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Poorly Soluble Phytochemicals Change Rank After Formulation: A Developability Model Connecting Solid State, Dissolution, Biorelevant Exposure, and Delivery-Strategy Selection

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ABSTRACT

Poor aqueous solubility frequently lowers the apparent developability of phytochemical candidates, yet that judgment is often made before formulation has revealed whether the limitation is intrinsic, state-dependent, or technologically tractable. This article develops an original formulation-aware developability model in which candidate quality is treated as conditional on material state, gastrointestinal dissolution behavior, exposure-relevant solution state, and the suitability of the selected delivery strategy. Evidence from formulated phytochemicals and mechanistic pharmaceutics shows that formulation can alter oral exposure, but also that increased apparent solubility does not necessarily translate into greater absorption. Solid-state conversion, supersaturation, precipitation, colloidal association, thermodynamic activity, permeability, digestion, and presystemic handling may reinforce or oppose one another. The proposed model therefore distinguishes native-state deficit, formulation leverage, residual developability liabilities, and confidence in translation rather than ranking candidates solely by equilibrium solubility or an isolated dissolution endpoint. Biorelevant testing is positioned as an interpretive bridge between material properties and exposure, with physiological buffer conditions, transfer behavior, colloidal states, and absorption-relevant sinks determining what a dissolution result can legitimately imply. Rank reversal is consequently treated as a testable change in relative candidate priority after strategy-conditioned evaluation, not as evidence that formulation universally rescues poor compounds. The framework is intended for comparative prioritization and hypothesis generation. It remains nonvalidated prospectively, depends on compound-specific evidence, and requires external testing across chemically diverse phytochemicals, formulation classes, and progressively more physiologically informative experimental systems.

Keywords: Phytochemicals, Poor solubility, Developability, Biorelevant dissolution, Formulation, Oral exposure

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Introduction

Poor aqueous solubility is commonly treated as an early liability in phytochemical development, but the measured liability belongs to a compound in a particular material and formulation state rather than to chemical identity alone. Human evidence demonstrates that changing formulation can materially alter systemic exposure. Micellar solubilization substantially changed oral exposure to trans-resveratrol in healthy participants, establishing that apparent candidate performance can depend on how the molecule is presented to the gastrointestinal tract [1]. Curcumin provides a complementary example: a biphasic dissolution approach differentiated formulation performance in a manner consistent with human bioavailability, linking formulation-dependent in vitro behavior with an exposure-relevant endpoint [2]. These observations do not establish that formulation rescues every poorly soluble phytochemical; they establish that candidate quality cannot always be inferred from the unformulated state.

The mechanism of improvement is equally important. In a randomized crossover evaluation of curcumin formulations, greater post-digestive solubility emerged as an important determinant of improved oral bioavailability, showing that the relevant state may be the one produced after gastrointestinal processing rather than the nominal state before administration [3]. Recent work with poorly soluble andrographolide likewise showed that stabilizer selection affected nanocrystal preparation and oral absorption, indicating that formulation composition itself can modify the performance of a phytochemical delivery system [4]. Together, these examples make formulation responsiveness a developability question, but they do not justify assuming a common mechanism or magnitude of benefit across chemical classes.

This article therefore proposes a formulation-aware developability model in which poorly soluble phytochemicals are evaluated in both their native state and plausible strategy-conditioned states. The central argument is that candidate ranking should integrate four separable questions: what limits the native material, whether a formulation can alter that limiting process, what liabilities remain after intervention, and how strongly the resulting performance is supported by exposure-relevant evidence. The purpose is not to replace conventional physicochemical characterization, but to prevent premature rejection or promotion when equilibrium solubility, dissolution, colloidal behavior, permeability, or formulation feasibility provide discordant signals. Rank reversal is treated here as a comparative development hypothesis requiring validation, not as an inevitable consequence of formulation.

Why formulation alters the meaning of candidate quality

The simplest reason formulation changes candidate interpretation is that solubility is only one determinant of absorbed exposure. In carbamazepine, formulation conditions that maximized apparent solubility did not necessarily maximize blood levels because solubility and permeability changed in opposing directions [5]. This finding is important beyond that specific drug because it demonstrates the logical weakness of ranking candidates through a single “more dissolved is better” assumption. A phytochemical may therefore appear attractive after a large solubility gain yet remain limited if the same formulation reduces thermodynamic activity, free-drug availability, membrane transport, or another exposure-controlling process.

Formulation comparison becomes more informative when the in vitro measurement is demonstrably connected to in vivo behavior. A two-step dissolution approach for telmisartan supported formulation selection through an in vitro–in vivo relationship, illustrating how dissolution can become decision-relevant when the method captures properties that matter to systemic performance [6]. Similarly, incorporation of biphasic dissolution information into physiologically based pharmacokinetic models improved the mechanistic connection between formulation release and predicted in vivo exposure in the studied systems [7]. Neither example validates a universal assay; both show why candidate ranking should depend on the evidential meaning of the test rather than on dissolution magnitude alone.

The experimental platform itself can alter that meaning. Dynamic gastrointestinal simulation produced dissolution profiles for BCS class II drugs that differed in interpretive value from those generated by conventional USP II testing [8]. The implication proposed here is that candidate quality has at least two states: native apparent quality, derived from intrinsic material and simple assay behavior, and strategy-conditioned quality, derived after a formulation has been examined under conditions capable of revealing its relevant strengths and liabilities. Formulation does not erase intrinsic weakness; it changes which weaknesses remain development-limiting.

Solid-state and solution-state constraints

Solid-state modification is one route by which candidate behavior can change before absorption is considered. Curcumin can be converted into a coamorphous system through interaction with a coformer, demonstrating that a poorly soluble phytochemical need not remain in its original crystalline organization during formulation development [9]. Amorphous solid dispersions similarly alter the energetic basis of dissolution and can generate supersaturation, but the magnitude and persistence of that supersaturation depend on formulation design rather than on amorphization alone [10]. Consequently, the relevant question is not whether crystallinity has been removed, but whether the resulting state remains physically and biopharmaceutically advantageous under use conditions.

Drug loading and polymer selection further condition performance. In telaprevir dispersions, these variables affected release behavior and membrane transport [11]. Water exposure can also induce phase separation within spray-dried amorphous dispersions, meaning that an initially homogeneous solid may evolve during dissolution

into states with different release properties [12]. Preformulation tools can help reduce this uncertainty: liquid-state NMR has been used to distinguish drug–polymer pairings associated with successful amorphous dispersions [13], while high-throughput microarray approaches can screen relative physical stability across drug–polymer combinations [14]. Such methods support triage, but neither constitutes proof of in vivo success.

The solution state generated after dissolution adds another layer. Drug loading and microenvironmental pH can govern the generation of nanospecies during dissolution of polymeric amorphous systems [15]. Solid-form alternatives can likewise produce different systemic consequences; distinct quabodepistat cocrystals showed different oral-bioavailability behavior despite sharing the same active chemical entity [16]. Thus, an initially favorable amorphous formulation can lose or redistribute its apparent advantage when supersaturation, water-induced phase separation, or nanospecies formation changes during dissolution [10, 12, 15].

These distinctions are organized in **Table 1**, which separates material-state modification from the post-dissolution conditions that determine whether an apparent physicochemical advantage remains developability-relevant.

Table 1. Material-state constraints that can change the interpretation of poorly soluble candidate quality

Developability layer	Evidence-supported constraint	Consequence during formulation	Ranking implication proposed here
Native crystalline state	Lattice-controlled dissolution can restrict attainable dissolved concentration	Alternative solid states may raise apparent dissolution potential	Do not equate native-state performance with final developability
Coamorphous or amorphous state	Higher-energy material can generate supersaturation but requires stabilization	Benefit depends on persistence rather than initial release alone	Credit the gain only while the advantageous state is maintained
Polymer–drug system	Loading, compatibility, and hydration can change release and transport	Phase separation or weak compatibility can erode expected advantage	Discount formulation leverage when physical-state instability remains
Dynamic solution state	Dissolution may generate molecularly dissolved drug, nanospecies, or precipitated material	The post-dissolution state may differ from the nominal dosage-form state	Rank the exposure-relevant state, not the label "amorphous"
Alternative crystalline form	Cocrystals can alter dissolution and subsequent exposure	Different forms of the same active may behave differently in vivo	Treat solid-form selection as a candidate-specific decision variable

Note: The final column represents the proposed interpretive synthesis of this article; it is not a validated scoring system.

Biorelevant dissolution and exposure

Once a formulation enters gastrointestinal fluid, dissolution becomes a dynamic competition among release, supersaturation, precipitation, partitioning, colloidal association, and removal by absorption. These processes are highly assay-dependent. An interlaboratory study of a poorly soluble weak base showed that biorelevant precipitation testing is sensitive to experimental parameters, emphasizing that reproducibility depends on how the assay is constructed [17]. In gastrointestinal transfer experiments, use of a physiologically relevant bicarbonate buffer improved prediction of supersaturation and precipitation behavior for poorly soluble weak bases under the studied conditions [18]. "Biorelevant dissolution" therefore describes a design objective rather than a guarantee of physiological fidelity.

Buffer identity is one reason apparently similar tests can disagree. Direct comparison of phosphate and bicarbonate systems demonstrated that buffer species can materially alter dissolution and precipitation outcomes [19]. The medium may also modify excipient performance: the precipitation-inhibitory behavior of hydroxypropyl cellulose depended on the surrounding physiological-buffer conditions [20]. Controlled work comparing bicarbonate and phosphate further demonstrated differences in drug-crystal precipitation behavior [21], while subsequent investigation showed that both pH and bicarbonate buffer capacity influence precipitation of ionizable drugs [22]. These effects make it hazardous to attribute all precipitation differences to the compound or formulation when the assay environment itself can generate part of the observed phenotype.

Dissolved concentration also does not exhaust the exposure question. Drug-rich nanodroplets formed through liquid–liquid phase separation can contribute to intestinal absorption under defined conditions [23]. Conversely, the magnitude of colloid-associated transport enhancement depends on properties of both the colloidal particles and the drug, rather than being a fixed benefit of particle formation [24]. Biorelevant interpretation should

therefore distinguish molecularly dissolved, colloid-associated, and precipitated states while asking which fraction can contribute to membrane delivery.

Table 2 summarizes the analytical decisions that determine what a dissolution result can legitimately say about candidate quality.

Table 2. Analytical features that determine the exposure relevance of dissolution measurements

Analytical feature	What it resolves	Potential misinterpretation if omitted	Appropriate interpretation boundary
Buffer species	Environment-dependent ionization and precipitation behavior	Treating phosphate behavior as physiologically interchangeable with bicarbonate	Medium effects must be separated from compound effects
pH and buffer capacity	Driving forces for supersaturation and precipitation	Assigning precipitation solely to intrinsic poor solubility	Conditions must approximate the intended gastrointestinal question
Gastrointestinal transfer	Response to changing luminal environments	Evaluating release under a single static state	Transfer behavior is formulation- and compound-dependent
Colloidal phase state	Molecular versus particle- or droplet-associated drug	Counting all solubilized material as equivalently absorbable	Colloidal concentration does not equal free-drug activity
Absorption-relevant sink	Removal of available drug from the lumen	Ranking only by maximum dissolved concentration	Exposure interpretation requires linkage to transport or validated prediction

Note: The matrix distinguishes analytical interpretation from direct proof of systemic exposure.

Phosphate and physiological bicarbonate media are therefore not interchangeable when interpreting supersaturation and precipitation behavior of ionizable poorly soluble drugs [18, 19, 21]. Building on these findings and the later formulation-selection and ranking logic, **Figure 1** integrates the article's proposed transition from material-state assessment to exposure-informed candidate ranking while preserving the boundary between evidence-supported mechanisms and the new developability synthesis.

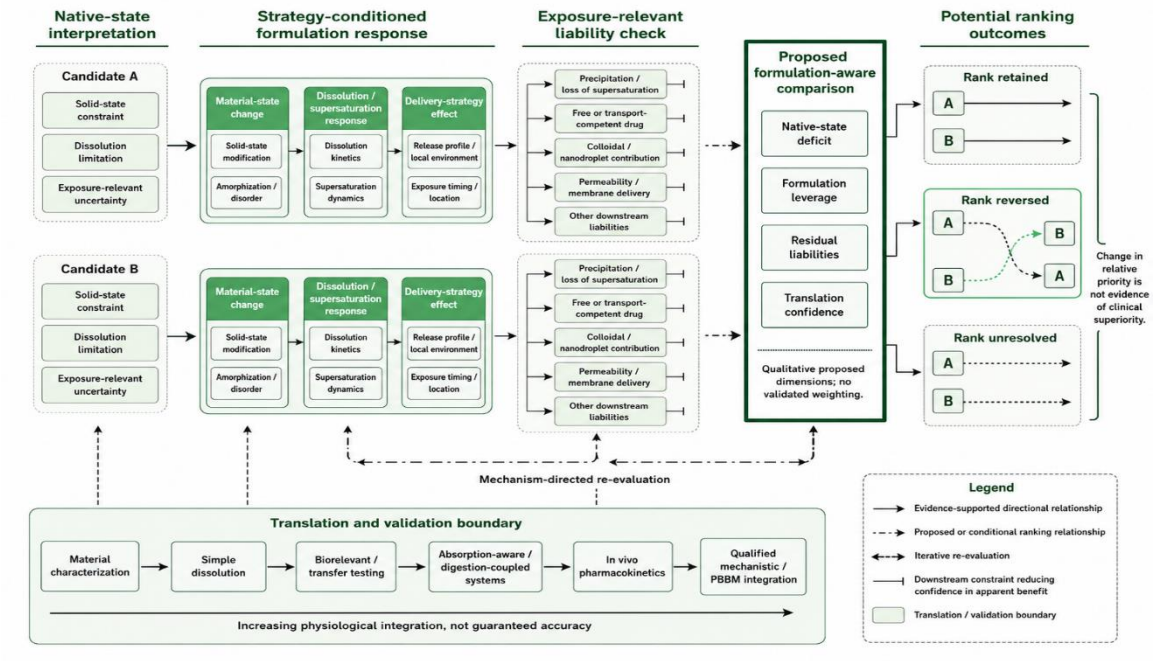

Figure 1. From native-state liability to exposure-informed candidate rank: a proposed formulation-aware developability architecture

Formulation options across different failure modes

Formulation strategies should be selected against the dominant failure mode rather than ranked as a universal hierarchy. Nanocrystal-loaded lipid carriers illustrate how combined approaches can simultaneously modify

dissolution, colloidal presentation, and intestinal transport; improved oral absorption of etoposide was demonstrated in a formulation-specific setting [25]. Lipid-based formulations provide a clearer mechanistic warning against strategy-by-solubility selection. During digestion, changes in solubilization may occur together with changes in thermodynamic activity and permeability, so the formulation producing the highest total solubilized concentration need not create the greatest membrane-driving force [26]. For poorly soluble phytochemicals, this means that a lipid-rich state should be credited only when its post-digestion behavior remains compatible with absorption.

Experimental geometry also affects interpretation. A digestion–absorption setup incorporating a physiologically relevant membrane surface-area-to-volume relationship changed evaluation of lipid formulation performance relative to a conventional digestion–permeation configuration [27]. Formulation composition may additionally influence presystemic metabolism, as demonstrated for lipid-based systems in vivo [28]. These findings broaden the failure diagnosis beyond dissolution: a candidate can remain constrained by transport, digestion-dependent speciation, or first-pass handling after solubility has been improved.

Solid-form strategies carry different liabilities. Ketoconazole cocrystal performance depended on the balance between enhanced dissolution, supersaturation, and subsequent precipitation [29]. Modeling of cocrystal dissolution likewise distinguished surface precipitation from precipitation in the bulk medium, showing why nominal cocrystal solubility advantage can be lost through more than one pathway [30]. Mesoporous silica offers another route for high loading and improved dissolution of lipophilic compounds, but dissolution enhancement by itself does not establish higher systemic exposure [31]. The proposed decision principle is therefore diagnostic: choose a strategy because it addresses the identified limiting process, then test whether it creates a new limitation downstream. A candidate dominated by lattice resistance, one dominated by precipitation after rapid release, and one dominated by poor membrane delivery should not automatically enter the same formulation pathway. Strategy selection is thus part of candidate characterization: the ease, specificity, and stability with which a plausible intervention changes the limiting mechanism provide information that the native compound alone cannot supply.

A formulation-aware candidate ranking model

A formulation-aware rank should represent more than the performance of the best formulation found so far. Mechanistic biopharmaceutics modeling provides a precedent for integrating formulation behavior with expected exposure. In an acalabrutinib case, a physiologically based biopharmaceutics model connected product dissolution behavior with clinically relevant exposure considerations and specification setting [32]. Contemporary PBBM practice also emphasizes purpose of use, model qualification, and explicit safe-space boundaries rather than treating model output as intrinsically decision-valid [33]. These principles support a confidence-aware ranking architecture, although they do not validate the phytochemical ranking model proposed here.

The model contains four proposed dimensions. Native-state deficit describes the severity and mechanism of the candidate's limitation before enabling formulation. Formulation leverage describes how strongly a scientifically plausible strategy changes the limiting process. Residual liabilities capture constraints that remain or appear after intervention, including unstable supersaturation, precipitation, reduced free-drug activity, permeability limitation, or formulation fragility. Translation confidence describes how strongly the apparent improvement survives progression from simple physicochemical tests toward exposure-relevant experimental systems. These dimensions are intentionally qualitative at this stage; no universal weighting or numerical threshold is justified by the present evidence.

Candidate comparison then becomes conditional rather than absolute. A molecule with poor native dissolution but high, reproducible formulation leverage may deserve higher priority than a molecule with moderately better intrinsic solubility whose exposure cannot be improved without introducing a larger downstream liability. Conversely, dramatic apparent solubility enhancement should not compensate automatically for weak transport or unstable solution behavior [5]. Different cocrystal forms can produce different bioavailability outcomes [16], colloidal transport depends on both drug and particle properties [24], and porous carriers can improve dissolution without proving exposure gain [31]. The proposed model therefore treats candidate rank as an evidence-weighted development hypothesis rather than a property of chemical identity.

The four dimensions should be interpreted jointly rather than sequentially scored. A severe native deficit may remain acceptable when the mechanism is well diagnosed, a feasible strategy directly addresses it, and residual liabilities are minor. A smaller native deficit may be less attractive when its cause is uncertain or when the apparent rescue is assay-sensitive. Translation confidence modifies the certainty of that comparison rather than acting as a

surrogate for efficacy. Crucially, candidates should be compared at approximately matched evidence depth. Otherwise, a thoroughly characterized candidate can appear worse merely because more of its liabilities have been discovered, whereas a superficially tested candidate appears cleaner because its failure modes remain unmeasured. **Table 3** converts these dimensions into a decision workflow that can be applied without assigning fabricated scores.

Table 3. proposed decision workflow for formulation-aware ranking of poorly soluble phytochemicals

Decision step	Question	Evidence sought	Rank consequence
Diagnose native deficit	What limits the unformulated candidate?	Solid form, dissolution, precipitation, permeability context	Establish baseline liability
Test formulation leverage	Can a plausible strategy alter that limitation?	Strategy-conditioned material and dissolution behavior	Increase priority only for reproducible gain
Check residual liabilities	What new constraint appears after intervention?	Supersaturation persistence, free-drug availability, transport, stability	Discount apparent improvement when downstream failure remains
Escalate translation	Does the advantage persist in more physiological systems?	Biorelevant, absorption-aware, in vivo, or qualified modeling evidence	Increase confidence, not the intrinsic score
Compare candidates	Does relative priority change after equivalent evidence depth?	Matched evidence across candidates	Classify rank as retained, reversed, or unresolved

Note: The workflow and rank consequences are proposed constructs. They do not constitute a validated quantitative scoring system.

Rank reversal and development decisions

Rank reversal occurs when relative candidate priority changes after strategy-conditioned evaluation. It is therefore comparative: a compound initially penalized for poor native dissolution may overtake another candidate only if its formulation-responsive advantage survives downstream scrutiny. Human resveratrol evidence shows that formulation can markedly alter exposure [1], and andrographolide nanocrystal performance shows that formulation composition can affect absorption [4]. The solubility–permeability trade-off demonstrates why the opposite can also occur: an apparently stronger solubilization response can fail to produce the strongest systemic performance [5]. Rank reversal should therefore be inferred from the combined exposure-relevant consequence, not from the largest physicochemical gain.

Mechanistically, reversals can arise through different routes. Drug-rich nanodroplets can contribute to absorption under defined conditions [23], whereas lipid formulations may change thermodynamic activity and permeability even when solubilization improves [26]. Cocrystals may increase dissolution yet lose advantage through precipitation [29]. These cases support separating *formulation response* from *developability benefit*. A candidate changes rank only when intervention changes the decision-relevant limitation without creating an equal or larger residual liability.

Development decisions should consequently preserve an unresolved state. When candidates have been evaluated at different evidence depths, apparent rank differences may reflect assay maturity rather than true developability. A PBBM-informed product decision illustrates how mechanistic integration can support development when the model is appropriately qualified [32], but the proposed rank model still requires prospective testing before it can be used predictively. The decision categories are therefore deliberately broader than advance or reject. A candidate may be retained at its original rank, promoted after a reproducible strategy-conditioned advantage, deprioritized when residual liabilities dominate, or held unresolved until the competing candidates have comparable evidence. This prevents formulation screening from becoming a post hoc exercise in finding any condition under which a favored molecule looks better.

Table 4 makes those decision boundaries explicit.

Table 4. Boundary and validation conditions for interpreting candidate rank reversal

Observed situation	Permitted interpretation	Do not infer	Validation need
Native performance improves after formulation	Formulation leverage is present	Candidate is clinically superior	Confirm downstream exposure relevance

Dissolution rises but transport worsens	Benefit is mechanistically incomplete	Higher dissolved concentration means higher exposure	Add permeability or absorption-aware testing
Supersaturation is transient	Apparent rescue may be unstable	Early dissolution peak represents durable advantage	Measure precipitation and time-dependent state
Rank differs across assay systems	Translation remains uncertain	One assay defines the true order	Reconcile systems and identify causal assay differences
Formulated candidate overtakes comparator	Rank reversal is plausible	Prospective predictive validity is established	Replicate under matched evidence depth and external conditions

Note: These boundaries are proposed interpretive rules rather than validated decision thresholds.

Figure 2 shows how the proposed model distinguishes genuine rank reversal from apparent reversal caused by unequal evidence depth or unresolved downstream liabilities.

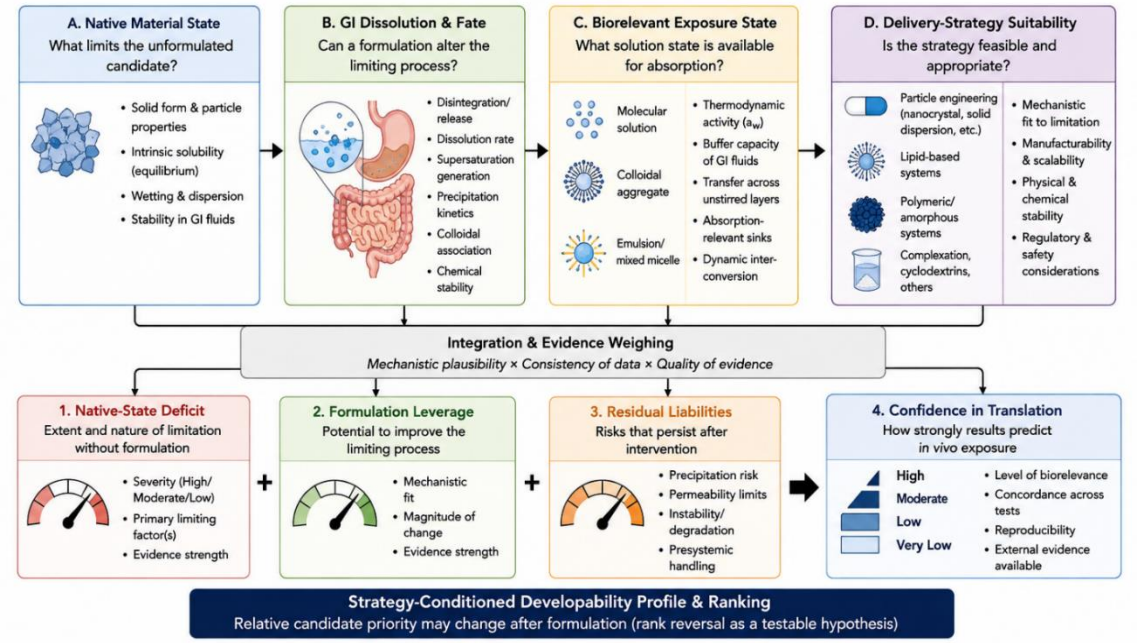

Figure 2. Rank reversal as a conditional development decision rather than a solubility-driven outcome

Translation across experimental systems

Translation confidence should increase only when the claimed advantage survives testing appropriate to its mechanism. Reporting guidance for physiologically based biopharmaceutics models emphasizes transparent parameterization, assumptions, qualification, and intended use [34]. This principle is equally important before modeling: the experimental system must be capable of observing the process used to justify the rank. A candidate credited for sustained supersaturation requires a test that captures precipitation over time; a lipid-based strategy requires digestion-aware evaluation; a colloidal mechanism requires methods that distinguish phase state and membrane-relevant delivery.

Accordingly, the proposed escalation pathway begins with material-state characterization and simple dissolution but does not end there. Biphasic dissolution can provide exposure-relevant information when partitioning and precipitation matter [7]. Dynamic gastrointestinal simulation can reveal behavior obscured by a conventional compendial setup [8]. For lipid systems, incorporating physiologically relevant absorption geometry can materially change formulation interpretation [27]. More complex systems, however, are not automatically more accurate; each adds assumptions, sources of variability, and a narrower domain of qualification.

Escalation should therefore be mechanism-triggered. Unexpected precipitation justifies experiments that resolve precipitation kinetics and solid phase; a claimed colloidal contribution justifies phase-sensitive and transport-aware measurements; a digestion-dependent advantage requires digestion-coupled assessment. Agreement across

increasingly relevant systems can strengthen confidence, whereas disagreement should trigger mechanism revision rather than automatic preference for the most complex assay. The key translational question is not which platform is most sophisticated, but whether the platform represents the process responsible for the proposed ranking difference.

In vivo pharmacokinetics remains the strongest direct test of systemic exposure within the scope of this model, but even an in vivo exposure advantage does not establish therapeutic effectiveness. Mechanistic PBBM can integrate formulation and physiological information when appropriately qualified [32], while current practice emphasizes safe spaces and purpose-specific validation [33]. The translation boundary therefore acts as a confidence filter: evidence may strengthen or weaken a proposed rank, but no single experimental platform converts the model into a universally validated predictor.

Limitations

The framework integrates evidence generated across phytochemicals and conventional poorly soluble drugs, formulation classes, assay designs, and biological systems. That heterogeneity is useful mechanistically but constrains direct generalization. Curcumin coamorphization demonstrates that phytochemical solid state can be altered [9], cocrystal studies show that different solid forms can produce different exposure behavior [16], and nanocrystal–lipid systems demonstrate formulation-dependent oral performance [25]; none establishes a universal magnitude of formulation leverage across structurally diverse phytochemicals.

Assay dependence is a second limitation. Interlaboratory precipitation testing shows that experimental parameters influence apparent behavior [17], physiological-buffer studies demonstrate that precipitation can shift with medium composition [21], and colloidal transport depends on drug and particle properties [24]. Consequently, a formulation-aware rank may change because a better experiment reveals a different mechanism, not because the molecule itself changed. This is a feature of the framework's conditional logic but a challenge for reproducibility.

Finally, the model is not prospectively validated. PBBM case studies demonstrate that mechanistic integration can support product decisions [32], while current PBBM practice stresses application-specific qualification and safe-space definition [33]. Transparent reporting improves interpretability but cannot substitute for predictive validation [34]. The proposed dimensions also lack established weights, and their relative importance may change with dose, ionization behavior, formulation class, and the dominant absorption barrier. The framework should therefore not be converted prematurely into a composite numerical score.

Future testing should compare chemically diverse phytochemicals under matched evidence depth, predeclare candidate ordering, apply multiple plausible formulation strategies, and assess whether observed rank changes reproduce across laboratories and, where justified, in vivo systems. Prospective failure is informative: if native rankings consistently predict exposure as well as or better than formulation-aware rankings, the added model complexity would not be justified.

Conclusion

Poor solubility should be treated as a developability diagnosis rather than an immutable verdict on phytochemical quality. Formulation can alter the material state presented to gastrointestinal fluid, the persistence of supersaturation, the balance between molecular and colloidal drug, the likelihood of precipitation, membrane delivery, and presystemic handling. Because these effects may reinforce or oppose one another, the candidate with the largest solubility gain is not necessarily the candidate with the strongest exposure-relevant improvement.

The formulation-aware developability model proposed here therefore separates native-state deficit, formulation leverage, residual liabilities, and translation confidence. This architecture makes rank reversal interpretable as a conditional development outcome: a poorly ranked native compound may move upward only when an appropriate formulation addresses the dominant limitation and the resulting advantage survives increasingly exposure-relevant testing. Conversely, an apparently attractive formulation should be discounted when its gain depends on unstable supersaturation, nontransportable solubilized drug, assay-specific behavior, or an unqualified model.

The framework is intended to structure comparative reasoning, not to supply universal scores or predict clinical success. Its practical value will depend on prospective validation across chemically diverse phytochemicals, equivalent evidence depth between candidates, explicit mechanism-based formulation selection, and transparent reporting of uncertainty. It also requires a willingness to leave candidates unresolved when the experiments cannot

distinguish formulation leverage from assay artifact or downstream liability. This is preferable to forcing a precise hierarchy from incomparable evidence.

The central change in perspective is therefore modest but consequential: assess the compound that can plausibly be delivered, while retaining full visibility of the constraints introduced by making it deliverable. Until prospective studies establish otherwise, formulation-aware ranking should remain a disciplined hypothesis for prioritization rather than a validated decision instrument.

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