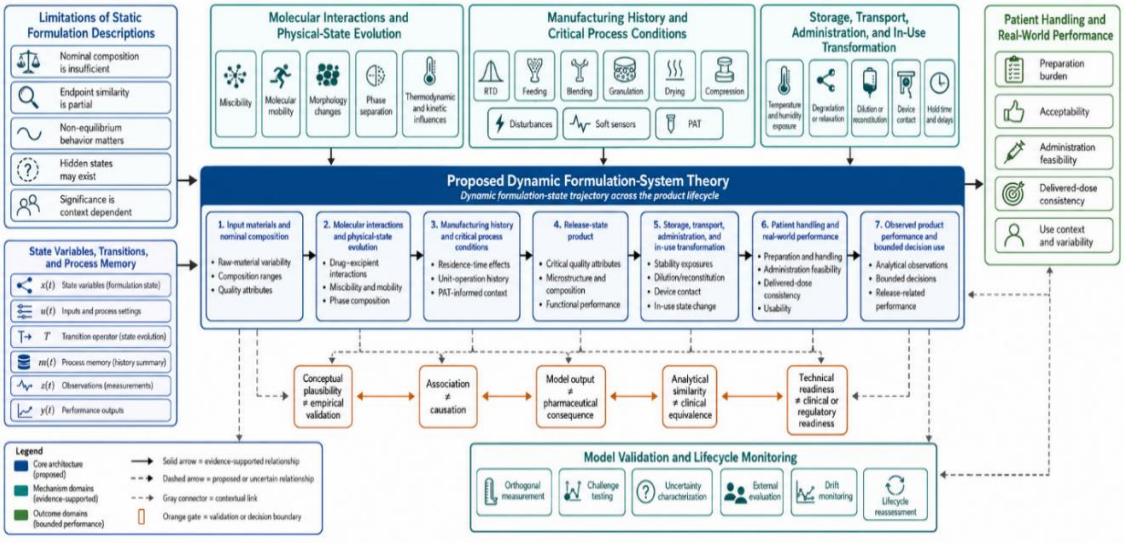

Figure 1. Dynamic Pharmaceutical Formulation System across the Product Lifecycle.

The figure is an original conceptual synthesis developed for "Pharmaceutical Formulation as a Dynamic System Linking Molecular Stability, Process History, Manufacturability, and In-Use Performance throughout the Product Lifecycle." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

The architecture contains five connected domains: molecular and physical state, manufacturing transitions, storage and transport, administration and in-use handling, and patient or real-world use. Together, they include variables such as miscibility, mobility, microstructure, raw-material attributes, process exposure, environmental conditions, packaging interactions, device contact, preparation procedures, and user capabilities. A separate observation layer integrates evidence from analytical testing, process analytical technology, stability studies, device assessment, and use-context evaluation.

The theory distinguishes physical integration from digital representation. Pharmaceutical Industry 4.0 connects manufacturing equipment, sensors, data infrastructure, computational models, and control systems [11]. Connectivity, however, does not prove that the relevant formulation state is observable or that a model can safely guide decisions. Sensors may measure surrogates, models may operate only within narrow domains, and automated responses may create unrepresented consequences. Validation gates are therefore required between observation, inference, pharmaceutical consequence, and decision use.

Model purpose and risk form the governance layer. Pharmaceutical process models differ in intended use, consequence, evidence requirements, validation burden, and lifecycle maintenance [12]. A model developed for scientific interpretation is not automatically suitable for process control, release support, clinical inference, or regulatory decisions. Each model should define its target state, decision context, applicability domain, uncertainty, comparator, monitoring strategy, and reassessment conditions. Changes in materials, equipment, scale, site, packaging, storage, administration, or patient context may invalidate an earlier representation.

The central propositions are conditional. Nominally equivalent products may diverge when different histories create performance-relevant states. History-sensitive models should outperform composition-only representations only when process memory is materially present and observable. Disturbances may be transmitted, reduced, amplified, transformed, or eliminated by later transitions. Administration may create a new formulation state, making real-world performance dependent on both product attributes and user context. These propositions define empirical questions rather than validated effects and do not establish a universal state vector or deployment-ready predictive system.

Molecular interactions and physical-state evolution

Drug–excipient associations, polymer chemistry, molecular mobility, and component distribution can influence miscibility, phase stability, dissolution, and resistance to crystallization. In amorphous solid dispersions, polymer properties and drug–polymer interactions affect physical stability and in-vitro performance through interconnected thermodynamic and kinetic mechanisms [13].

Although composition may remain unchanged, morphology and phase distribution can evolve through surfactants, polymers, moisture, heat, and processing. Because bulk measurements may miss localized or compositionally distinct states, orthogonal analytical methods may be necessary. Studies of surfactant-containing amorphous solid dispersions show that morphology and phase composition cannot always be inferred from nominal composition alone [14].

Thermodynamic tools, including phase diagrams, free-energy estimates, solubility parameters, and interaction models, can support polymer and excipient screening. Their value depends on model assumptions, parameter quality, temperature, composition, and kinetic accessibility. Phase-diagram analysis should therefore be treated as a structured decision aid rather than a universal predictor [15].

The theory represents physical-state evolution as product-specific transitions rather than a universal mechanistic sequence. A state variable is relevant only when linked to manufacturability, stability, release, delivered dose, or in-use performance. Minor differences may become consequential when processing, storage, dilution, or administration increases mobility or exposes unstable interfaces, whereas differences that do not persist may remain operationally irrelevant.

Manufacturing history and critical process conditions

Manufacturing converts composition into dosage-form structure through ordered mechanical, thermal, interfacial, and environmental exposures. Process analytical technology can provide time-resolved information during continuous manufacturing, allowing selected transitions to be observed closer to their occurrence and reducing reliance on final-product testing [16].

Soft sensors combine measurements with mathematical or statistical models to estimate difficult-to-measure states. Residence-time-informed soft sensors have been used to estimate downstream concentration behaviour in continuous pharmaceutical processes [17]. Their outputs depend on measurement quality, process structure, calibration data, and the stability of relationships between observed and estimated variables, and should therefore be treated as model-based evidence rather than direct measurement.

Process history becomes important when upstream disturbances alter downstream states or performance. Variations in particle properties, moisture, feeding, composition, or operating conditions may be transmitted, attenuated, amplified, or transformed across the process train. Dynamic modelling of continuous direct compression has shown that raw-material disturbances can propagate into tablet attributes and that residence-time behaviour alone may not fully explain the resulting quality response [18].

A critical process condition is consequently proposed as a condition whose timing, magnitude, duration, or interaction with the current formulation state can produce a performance-relevant transition. This definition is narrower than a list of all controllable process parameters and broader than a setting associated statistically with an endpoint. It requires a plausible transition mechanism, an observable or inferable state change, and a defined downstream consequence.

Table 1 defines the main components, relationships, evidence needs, uncertainties, and boundaries of pharmaceutical formulation as a dynamic system.

Table 1. Core components and evidence requirements for pharmaceutical formulation as a dynamic system

Component	Scientific role and proposed relationship	Expected contribution	Evidence required	Main uncertainty or failure risk	Boundary condition
Nominal composition	API, excipients, concentrations, and dosage-form design constrain possible states but do not uniquely determine the current state.	Establishes the material basis for dynamic interpretation.	Verified composition, identity, lot attributes, and analytical characterization.	Identical compositions may contain different internal states.	Composition equivalence does not establish state, performance, or clinical equivalence.
Molecular-interaction state	Drug–excipient interactions, polymer properties, moisture, and	Identifies candidate	Interaction, miscibility, mobility, and	Relationships may be formulation-specific or	Molecular interaction alone does not

	temperature can alter stability and in-vitro behavior [13].	mechanistic state variables.	phase measurements.	analytically ambiguous.	establish improved performance.
Physical state and morphology	Phase composition, morphology, and heterogeneity may change without altering the component list [14].	Explains how internal structure can influence later performance.	Imaging, spectroscopy, thermal analysis, diffraction, or complementary methods.	Relevant domains may remain below analytical resolution.	Analytical differences do not automatically imply pharmaceutical significance.
Thermodynamic and kinetic state	Thermodynamic tendency interacts with kinetic accessibility, mobility, nucleation, and viscosity [15].	Distinguishes predicted equilibrium from observed lifecycle behavior.	Product-specific phase analysis, kinetic studies, and stress testing.	Parameters may be uncertain or context-dependent.	Thermodynamic screening is not complete stability validation.
Process memory	Prior exposure to residence time, shear, heat, compression, mixing, drying, or hold-up may influence the current state.	Supports interpretation of path-dependent manufacturing and quality.	Traceability, residence-time distribution, challenge studies, and before-and-after state measurements.	Process history may be unobserved, irrelevant, or confounded.	History should be retained only when downstream relevance is demonstrated.
Critical process condition	A process condition becomes critical when it reproducibly causes a performance-relevant state transition.	Links process settings to mechanistic state change.	Designed perturbations, reference analytics, repeatability, and downstream assessment.	Statistical association may be mistaken for causality.	No universal critical-condition threshold is proposed.
PAT and soft sensors	PAT provides real-time observations, while soft sensors estimate otherwise inaccessible states [16, 17].	Improves temporal observability and supports process testing.	Calibration, validation, uncertainty analysis, drift monitoring, and reference comparison.	Surrogate signals may stop representing the target state.	Model estimates are not equivalent to direct measurements without validation.
Disturbance propagation	Upstream disturbances may be transmitted, attenuated, amplified, transformed, or terminated [18].	Explains how raw-material or process variation may reach product performance.	Process-train challenge studies and matched downstream measurements.	Propagation may be nonlinear, product-specific, or masked.	Upstream variation must not be assumed to cause downstream effects.
Lifecycle performance	Product performance emerges from the current state interacting with storage, administration, devices, and user handling.	Extends assessment beyond manufacturing and release testing.	Stability, in-use, device, release, bioavailability-related, and use-context evidence.	Later transitions may dominate earlier formulation differences.	Formulation evidence alone cannot establish clinical effectiveness or regulatory suitability.
Model and decision boundary	Model validity depends on intended use, applicability, uncertainty, and decision consequence [12].	Defines permitted uses and reassessment triggers.	Purpose-specific validation, comparators, uncertainty analysis, and monitoring.	Validity may be lost after changes in material, site, scale, equipment, or use context.	The architecture is not a qualified release, clinical, or regulatory decision system.

Storage, transport, administration, and in-use transformation

Product state may continue to change after manufacturing. Stability predictions depend on assumptions about stress conditions, degradation pathways, kinetics, packaging, and the relevance of accelerated studies to intended storage. Conventional stability programs and accelerated predictive approaches therefore involve different

evidentiary assumptions and limitations [19]. Any predicted trajectory should be interpreted within the conditions and mechanisms used to construct it.

Transport adds time-dependent exposures such as temperature excursions, vibration, pressure changes, humidity, and repeated handling. These may be irrelevant for robust products or may alter phase state, aggregation, moisture distribution, device function, or mechanical integrity. The theory therefore represents transport as an exposure trajectory whose importance depends on whether it changes a state linked to stability, administration, delivered dose, or performance.

Administration may create a new formulation state through dilution, reconstitution, mixing, transfer, pumping, contact materials, hold time, and light exposure. These factors can affect concentration, aggregation, adsorption, particulates, or chemical stability. Biopharmaceutical in-use stability assessments demonstrate the need to evaluate preparation and administration conditions rather than assume that packaged-product stability persists throughout use [20]. These findings remain product-class specific.

Product–device interactions create another transition because formulations may encounter surfaces, pressures, connectors, filters, syringes, or transfer systems absent during manufacturing and storage. Studies of closed-system drug-transfer devices for biologics show that device contact introduces distinct compatibility and performance questions [21]. The packaged and administered products may therefore represent different states, although measurable changes should not be considered clinically meaningful without evidence of consequences for dose, quality, safety, or performance.

Patient handling and real-world performance

Patient-centric development requires coordination among formulation design, manufacturing controls, packaging or device configuration, instructions, dosing frequency, preparation procedures, and care setting. Patient-centric frameworks emphasize that these elements should be considered together rather than as separate development decisions [22]. Integration may improve alignment with use conditions but does not independently establish safety, adherence, effectiveness, or regulatory acceptability.

Handling requirements vary among populations and settings. Swallowing ability, dexterity, cognition, sensory capacity, caregiver support, dosing flexibility, and access to administration resources may affect whether a product is used correctly. Research on paediatric and geriatric oral dosage forms shows that acceptability, safety, and access must be balanced when selecting age-appropriate products [23]. Acceptability does not necessarily imply adherence, correct exposure, or therapeutic benefit.

Long-acting injectable and implantable systems further illustrate the interaction between formulation and use context. Release duration, administration procedures, device requirements, reversibility, retrievability, and burden on patients and professionals can determine platform suitability. Patient-centric analyses indicate that long-acting formulations must be aligned with administration realities and patient needs [24]. Longer duration alone does not establish superior adherence, safety, effectiveness, or preference.

Real-world performance is therefore represented as a bounded set of outcomes, including successful preparation, dose consistency, administration feasibility, acceptability, use error, and route-specific burden. These outcomes may depend jointly on formulation state, device interaction, instructions, user capability, and care context**Table 2** summarizes the evidence, validation needs, failure modes, and boundaries for treating pharmaceutical formulation as a dynamic system.

Table 2. Evidence and validation framework for pharmaceutical formulation as a dynamic system

Architecture layer	Function and key interactions	Validation requirement	Main failure mode	Responsibility	Readiness boundary
Molecular and physical state	Represents molecular interactions, phase, mobility, moisture, and morphology affecting processing, stability, and release.	Orthogonal methods reproducibly distinguish performance-relevant states.	The proposed state is unresolved or unrelated to performance.	Formulation scientists define states and falsification tests.	Mechanistic plausibility does not establish predictive validity.
Manufacturing transition	Tracks how shear, heat, compression, drying, and coating	Controlled process histories produce reproducible,	Process history is confounded by material variability.	Process scientists design perturbation and traceability studies.	Association does not establish causality.

	create or remove process memory.	interpretable state changes.			
Residence and traceability	Links material delay, mixing, hold-up, and sequence across unit operations [7, 9].	Predicted arrival and mixing agree with tracer measurements.	Residence-time distribution is treated as a complete physicochemical model.	Engineers validate traceability assumptions.	Traceability alone does not establish performance consequences.
Disturbance propagation	Determines whether upstream variation is transmitted, attenuated, amplified, transformed, or terminated [18].	Prespecified challenge studies identify downstream effects.	Routine variability is mistaken for meaningful propagation.	Experimental teams define disturbances and consequences.	No universal pathway or threshold is assumed.
Storage and transport	Examines changes caused by time, temperature, humidity, vibration, and packaging [19].	Defined exposures generate reproducible state and performance changes.	Accelerated studies activate irrelevant degradation mechanisms.	Stability teams justify conditions and model scope.	Predictive stability does not independently establish shelf life.
Administration and in-use	Assesses changes during dilution, reconstitution, transfer, pumping, holding, or device contact [20].	Tests reproduce realistic preparation and administration conditions.	Laboratory procedures omit relevant use variability.	Product, device, clinical, and human-factor teams define scenarios.	In-use compatibility does not establish clinical equivalence.
Product–device interface	Evaluates effects of surfaces, flow paths, pressure, filters, connectors, and transfer devices [21].	Compatibility is demonstrated for the intended product, device, and procedure.	Evidence is generalized across non-equivalent products or devices.	Device and formulation specialists share responsibility.	Technical compatibility does not establish approval or therapeutic benefit.
Patient and use context	Examines whether intended users can correctly prepare and administer the product.	Representative users complete defined tasks with interpretable error analysis.	Acceptability is treated as evidence of adherence or outcomes.	Human-factor and clinical experts define representative conditions.	Patient-centered design is not a clinical recommendation.
Model and observation	Integrates sensor, analytical, process, stability, and use data to estimate hidden states.	Purpose, applicability, uncertainty, comparators, and updating rules are prespecified [12].	Model estimates are treated as direct observations or causal evidence.	Developers and independent evaluators separate development from assessment.	Scientific utility does not establish decision readiness.
Lifecycle decision	Restricts interpretation to validated materials, processes, sites, scales, packaging, devices, and users.	Reassessment follows relevant changes or detected drift.	A previously valid model remains in use after domain shift.	Cross-functional governance assigns ownership and review.	The architecture remains proposed until validated for a defined use.

Model validation and lifecycle monitoring

Validation should begin with observability. A state cannot support strong mechanistic or predictive claims unless it is measured or estimated with validated uncertainty. Process analytical technology can provide real-time information across unit operations and support continuous process verification when measurements are fit for purpose [25]. However, instrument availability does not prove that a signal represents the performance-relevant state. Each observation therefore requires a defined target, reference method, calibration range, uncertainty estimate, and drift-monitoring plan.

Sampling and material-diversion strategies must reflect process dynamics. In continuous manufacturing, the observed location and duration of a disturbance may differ from the affected material because of residence time, mixing, sensor delay, and transformation. Statistical monitoring approaches for twin-screw granulation show how

sampling and diversion can be aligned with time-dependent process behaviour [26]. Such strategies remain line-specific and require independent validation before transfer.

Experimental validation should use deliberately designed histories rather than retrospective associations alone. Materials with matched nominal composition should undergo different process or environmental trajectories, followed by orthogonal measurement of candidate states and prespecified performance outcomes. Predicted disturbance pathways should be challenged directly, while negative controls should test conditions in which history is expected to be irrelevant. Evidence that raw-material variability can affect downstream quality supports this approach, although the pathways remain product- and process-specific [18]. In-use validation should likewise reproduce realistic preparation and administration conditions [20].

Lifecycle monitoring continues after initial validation. Models should be reassessed when signals drift, residual errors increase, materials or processes change, new failure modes appear, or the decision context expands. Updates must distinguish recalibration from structural revision and preserve an auditable record of assumptions, evidence, uncertainty, and changed boundaries. Decision readiness remains conditional on intended use and the consequences of error; the proposed criteria are not universal release limits, clinical thresholds, or regulator-qualified pathways.

Boundary conditions and implementation requirements

Implementation depends on technical capacity, organizational structure, economic justification, workforce expertise, data governance, and regulatory context. Experience with continuous manufacturing shows that scientific feasibility does not remove barriers related to infrastructure, integration, business models, organizational change, and regulatory expectations [27]. A dynamic formulation system is therefore not a single software installation or modelling project. It requires coordinated ownership across formulation, process development, analytics, stability, devices, clinical development, quality, manufacturing, and human factors.

Algorithmic components introduce further constraints. Formulation datasets may be small, heterogeneous, poorly standardized, biased toward successful studies, or limited to narrow material and process domains. Guidance for machine learning in formulation development emphasizes data quality, applicability domains, interpretability, uncertainty, external evaluation, and reproducibility [28]. These principles are essential, but a statistically accurate model may still represent the wrong state, omit a causal transition, or be unsuitable for a consequential decision.

Implementation should therefore begin with bounded applications such as scientific interpretation, disturbance investigation, experiment design, or monitoring. Expansion toward automated control or release support should occur only after prospective validation, independent review, drift monitoring, change control, and reassessment of applicability. The architecture does not establish regulatory acceptance, clinical utility, autonomous-control suitability, or deployment readiness.

Research agenda

The first priority is to determine when dynamic models add value beyond static approaches. Machine-learning studies increasingly integrate material, process, and performance data, but remain limited by dataset size, heterogeneity, standardization, and generalizability [29]. Comparative studies should test whether history-sensitive models outperform composition-only or endpoint-based alternatives and identify cases in which greater complexity provides no meaningful benefit.

A second priority is integrating mechanistic knowledge with heterogeneous data. Formulation research increasingly combines experimental databases, molecular descriptors, process variables, and predictive algorithms, but progress depends on uncertainty-aware modelling and experimentally informative updating rather than algorithmic complexity alone [30]. Studies should distinguish narrow interpolation from models that represent mechanisms, identify transitions, or transfer across materials, processes, sites, and lifecycle stages.

A third priority is the direct study of propagation. Experiments should vary process history while holding nominal composition constant, localize where states diverge, determine whether later operations attenuate or amplify those differences, and establish whether the observed state reaches storage, administration, or patient-facing performance. **Figure 2** presents the original conceptual synthesis for propagation of process history into product performance, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

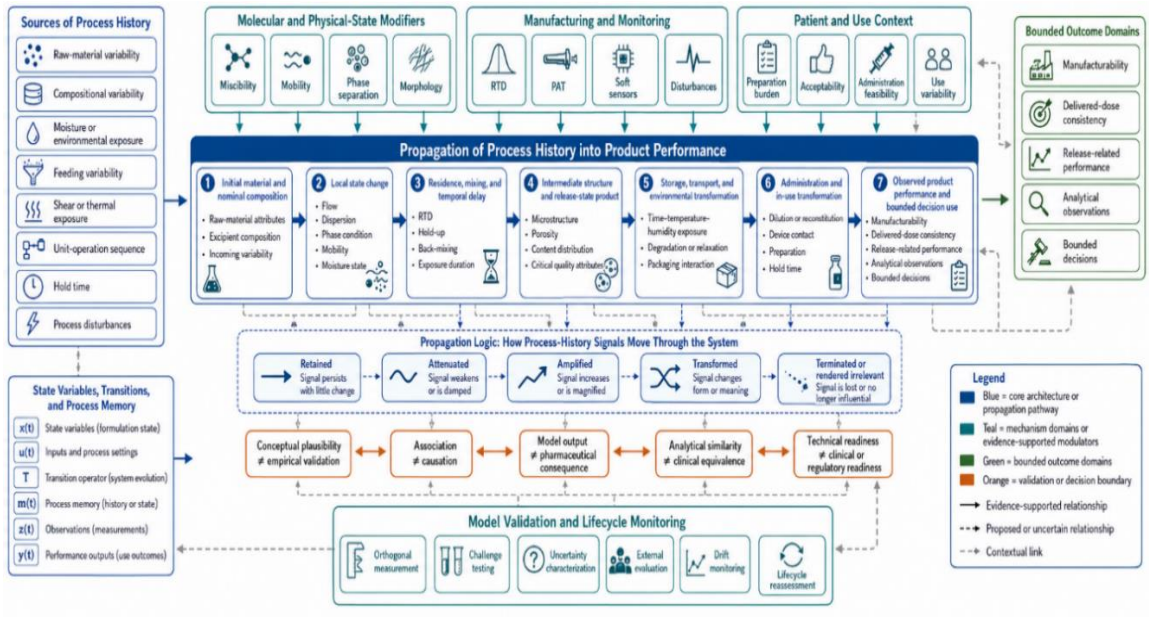

Figure 2. Propagation of Process History into Product Performance.

The figure is an original conceptual synthesis developed for "Pharmaceutical Formulation as a Dynamic System Linking Molecular Stability, Process History, Manufacturability, and In-Use Performance throughout the Product Lifecycle." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

A fourth priority is to connect formulation-system validation with responsible decision use. Research should define minimum evidence for scientific interpretation, process investigation, monitoring, control, diversion, release support, and post-change reassessment as distinct purposes. It should also examine latent-state observability, uncertainty propagation, negative controls, model drift, human oversight, and failure recovery. The most informative outcome would not be a universal dynamic model, but a set of falsifiable product-class theories that specify when history matters, which transitions preserve it, how it can be observed, and where its consequences cease.

CONCLUSION

Pharmaceutical formulation is proposed here as a dynamic, path-dependent system in which molecular organization, physical state, process history, storage exposure, administration, device interaction, and patient handling may jointly determine manufacturability and in-use performance. The theory contributes an integrated vocabulary of state variables, transitions, process memory, observation layers, propagation pathways, validation gates, and lifecycle-update rules. Its central implication is not that every historical difference is important, but that importance should be tested rather than assumed from composition or endpoint conformity. The framework remains an original conceptual synthesis requiring product-, process-, route-, and context-specific validation. It does not establish a universal model, clinical recommendation, regulatory determination, or deployment-ready control system. Its scientific value will depend on whether future studies can falsify its propositions, identify bounded applicability domains, and distinguish analytically detectable history from history that materially changes pharmaceutical performance.

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