



Physics-Informed Learning for Dissolution and Precipitation of Poorly Soluble Phytochemicals Across Formulation Conditions, Gastrointestinal Environments, and Dynamic Exposure States

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ABSTRACT

Poorly soluble phytochemicals frequently encounter a moving physicochemical target after oral administration, as dissolution, supersaturation, precipitation, colloidal association, formulation disintegration, gastrointestinal transit, and changes in luminal composition occur on overlapping time scales. Predictive approaches often simplify these processes into equilibrium properties or isolated empirical relationships. This article develops a proposed physics-informed pharmaceutical-science framework for learning dissolution and precipitation behavior across formulation conditions and dynamic gastrointestinal environments. The framework treats experimentally accessible concentration trajectories and formulation attributes as observations of latent physical states governed, where defensible, by mass balance, dissolution, transport, and precipitation relationships. Physics-informed neural or hybrid architectures are proposed to constrain learning while retaining data-driven components for processes that are incompletely specified. Particular attention is given to distinguishing molecularly dissolved drug from apparent dissolved or colloid-associated material, learning uncertain kinetic parameters from sparse experiments, and representing pH, bile-related composition, hydrodynamics, digestion, and transit as changing boundary conditions rather than fixed labels. The intended output is not a universally predictive model but an evidence-bounded strategy for linking mechanistic structure, incomplete experimental data, and exposure-relevant state estimation. Poorly soluble phytochemicals provide a demanding application space because formulation engineering may substantially alter their apparent dissolution and subsequent exposure. The proposed framework therefore requires compound-specific parameterization, uncertainty analysis, orthogonal experimental validation, comparison with mechanistic and data-only baselines, and prospective testing outside the calibration domain before claims of generalizability or translational utility are warranted.

Key Words: *Physics-informed learning, Dissolution, Precipitation, Supersaturation, Gastrointestinal dynamics, Phytochemicals*

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INTRODUCTION

For poorly soluble compounds, dissolution cannot be treated adequately as a single equilibrium outcome when the dissolved state itself is transient. Experimental work

designed specifically to acquire precipitation-relevant information demonstrates that supersaturated solutions can lose dissolved drug according to measurable kinetics that depend on the chemical and experimental system [1]. The corresponding predictive analysis shows that such kinetic

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information can be incorporated into mechanistic modeling rather than represented only as an empirical endpoint [2]. Formulation strategy further complicates this picture: combining supersaturating and solubilizing approaches can modify dissolution and transfer behavior in ways that are not reducible to a single solubility value or an assumption that more apparent dissolved drug is necessarily better [3]. During amorphous-solid-dispersion dissolution, supersaturation may also coexist with drug-rich phase formation and other evolving phase states [4]. These observations motivate a different computational framing. The relevant target is not simply “solubility,” but a trajectory through interacting physical states: undissolved material is depleted, molecularly dissolved drug appears, supersaturation may emerge, nucleation and precipitation can remove material from solution, and formulation-associated or colloidal reservoirs may temporarily retain drug. Across experimental precipitation, predictive modeling, and enabling-formulation studies, the evidence therefore supports treating oral performance as dependent on evolving dissolution–precipitation–transfer relationships rather than equilibrium solubility alone [1–3]. The present article proposes that these dynamics are particularly suitable for physics-informed learning. The proposed contribution is not a new universal dissolution equation and does not assume that neural constraints reveal the true mechanism automatically. Instead, it organizes known physical relationships, experimentally measurable states, uncertain kinetic parameters, formulation descriptors, and changing gastrointestinal boundary conditions into a hybrid inference problem. Mechanistic terms should be imposed only where sufficiently justified; incompletely understood processes may instead be represented by learned closure terms whose behavior remains constrained by mass balance, physical admissibility, and external validation.

For poorly soluble phytochemicals, this distinction matters because formulation intervention often precedes exposure prediction. Particle engineering, amorphous or colloidal states, lipidic environments, polymers, and carrier systems can change the pathway by which a compound enters and leaves solution. Consequently, a useful model should represent not only compound identity but the formulation-conditioned physical state and the environment through which that state evolves.

Solubility, supersaturation, and nucleation physics

Supersaturation is a nonequilibrium condition and therefore requires a kinetic interpretation. Its pharmaceutical relevance depends not only on the maximum concentration reached but also on how long molecularly dissolved drug persists before nucleation, precipitation, or redistribution into other phases. The

surrounding matrix participates in that process. In mucus-mimetic experiments, mucin altered the action of polymeric precipitation inhibitors and consequently changed supersaturation stabilization behavior [5]. Such findings caution against treating precipitation parameters obtained in simple buffer as invariant gastrointestinal constants.

Thermodynamic and kinetic effects should also remain distinct. NMR-based mechanistic work has shown that polymer type can influence amorphous solubility as well as the stability of drug-rich colloidal phases [6]. A formulation can therefore modify the apparent concentration trajectory through more than one mechanism: changing the effective thermodynamic state, delaying crystallization, stabilizing colloidal material, or combinations of these processes. A model that collapses these effects into one empirical “solubility enhancement” term would lose physically meaningful distinctions.

A second boundary concerns what is meant by dissolved drug. Coupled dissolution and membrane-mass-transfer measurements demonstrate that high apparent solution concentration does not necessarily translate proportionally into membrane-transferable drug [7]. For the proposed framework, this motivates separate state variables whenever the experiment permits them: solid drug, molecularly dissolved drug, supersaturated molecular drug, precipitated material, and formulation- or colloid-associated reservoirs. Not every experiment can identify all states, and forcing such separation without adequate observability would create parameter non-identifiability rather than mechanistic clarity. The required model complexity should therefore be determined jointly by physical plausibility and what the available measurements can actually resolve.

Formulation and gastrointestinal boundary conditions

Dissolution measurements are conditional observations. Intrinsic dissolution methodology emphasizes that medium composition, hydrodynamics, solid-surface conditions, and experimental configuration are integral to the measured process rather than incidental laboratory details [8]. Experimental profiling in biorelevant media further demonstrates that dissolution behavior changes with physiologically motivated media conditions and compound properties [9]. Accordingly, a physics-informed formulation model should not learn one context-free dissolution rate and then assume transfer across gastrointestinal environments.

The gastrointestinal compartment should instead be represented through boundary conditions that can vary with location and time. Relevant inputs may include pH, ionic environment, bile-related solubilization capacity, buffer behavior, fluid volume, hydrodynamic exposure,

digestion, and absorptive removal. Which variables must be modeled explicitly depends on formulation type and compound properties. The framework therefore does not require every possible gastrointestinal variable for every drug; it requires that omitted variables be treated as assumptions rather than silently absorbed into apparently universal kinetic parameters.

Fed-state behavior illustrates the need for this separation. Mechanistic analysis of itraconazole amorphous-solid-dispersion pellets after a high-calorie, high-fat meal identified interacting formulation and gastrointestinal processes that constrained absorption, rather than a single uniform “food effect” mechanism [10]. A binary fasted/fed label can consequently be insufficient when the scientific task is to extrapolate across conditions.

This leads to a central boundary rule for the proposed model: formulation attributes and gastrointestinal states are not interchangeable predictors. Formulation variables specify the initial material and release context; gastrointestinal variables determine the environment through which that material evolves. Their interaction may alter dissolution, supersaturation, precipitation, colloidal association, and subsequent transfer. A physics-informed architecture should therefore preserve this conditional structure explicitly instead of asking an unconstrained predictor to infer it from pooled profiles without mechanistic organization.

Physics-informed neural and hybrid model architectures

Physics-informed neural networks provide a general computational principle for combining observations with governing equations by penalizing solutions that violate specified differential relationships [11]. For pharmaceutical dissolution, the relevant attraction is not neural-network complexity itself but the possibility of learning from incomplete concentration-time measurements while enforcing mass conservation and selected kinetic or transport relationships. The governing structure might include depletion of solid mass, appearance of dissolved material, precipitation loss, intercompartmental transfer, or other states justified by the experimental design.

Related applications indicate how this principle can be extended without assuming that every process is fully known. Physics-informed modeling of reactive diffusion has combined transport and reaction relationships with experimental observations, illustrating the feasibility of learning coupled physical processes rather than fitting independent response curves [12]. In pharmacological systems, compartment-model-informed neural networks

have likewise coupled neural inference with ordinary or fractional differential-equation descriptions of drug dynamics [13]. These studies support the architectural possibility of hybridization; they do not establish that the same architecture is already predictive for gastrointestinal dissolution or poorly soluble phytochemicals.

For the present framework, three model layers are proposed. A physical-state layer contains variables whose conservation relationships are defensible, such as remaining solid, molecularly dissolved material, precipitated mass, and transferable material where experimentally observable. A condition layer supplies formulation attributes and time-varying environmental inputs. A learned-closure layer represents processes that cannot yet be specified adequately from first principles, for example condition-dependent kinetic coefficients or residual interactions between formulation and luminal composition. Learned terms should be bounded where physical knowledge permits and should not be allowed to compensate silently for violations of conservation.

Several implementation choices remain legitimate. A tightly specified mechanistic model may require neural learning only for a small number of uncertain functions. At the opposite extreme, a neural state model may be regularized by differential residuals and physical constraints. Between these lies a hybrid compartment architecture in which mechanistic state transitions are retained but selected rate expressions become condition-dependent learned functions. Across equation-constrained, reactive-transport, and compartment-informed examples, the literature supports this broader physics-informed design space [11–13]. It does not establish that one member of that design space is universally preferable.

The central design question is therefore not whether to use a PINN, but where mechanistic certainty ends and learned approximation should begin. Adding more governing equations is beneficial only when those equations describe the relevant pharmaceutical process adequately; an incorrect physical constraint can systematically bias inference. Conversely, a highly flexible data-only model may interpolate concentration profiles without preserving meaningful states or extrapolating coherently to new formulation and gastrointestinal conditions. The proposed architecture uses physical structure as an explicit scientific hypothesis that remains open to experimental rejection.

The distinctions developed above are summarized in **Table 1** as a comparative architecture for deciding which components should be mechanistically constrained, conditionally learned, or treated as unresolved.

Table 1. Comparative architecture for allocating mechanistic constraints and learned components in dynamic dissolution–precipitation models

Model component	Pharmaceutical meaning	Preferred representation	Evidence status	Principal failure condition
Solid-state reservoir	Material remaining available for dissolution	Mass-balance state with formulation-dependent initialization	Evidence-supported physical construct	Solid-state transformation is ignored
Molecularly dissolved drug	Exposure-relevant solution fraction	Explicit dynamic state when analytically observable	Evidence-supported distinction	Apparent and molecular concentration are conflated
Supersaturation and precipitation	Departure from equilibrium followed by kinetic loss or phase change	Mechanistic or semi-mechanistic rate expression	Evidence-supported process; exact kinetics system-dependent	Universal rate law is imposed across compounds
Formulation context	Particle, polymer, carrier, dispersion, or release environment	Initial conditions plus formulation-conditioned parameters	Evidence-supported dependency	Formulation is reduced to a generic categorical label
Gastrointestinal context	Changing medium and transport environment	Time- or compartment-dependent boundary conditions	Evidence-supported dependency	Static conditions are used despite dynamic exposure
Learned closure terms	Unresolved condition-dependent kinetics or interactions	Constrained neural function within the physical model	Proposed	Flexible term compensates for incorrect physics
Model output	Predicted physical-state trajectories	State estimates with uncertainty, not a single unconstrained endpoint	Proposed synthesis	Numerical fit is interpreted as mechanistic truth

Note: Evidence-supported entries summarize distinctions established by the approved literature discussed in the preceding sections. Elements marked Proposed are original components of the present framework and require prospective validation.

Learning kinetic parameters from sparse experimental data

Pharmaceutical dissolution experiments rarely observe every state required by a mechanistic model. Measurements may provide concentration at selected times while leaving precipitation rate constants, effective dissolution coefficients, transfer terms, or transient phase fractions unobserved. Inverse physics-informed modeling offers one route to estimating parameters from incomplete observations when the governing relationships are sufficiently specified. Parameter-estimation studies in other physical systems demonstrate that physics-informed neural networks can recover unknown quantities from partial observations, although success depends on model structure and information content [14]. For the proposed pharmaceutical framework, such evidence supports the feasibility of constrained inverse estimation, not the assumption that every kinetic parameter is identifiable. Timescale separation creates an additional problem. Reaction-kinetic physics-informed models show that stiff systems can be difficult to learn when rapidly and slowly

changing states coexist [15]. Dissolution and precipitation can generate an analogous numerical challenge when fast initial dissolution, delayed nucleation, subsequent precipitation, and slower gastrointestinal transfer overlap. This is a computational analogy rather than evidence that pharmaceutical and combustion chemistry share identical kinetics.

Noise further limits inverse inference. Bayesian physics-informed neural networks provide a formal route for propagating observational and parameter uncertainty instead of returning only point estimates [16]. In the proposed framework, uncertainty should accompany learned kinetic parameters and predicted state trajectories. A parameter that is weakly identified by the available experiment should remain uncertain rather than being converted into an apparently precise mechanistic constant. **Table 2** translates this principle into an evidence-provenance hierarchy for deciding which quantities may reasonably be fixed, estimated, learned conditionally, or left unresolved.

Table 2. Evidence provenance and confidence hierarchy for parameters and latent states in physics-informed dissolution modeling

Quantity class	Preferred provenance	Modeling treatment	Confidence interpretation	Principal caution
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Directly observed concentration	Time-resolved experiment with measurement-error	Training observation model	Highest confidence in the observation, not necessarily in its mechanistic meaning	Analytical method may combine molecular and colloidal material
Independently measured material property	Separate validated experiment	Fixed or narrowly bounded input	Strong when measurement conditions match the modeled system	Transfer across media or formulations may be invalid
Mechanistically fitted kinetic parameter	Dynamic experiment plus governing model	Inverse-estimated parameter	Conditional on model identifiability	Different parameter combinations may fit the same trajectory
Environment-dependent rate term	Multiple formulation or GI conditions	Condition-dependent estimated function	Moderate and domain-specific	Sparse condition coverage encourages extrapolation error
Latent physical state	Governing relationships plus indirect observations	Constrained hidden state	Model-dependent	Good fit does not prove the latent state exists as represented
Learned closure term	Residual process not adequately specified mechanistically	Bounded neural component	Proposed and conditional	Can absorb missing physics or experimental bias

Note: Confidence refers to evidential provenance within the proposed modeling workflow, not to numerical probability or regulatory qualification. The learned-closure category is an original proposed component.

Coupling dissolution, precipitation, and transit

Once dissolution and precipitation are represented dynamically, gastrointestinal movement cannot remain an external afterthought. Material leaving one state or location becomes an input to another. The most consequential distinction is between apparently dissolved drug and the fraction that is molecularly available for transfer. In supersaturating formulations, using molecularly dissolved concentrations rather than broader apparent concentrations improved absorption prediction in the studied physiologically based biopharmaceutics models [17]. The finding does not establish molecular concentration as a universal determinant of absorption, but it supports maintaining that state separately when the analytical system can resolve it.

Mechanistic PBBM development also demonstrates that formulation dissolution and related in vitro processes can be embedded within a compartmental representation of oral drug performance [18]. The proposed framework extends that logic by allowing selected state-transition terms to be learned under physical constraints rather than requiring every rate expression to be fixed in advance.

Time-varying formulation transformation adds another coupling layer. Real-time measurements during digestion of lipid-based formulations show that luminally relevant concentration can evolve continuously as formulation components are processed [19]. Accordingly, the proposed state equations should permit drug to move among solid, molecularly dissolved, precipitated, formulation-associated, and spatially transferred pools where those states are experimentally defensible.

Transit then becomes more than a residence-time correction. It changes which environmental conditions act on the evolving material and how long competing

dissolution and precipitation processes can proceed. A useful coupled model should therefore conserve material across state transitions and gastrointestinal compartments while distinguishing removal by precipitation, downstream transit, and exposure-relevant transfer. Failure to make these distinctions can produce a mathematically accurate concentration curve for the wrong physical reason.

Prediction under changing ph, bile, and hydrodynamics

The gastrointestinal environment itself changes during the trajectory being predicted. Human upper-gastrointestinal aspiration data show that pH is dynamically variable rather than adequately represented by one universal fixed value [20]. The appropriate model input is therefore not necessarily a scalar pH label but, where justified, a time- or compartment-dependent environmental state.

Bile-associated and lipid environments introduce additional dynamics. Mechanistic cryogenic transmission electron microscopy and NMR work during lipid digestion demonstrates that supersaturation can evolve together with changes in formulation microstructure and digestion state [21]. These observations argue against transferring a precipitation parameter measured in one medium unchanged into a chemically different luminal environment.

A mechanistic gastrointestinal representation can nevertheless be connected to systemic prediction when its components are appropriately parameterized and validated. In vivo PBBM development for vericiguat illustrates how drug-specific gastrointestinal processes can be propagated into pharmacokinetic predictions within a qualified model [22]. It does not validate such extrapolation for phytochemicals automatically.

The proposed framework therefore treats pH, bile-related composition, hydrodynamics, digestion, and transit as potential dynamic boundary conditions whose inclusion is dictated by mechanistic relevance and available

information. **Table 3** summarizes the decision criteria for deciding when an environmental factor should enter the model explicitly.

Table 3. Decision criteria for representing changing gastrointestinal conditions in a physics-informed model

Environmental factor	Explicit dynamic representation favored when	Simpler representation may suffice when	Main prediction at risk if oversimplified
pH	Ionization, solubility, dissolution, or precipitation is strongly condition-dependent	Relevant process is demonstrably insensitive within the studied range	Dissolution and supersaturation trajectory
Bile-related solubilization	Colloidal or micellar association materially changes apparent solution state	Formulation and compound show limited interaction with those phases	Molecularly available concentration
Digestion state	Formulation composition evolves during gastrointestinal processing	Dosage form does not undergo relevant digestive transformation	Time-dependent solubilization or release
Hydrodynamics	Boundary-layer transport or dispersion materially controls observed dissolution	Mass-transfer resistance is negligible or experimentally controlled	Effective dissolution rate
Transit	Competing physical processes occur on similar timescales to gastrointestinal movement	Process reaches a stable state well before relocation	Location and duration of supersaturation
Absorptive removal	Depletion of molecular drug changes the luminal concentration trajectory	Transfer is negligible in the modeled experiment	Coupling between luminal state and exposure

Note: These are proposed decision criteria derived from the manuscript's physical distinctions; they are not universal quantitative thresholds.

These interacting state and boundary distinctions are consolidated visually in **Figure 1** before the formal exposure framework is specified.

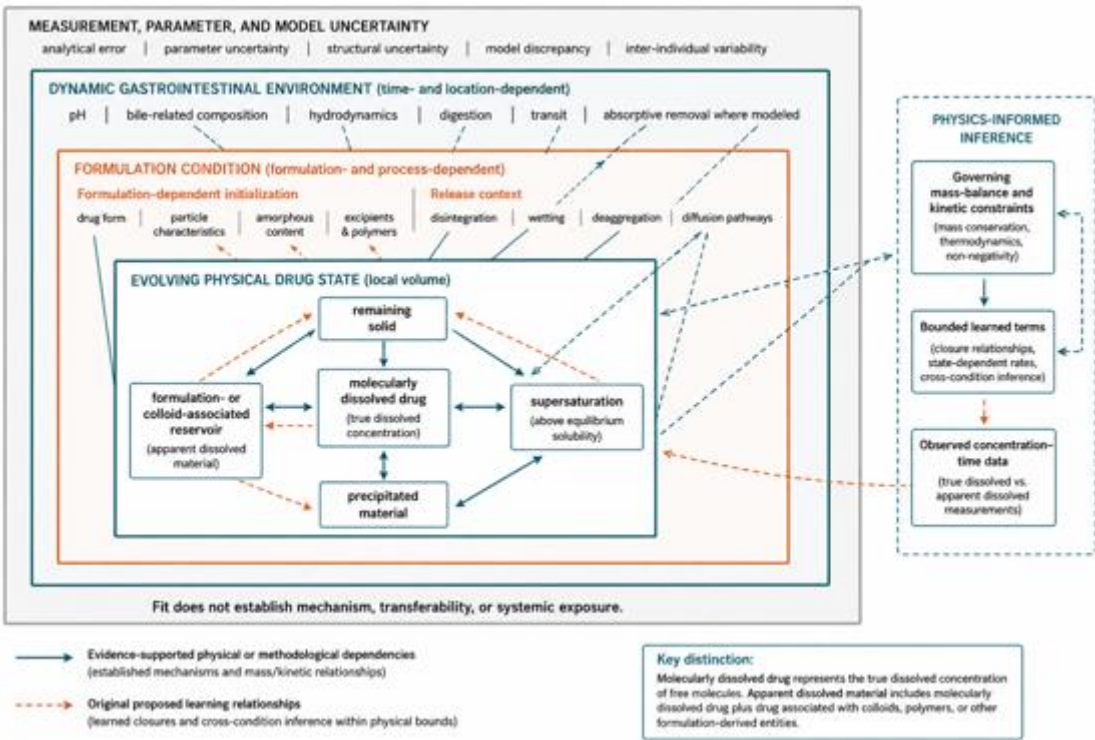


Figure 1. From formulation-conditioned material states to dynamically bounded dissolution–precipitation prediction

The physics-informed exposure framework

The proposed Physics-Informed Exposure Framework integrates the preceding elements into a layered inference

strategy rather than a single universal model equation. Its first requirement is parameter provenance. PBBM parameterization guidance emphasizes that model inputs should have transparent sources, biological or pharmaceutical justification, and appropriate context [23]. Accordingly, experimentally measured material properties should remain distinguishable from fitted kinetic parameters, inferred latent states, and neural closure terms. The second requirement is context-of-use validation. PBBM methodology stresses that model validation should be aligned with the question the model is expected to answer rather than treated as a generic certification step [24]. For the present framework, interpolation within one formulation and medium, prediction under a new pH trajectory, transfer to an unseen formulation, and extrapolation to a new phytochemical are progressively different scientific claims. Success at one level does not establish the next.

The third requirement is transparent model disclosure. Recent PBBM reporting work emphasizes explicit description of assumptions, parameters, validation, and model structure [25]. A physics-informed implementation should therefore report which equations are imposed,

which coefficients are fixed, which quantities are learned, what data constrain each component, and where uncertainty enters.

On this basis, the proposed framework contains four interoperable layers. The pharmaceutical initialization layer defines compound and formulation state. The dynamic physical layer tracks dissolution, molecular solution, supersaturation, precipitation, and other justified material reservoirs. The gastrointestinal boundary layer supplies changing environmental and transit conditions. The inference and credibility layer combines physical residuals, observations, learned closure functions, uncertainty, and validation tests.

Crucially, the exposure label is bounded. The framework predicts exposure-relevant luminal states unless an independently parameterized absorption and pharmacokinetic layer is added. It must not rename luminal concentration as systemic exposure merely because both appear in the same computational architecture.

Table 4 crosswalks model context against the methodological treatment that follows from this proposed architecture.

Table 4. Context-by-method crosswalk for constructing and interpreting the proposed Physics-Informed Exposure Framework

Modeling context	Mechanistic component	Data contribution	Learned component	Required credibility check
Known formulation, known medium	Mass balance and defensible dissolution/precipitation relations	Dense or sparse concentration-time measurements	Selected uncertain rate functions	Recover held-out trajectories without violating conservation
Known formulation, changed GI condition	Same physical-state architecture with altered boundaries	Measurements across environmental conditions	Condition-dependent kinetics where necessary	Test prediction at withheld conditions
New formulation of same compound	Formulation-specific initialization and release terms	Cross-formulation experiments	Formulation-to-parameter relationship	Compare with formulation-specific mechanistic baseline
New compound within related chemical space	Conserved generic physical principles only	Multicompound evidence	Compound-sensitive parameters or representations	External compound holdout and uncertainty assessment
Poorly soluble phytochemical application	Compound- and formulation-specific physical model	Dedicated phytochemical dissolution/precipitation data	Only unresolved terms justified by data	Prospective formulation and condition challenge
Luminal-to-systemic extension	Absorption and pharmacokinetic equations added explicitly	Permeability, absorption, and PK observations	Uncertain transfer terms if identifiable	Separate validation of luminal and systemic predictions

Note: The crosswalk is an original proposed synthesis. Moving down the table represents changing modeling contexts, not an established hierarchy of regulatory acceptance or predictive readiness.

Experimental validation and extrapolation

Validation should test both prediction and the physical interpretation assigned to that prediction. Dissolution/permeation comparison using μ FLUX and PermeaLoop demonstrates that biopredictive conclusions can depend on assay configuration even when the same supersaturating formulation is being investigated [26]. A physics-informed model should therefore not be validated

against one apparatus and then assumed to represent a platform-independent physical truth.

The proposed validation strategy has three complementary comparisons. First, it should be tested against an appropriately specified mechanistic baseline to determine whether learned components add information beyond conventional parameter fitting. Second, it should be compared with a data-only model. Machine-learning work

on quantitative structure–dissolution–profile relationships demonstrates that dissolution trajectories can be approached directly from molecular and formulation information without explicit physical constraints [27]. Such models provide a necessary comparator because a more mechanistically elaborate architecture is not justified merely by being interpretable.

Third, validation should deliberately separate interpolation from extrapolation. Withheld time points from an already observed formulation test interpolation weakly. Withheld environmental conditions test conditional generalization. Withheld formulations test transfer across material contexts, while unseen compounds test a substantially stronger claim.

Parameter recovery is also important. When independently measurable kinetic or material parameters exist, the inverse model should be challenged to recover them rather than evaluated solely by curve fit. Uncertainty should widen when data become sparse or conditions move beyond the calibration domain. If a physics-informed system produces low trajectory error but systematically wrong parameter estimates, violates independently observed phase behavior, or fails under orthogonal assays, the appropriate conclusion is model misspecification, not successful mechanistic learning.

Implications for poorly soluble phytochemicals

Poorly soluble phytochemicals are a demanding application because formulation changes can dominate the pharmaceutical state presented to the gastrointestinal tract. Curcumin nanocrystal preparation illustrates how particle-engineering decisions can materially alter formulation and dissolution-related behavior [28]. Quercetin nanoformulation and hydrogel-microsphere delivery similarly demonstrate that the administered physical form can differ substantially from the unformulated poorly soluble compound [29]. A resveratrol nanocrystal system developed through a quality-by-design strategy further showed that formulation engineering can influence both pharmaceutical performance and measured pharmacokinetic behavior in the studied system [30].

These examples support a class-level caution rather than a universal phytochemical mechanism. Curcumin, quercetin, and resveratrol differ in structure, solid-state behavior, ionization, carrier interactions, metabolism, and formulation context. Recent formulation studies across these three compounds therefore illustrate strong formulation dependence without establishing one common kinetic solution for poorly soluble phytochemicals [28–30].

The proposed framework should consequently begin with compound-specific physical parameterization. Shared learning across phytochemicals may become useful only

after determining which quantities can legitimately transfer. Conservation relationships may be broadly reusable, whereas equilibrium properties, nucleation propensity, polymer interactions, colloidal behavior, digestion sensitivity, and formulation-specific release terms may require compound-level or formulation-level information.

A productive future strategy would be hierarchical rather than universal. A shared model could encode general mass-balance structure and common environmental variables, while compound- and formulation-specific branches learn bounded kinetic differences. Such a strategy could potentially exploit information across sparse phytochemical datasets without pretending that chemical similarity guarantees pharmaceutical equivalence.

The translational boundary must remain explicit. Improved dissolution prediction does not establish improved therapeutic efficacy; increased systemic exposure may be beneficial, irrelevant, or undesirable depending on pharmacology and safety. Likewise, a formulation study demonstrating higher exposure does not prove that the proposed dissolution–precipitation mechanism caused that outcome. The immediate value of physics-informed learning is therefore better framed as disciplined prediction and hypothesis organization for formulation development, followed by independent experimental and pharmacokinetic testing.

Limitations

The framework is constrained first by measurement. Microdialysis integrated with dissolution/permeation testing has demonstrated both useful capabilities and system-dependent limitations in supersaturating formulations [31]. Sampling devices, membranes, equilibration, temporal resolution, and recovery can affect what portion of a rapidly changing system is actually observed.

The definition of “dissolved” is itself method dependent. Microdialysis and nanofiltration studies have shown that molecularly dissolved and colloid-associated drug can be distinguished analytically under relevant supersaturating conditions [32]. A model trained on an undifferentiated concentration signal may therefore learn an operational measurement state rather than the molecular state assumed by its equations.

Computational limitations remain equally important. Stiff or multiscale kinetics can destabilize learning [15], Bayesian uncertainty remains conditional on the assumed model and priors [16], and context-specific validation cannot be replaced by a low training error [24]. The proposed framework also lacks prospective validation as an integrated system and should not be treated as implementation-ready.

Finally, the selected evidence spans conventional poorly soluble drugs, formulation systems, computational physics, and a small set of phytochemical exemplars. Transfer among these domains is deliberately methodological rather than evidentiary proof of common mechanism. New compounds, formulations, analytical platforms, and gastrointestinal conditions may expose missing state variables or invalidate assumed rate relationships.

CONCLUSION

Dissolution and precipitation of poorly soluble phytochemicals are best conceptualized as evolving pharmaceutical processes rather than static solubility attributes. The framework proposed here combines physically interpretable state variables, formulation-specific initialization, changing gastrointestinal boundary conditions, constrained learning, uncertainty, and context-dependent validation within one pharmaceutical-science architecture.

Its central premise is deliberately limited: physical knowledge should constrain learning where governing relationships are defensible, while uncertain or incompletely specified processes may be learned only within explicit boundaries. Molecularly dissolved, colloid-associated, precipitated, and solid material should remain distinct whenever measurements can resolve those states, and gastrointestinal conditions should be dynamic when their variation is mechanistically consequential.

The framework does not establish a universal phytochemical model, mechanistic truth from numerical fit, or systemic exposure from luminal prediction alone. Its value lies in making assumptions, latent states, transferable knowledge, uncertainty, and failure conditions explicit. Prospective cross-formulation, cross-condition, and cross-compound testing will determine whether this proposed integration improves prediction beyond well-specified mechanistic models and data-only alternatives.

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